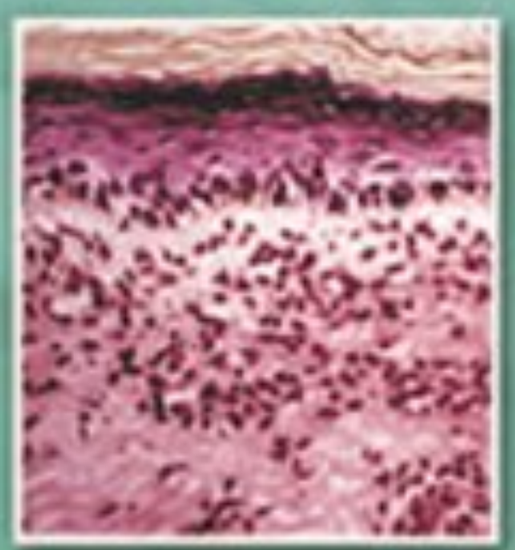
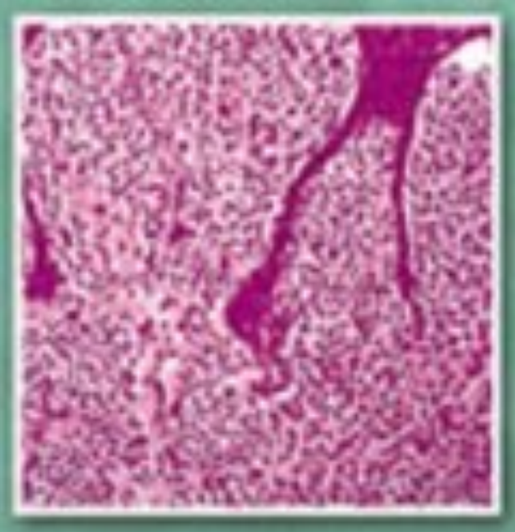
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LEVER'S HISTOPATHOLOGY OF THE SKIN







TENTH EDITION

EDITOR-IN-CHIEF:
David E. Elder

ASSOCIATE EDITORS:
Rosalie Elenitsas
Bernett L. Johnson, Jr.
George F. Murphy
Xiaowei Xu

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This Edition is dedicated to our teachers and mentors in medicine and surgery, pathology, and dermatopathology—too numerous to name individually—whose commitment to the discovery and dissemination of knowledge and patient tutoring at the bedside, bench, and microscope enabled this work to be accomplished.

CONTENTS

Preface to the Tenth Edition *ix*
Preface to the First Edition *xi*
Contributors *xv*

1 Introduction to Dermatopathologic Diagnosis 1
David E. Elder, George F. Murphy, Rosalie Elenitsas, Bernett L. Johnson, Jr., and Xiaowei Xu

2 Biopsy Techniques 5
Rosalie Elenitsas and Michael E. Ming

3 Histology of the Skin 7
Elsa F. Velazquez and George F. Murphy

4 Laboratory Methods 67
Rosalie Elenitsas, Carlos H. Nousari, Elias Ayli, and John T. Seykora

5 Outline of Cutaneous Pathology 83
David E. Elder, Rosalie Elenitsas, Bernett L. Johnson, Jr., George F. Murphy, and Xiaowei Xu

6 Congenital Diseases (Genodermatoses) 133
Bernett L. Johnson, Jr. and Albert C. Yan

7 Noninfectious Erythematous, Papular, and Squamous Diseases 169
Narciss Mobini, Sonia Toussaint, and Hideko Kamino

8 Vascular Diseases 205
Raymond L. Barnhill, Carlos H. Nousari, Xiaowei Xu, and Sarah K. Barksdale

9 Noninfectious Vesiculobullous and Vesiculopustular Diseases 235
Hong Wu, Heather A. Brandling-Bennett, and Terence J. Harrist

10 Connective Tissue Diseases 279
Harry Winfield and Christine Jaworsky

11 Cutaneous Toxicities of Drugs 311
Kim M. Hiatt and Thomas D. Horn

12 The Photosensitivity Disorders 333
Eduardo Calonje and John L.M. Hawk

13 Disorders Associated with Physical Agents: Heat, Cold, Radiation, and Trauma 343
Jacqueline M. Junkins-Hopkins

14 Noninfectious Granulomas 361
Christine J. Ko, Earl J. Glusac, and Philip E. Shapiro

15 Degenerative Diseases and Perforating Disorders 389
Michael K. Miller, Narayan S. Naik, Carlos H. Nousari, Robert J. Friedman, and Edward R. Heilman

16 Cutaneous Manifestations of Nutritional Deficiency States and Gastrointestinal Disease 407
Cynthia Magro, A. Neil Crowson, Molly Dyrsen, and Martin Mihm, Jr.

17 Metabolic Diseases of the Skin 425
John C. Maize, John C. Maize, Jr., and John Metcalf

18 Inflammatory Diseases of Hair Follicles, Sweat Glands, and Cartilage 459
Michael D. Ioffreda

19 Inflammatory Diseases of the Nail 503
Thomas D. Griffin

20 Inflammatory Diseases of the Subcutaneous Fat 509
N. Scott McNutt, Abelardo Moreno, and Felix Contreras

21 Bacterial Diseases 539
Sebastian Lucas

22 Treponemal Diseases 579
A. Neil Crowson, Cynthia Magro, and Martin Mihm, Jr.

23 Fungal Diseases 591
Molly Hinshaw and B. Jack Longley

24 Protozoan Diseases and Parasitic Infestations 621
Klaus Sellheyer and Eckart Haneke

25 Diseases Caused by Viruses 637
Xiaowei Xu, Lori Erickson, Lianjun Chen, and David E. Elder

26 The Histiocytoses 667
Walter H.C. Burgdorf and Bernhard Zelger

27 Pigmentary Disorders of the Skin 689
Carrie L. Kovarik, Richard L. Spielvogel, and Gary R. Kantor

28 Benign Pigmented Lesions and Malignant Melanoma 699
David E. Elder, Rosalie Elenitsas, George F. Murphy, and Xiaowei Xu

29 Tumors and Cysts of the Epidermis 791
Nigel Kirkham

30 Tumors of the Epidermal Appendages 851
Tamer S.S. Ahmed, Joseph Del Priore, and John T. Seykora

31 Cutaneous Lymphomas and Leukemias 911
Mei-Yu Hsu and George F. Murphy

32 Tumors of Fibrous Tissue Involving the Skin 969
Trevor W. Beer, Minh H. Lam, and Peter J. Heenan

33 Vascular Tumors: Tumors and Tumor-like Conditions of Blood Vessels and Lymphatics 1007
Eduardo Calonje

34 Tumors With Fatty, Muscular, Osseous, and/or Cartilaginous Differentiation 1057
Bruce D. Ragsdale

35 Tumors of Neural Tissue 1107
Richard J. Reed and Donald R. Pulitzer

36 Metastatic Carcinoma of the Skin 1151
Waine C. Johnson

Appendix 1161
Index 1187

PREFACE
TO THE TENTH EDITION

This book represents an incremental revision and update of the previous two editions, the first of which constituted a somewhat more extensive revision of the seven editions produced by Walter Lever, MD, beginning in 1949 as a 449-page volume with "221 Illustrations Including 8 Subjects in Color on 4 Plates." Thus, this will be the tenth edition of a book that has been continuously published for 60 years! In this second generation of the work, the principles that made "Lever" such a success for so long continue to be applied. These include, first and foremost, a continued organization of the book along the lines of a traditional clinicopathologic classification of cutaneous disease. This enables us to discuss lesions according to their clinical and etiological relationships, paralleling the organization of the major clinical texts. In some other dermatopathology works, a greater emphasis has been placed on histological patterns of disease as the underpinning of the chapter organization. This has advantages in enabling beginners to develop an appropriate differential diagnosis for a given pattern of disease, but can be confusing in that etiologically and clinically disparate conditions tend to be discussed in juxtaposition to each other, and also in that polymorphous conditions need to be discussed in multiple different places.

We have taken into account the modern emphasis on pattern recognition in several ways. First, within each chapter, the conditions considered are, when appropriate, organized and discussed along pattern lines. Second, we have, as in the past, included a chapter that presents an algorithmic classification of skin diseases according to histologic pattern features. It is intended that this chapter may serve as a means of developing a differential diagnosis from an unknown slide, following which references are provided for discussion of the disorders in other areas of the book. In addition, we have prepared a companion volume "Atlas and Synopsis of Lever's Histopathology of the Skin," now in its second edition. This Atlas has enabled us to greatly extend the number of illustrations including a larger number of clinical images, and is organized completely on the basis of histologic patterns. Unlike some other pattern-based works, this Atlas includes neoplastic disorders among the inflammatory conditions. Thus, it becomes clear to the reader that a lichenoid actinic keratosis or *in situ* melanoma may share features with (and potentially be misdiagnosed as) a plaque of lichen planus or a patch of lupus. This Atlas, which was produced as a companion to the last edition of the "Big Lever," will be continue to be updated and extended to incorporate the new information in successive editions of "Lever."

In another area of emphasis, we have continued the practice of providing clinical review prior to exposition of the histologic features for each group of disorders. This, in our opinion, greatly enhances the value of the work, not only for pathologists and others whose primary training is not in clinical dermatology, but also for dermatologists in training and, no doubt, for some who are more advanced in the field as well. In this present edition, we have included clinical images to enhance this distinctive aspect of the text, recognizing that the clinical morphology is the "gross pathology" of dermatopathology. Indeed, in today's environment of ubiquitous digital cameras and internet connections, we would take this opportunity to encourage clinicians to submit with their biopsies not only detailed clinical differentials, but also clinical images of selected cases, for the benefit of more accurate diagnosis and improved patient care.

At the other end of the spectrum of clinical science, we have continued and updated the classic work's emphasis on "histogenesis" by emphasizing underlying mechanisms of disease. To us, the term *histogenesis* includes mechanisms of development of histological patterns of disease and might equally well be (and sometime is) labeled "pathogenesis." In this edition, more than in any other because of the explosion of knowledge, molecular mechanisms of pathogenesis are presented for perhaps almost a majority of the diseases. However, it is interesting that, in most cases, these molecular mechanisms, while of explanatory interest, have not yet supplanted traditional histopathology and immunohistology as the "gold standard" for diagnosis of most of the conditions discussed in the book.

As in the past, the book does not attempt to be a compendium of all known skin diseases. However, we have tried to make it a reference work for those skin diseases in which histopathology plays an important role in diagnosis. Particular attention has been paid to the index in this edition, which we believe will further enhance the scholarly value of the work. We are grateful for this opportunity and are excited to present another edition of this revered work to a new generation of readers. At the same time, we hope that members of earlier generations who have used "Lever" as their primary skin pathology training and reference source will continue to find this new edition useful in their continuing development and in their daily practices.

David E. Elder
2008

PREFACE
TO THE FIRST EDITION

This book is based on the courses of dermatopathology that I have been giving in recent years to graduate students of dermatology enrolled at Harvard Medical School and Massachusetts General Hospital. The book is written primarily for dermatologists; I hope, however, that it may be useful also to pathologists, since dermatopathology is given little consideration in most textbooks of pathology.

I have attempted to keep this book short. Emphasis has been placed on the essential histologic features. Minor details and rare aberrations from the typical histologic picture have been omitted. I have allotted more space to the cutaneous diseases in which histologic examination is of diagnostic value than to those in which the histologic picture is not characteristic. In spite of my striving for brevity I have discussed the histogenesis of several dermatoses, because knowledge of the histogenesis often is of great value for the understanding of the pathologic process.

Primarily for the benefit of pathologists who usually are not too familiar with dermatologic diseases, I have preceded the histologic discussion of each disease with a short description of the clinical features.

A fairly extensive bibliography has been supplied for readers who are interested in obtaining additional information. In the selection of articles for the bibliography preference has been given, whenever possible, to those written in English.

I wish to express my deep gratitude to Dr. Tracy B. Mallory and Dr. Benjamin Castleman of the Pathology Laboratory at the Massachusetts General Hospital for the training in pathology they have given me. It has been invaluable to me. Their teaching is reflected in this book. Furthermore, I wish to thank Mr. Richard W. St. Clair, who with great skill and patience produced all the photomicrographs in this book.

Walter F. Lever
1949

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Introduction to Dermatopathologic Diagnosis

Readers of this book in its nine previous editions have relied on it to aid them in making accurate histologic diagnoses of cutaneous disease. A diagnosis is a clinical tool that assists in the process of codifying patients into disease groups that tend to share a common outcome and a common set of responses to therapy. The histologic diagnosis in turn is used by clinicians to aid in the management of patients. The most accurate diagnosis is the one that most closely correlates with clinical outcome and helps to direct the most appropriate clinical intervention. Thus, there is a close relationship between diagnosis and prognostication. By emphasizing certain key observations that have value in identifying particular diseases, this book aids observers to make appropriate histologic diagnoses, and to provide an estimate of prognosis, in most skin biopsies. Where applicable, ultrastructural, immunohistochemical, and molecular aids to diagnosis are discussed. These advances have resulted in increased specificity for many diagnoses. For example, immunofluorescence has long been used to differentiate among vesiculobullous disorders (see Chapter 9). In another example, an amelanotic dermal tumor composed of large, mitotically active cells that are positive in an immunohistochemical reaction for the HMB-45 or Melan-A antigens is almost certainly a malignant melanoma. In the absence of the immunologic criteria, these specific diagnoses could not have been made as reliably (see Chapter 28). In the next several years, it can be expected that molecular criteria will increasingly be used for diagnosis and prognosis. For example, a fusion transcript for EWS-ATF1 detected by reverse-transcriptase polymerase chain reaction (PCR) or potentially by fluorescence *in situ* hybridization (FISH) might be used to distinguish between a primary clear cell sarcoma and a malignant melanoma involving the soft tissue, a distinction that is not always possible to make with certainty by traditional means (1). Despite the incremental advances of molecular techniques in diagnosis and prognosis, it may seem surprising that morphology is still the basis of diagnosis for most neoplasms and many inflammatory dermatoses. Nonetheless, a histologic image represents a true synthesis of all of the molecular events acting in a given microscopic "scene," encompassing not only the concerted expression of genes, including oncogenes and tumor suppressor genes, but also the sum total of all epigenetic effects such as gene methylation, posttranslational modification, and the spatially and temporally segregated interactions of proteins and other gene products. This level of complexity of information cannot be captured by any high-throughput molecular testing that has yet been conceived.

Although histopathology remains the gold standard for most dermatologic diagnoses, it must be recognized that not all lesions are amenable to definitive "specific" histologic diagnosis. As reviewed by Foucar (2–4), specificity, or the "true negativity rate," is the frequency of a negative test result in individuals who actually do not have the disease of interest. Specificity studies are hard to do because they require large-scale studies of normal populations and because of the need for a gold standard for the disease independent of the test under consideration. Most studies in the literature begin with data demonstrating the "sensitivity" or "true positive rate," which is a measure of the frequency of a positive test result in individuals with the disease (2). These data do not, however, indicate that a diagnostic test is perfectly reliable. For example, most melanomas are positive for the immunohistochemical marker S100 (high sensitivity). However, almost all benign melanocytic neoplasms are also positive for the same marker (low specificity). Frequent mitoses in the dermal component of the neoplasm, on the other hand, are common in bulky tumorigenic melanomas but rare in most benign melanocytic neoplasms and are therefore a useful, relatively specific but not pathognomonic marker for melanoma. On the other hand, mitotic figures are absent in most thin nontumorigenic melanomas, so that their sensitivity for the diagnosis of "melanoma," overall, is low (see Chapter 28).

The histologic features of many inflammatory dermatoses in particular are nonspecific or, at best, only suggestive of a specific diagnosis. Even among the more readily characterized papulosquamous dermatoses, such as psoriasis or lichen planus (see Chapter 7), the histologic picture is more typically "compatible with" rather than "diagnostic of" the clinical process. Sometimes, however, the histopathology can contribute by ruling out an important diagnosis, even though an exact diagnosis cannot be made. For example, review of a biopsy of a psoriasiform plaque may rule out mycosis fungoides (see Chapter 31) but may not be able to establish the specific diagnosis of psoriasis (see Chapter 7). The obvious diagnostic limitations of histology extend to infectious and neoplastic processes as well. For example, infectious granulomas of different etiologies are not readily

distinguishable unless the causative organism can be demonstrated. This may not be possible without additional testing such as bacterial or fungal cultures (see Chapters 21 to 23). The same applies to noninfectious inflammatory disorders such as pyoderma gangrenosum in which infection needs to be ruled out as an etiologic possibility (see Chapter 16). Similarly, in the neoplastic realm, histology may not suffice to distinguish between keratoacanthoma and squamous cell carcinoma (5) (see Chapter 29), or between Spitz nevus and melanoma (6) (see Chapter 28).

Some of these "difficult" diagnoses result from the existence of important data that are undetectable by routine histologic methods, such as sparse organisms in a granulomatous process. In other instances, the data might be detectable if sought, but are obscure. For example, many granulomatous processes can be more specifically characterized if more sensitive staining for organisms is done, as in a Grocott or acid-fast stain. If the observer does not think of infection and order the stain, the diagnosis is never made. In many other situations, however, such as the diagnosis of keratoacanthoma versus squamous cell carcinoma or of Spitz nevus versus melanoma, the data may have been assiduously collected by the observer using complex algorithms published for these purposes, and yet the diagnosis may remain obscure and agreement among observers difficult or impossible to obtain. In such cases, there is typically a continuum of the traits that underlie diagnosis, and individual cases in the vicinity of the diagnostic cut-point are more likely to be misclassified than other cases (7).

In an interesting exercise published as a "Tutorial on Melanocytic Lesions" a panel of six experts in pigmented lesion pathology reviewed 71 "difficult" cases (8). Although agreement was substantial for many of the different categories of lesions, the categories of Spitz nevi and other variants of nevi and of nevoid melanoma were more difficult. Unanimity in diagnosis was reached in only 11 of 38 of these cases, and in 6 cases the opinions of the experts were equally divided between benign and malignant. In another category, that of six examples of "pseudomelanomas" in children, agreement on a benign diagnosis was almost unanimous, yet one of these patients had died of metastatic disease. In another study of 30 lesions selected for their difficulty, evaluation of 17 "Spitzean" lesions yielded no clear consensus as to diagnosis: "In only one case did six or more pathologists agree on a single category, regardless of clinical outcome" (9). In addition, some lesions that proved fatal were categorized by most observers as either Spitz nevi or atypical Spitz tumors (9). Thus, agreement on a diagnosis does not necessarily mean that the diagnosis is correct. Therefore, the best opinion that can be rendered about these lesions is that the true diagnosis is unknown, and the likely behavior of these lesions is uncertain.

Following practice in other areas of pathology in which similar problems exist (10–20), such lesions in our opinion are best categorized as "tumors of uncertain malignant potential." In these cases, we always provide a differential diagnosis, and therapy is usually tailored with the "worst-case scenario" taken into consideration. Even this latter assumption is not without potential for controversy, however; it is not at all clear, for example, that therapy devised for routine cases of melanoma should be uncritically applied to melanocytic tumors of uncertain potential (see Chapter 29). In these "borderline" or "difficult" lesions, the clinical usefulness of histology may be aided by effective communication between clinician and pathologist with appropriate attention to the clinical and epidemiologic context of the lesion under study, and also by ancillary testing such as comparative genomic hybridization or FISH for assessment of gene amplification profiles, which have been shown to differ between Spitz nevi and melanomas (21). Even when all of the clinical, histologic, and molecular information is at hand, however, a consensus diagnosis may be impossible, and there is no prospective assurance that any diagnosis is biologically "correct."

Elliott Foucar has elegantly discussed the difficulties inherent in making a histologic diagnosis (and these considerations apply to other forms of diagnosis as well), and the issues have also been well covered by Sackett and his colleagues (3,4,22,23). A major source of difficulty in making an exact diagnosis in pathology, as in clinical medicine, is that the information required to make the diagnosis is frequently incomplete at some level or at multiple levels. At the most fundamental level, there may simply be no standard for a particular diagnosis. For example, histopathology is often taken to be a gold standard for diagnosis of a particular disease. However, if the histopathologic parameters that are considered to define this disease have been determined in a clinically defined series of cases, their independence and specificity could be called into question. A histologic study of nummular dermatitis, however complete and accurate it may be, will not glean any information that reliably distinguishes between this diagnosis and that of another spongiotic dermatitis (see Chapter 7). Patches of early mycosis fungoides biopsied from patients with established plaque stage lesions may well represent examples of "early" mycosis fungoides, yet similar histologic changes in a patient with only a solitary lesion may or may not progress to established disease (see Chapter 31).

Another serious problem in histopathologic diagnosis results from the fact that specificity studies to determine the prevalence of criteria in diagnostically challenging cases are frequently not available. For example, early studies of the HMB-45 antibody determined that it had 100% specificity for melanoma cells in the dermis or deeper tissues (24). After the specificity studies were extended, however, it was recognized that this antigen is expressed not only in melanoma, but also in blue nevi (25) and in other benign lesions (see Chapter 28).

Foucar has pointed out that the diagnostic process is an example of complex decision making that has intrinsic uncertainty, usually resulting from one or more of the following: (a) The large number of variables that can be evaluated in an attempt to solve the problem results in novel combinations of variables that cannot be managed consistently by problem solvers; (b) one or more key variables lack clear definition; or (c) one or more key variables is hidden from the problem solver (22). To the uncertainty inherent in these complex problems can be added (d) the uncertainty (discussed previously) of the specificity of the individual findings and (e) the uncertainty that results from deficiencies in the observer's ability to evaluate and categorize histologic findings. Even the most expert

observers have inherent and often unrecognized deficiencies that result in less than perfect reproducibility of histopathologic observations and thus of diagnoses (26). Furthermore, there are limitations in the ability of even the most expert observers to communicate their diagnostic acumen to others (22).

The diagnostic difficulties that result from uncertainty are compounded when there is also failure to agree on the criteria for diagnosis. In a study of inter- and intraobserver reproducibility for the diagnosis of dysplastic nevi, intraobserver reproducibility was substantial, and interobserver concordance was fair, despite differences in criteria. It was concluded that, although experienced dermatopathologists in this study used different diagnostic criteria for histologic dysplasia, their usage was consistent (27). In another study in which observers agreed to abide by predetermined criteria and were provided reference photomicrographs illustrative of the criteria, agreement was substantial to excellent for the histopathologic diagnosis of 112 melanocytic tumors including typical and dysplastic nevi and melanomas. It was concluded that, with the use of predetermined criteria, melanocytic dysplasia can be reproducibly graded among diverse general dermatopathologists (28). It is also interesting to note that, even when reproducibility is less than what might be considered optimal, a diagnosis can still be meaningful if the association between the diagnostic observation and a biologically important result is sufficiently powerful. For example, in a recent case–control study of the association of histologic melanocytic dysplasia with melanoma risk, a statistically significant and biologically meaningful relative risk of 3.99 was observed despite κ values for agreement among observers that were in the "poor" range (29). In such a situation, there is an opportunity for observers to work together to develop a set of criteria that can achieve better agreement while retaining biological significance.

In another example, the criteria for diagnosis of vertical growth phase in thin melanomas have been rigorously evaluated in two large studies. In one of the studies, 94 slides of malignant melanoma were circulated to six pathologists in two university departments. For each slide, the growth phase of the lesion, the Breslow thickness, and the Clark level were determined by each observer. The aims of the study were "to evaluate agreement among nonspecialist pathologists in identifying the vertical growth phase in malignant melanoma and to compare agreement for the growth phase with agreement for Breslow thickness and the Clark level" (30). It was found that, although overall agreement for the growth phase was moderate, agreement among experienced observers was good (30). Although this was outside of the scope of the study, is it is likely that, with increased experience, the nonspecialist pathologists would attain the same level of agreement. In a similar study, 148 pathologists participated in two circulations of melanoma slides, and the results were compared with those of a national melanoma pathology panel that had developed and evaluated diagnostic criteria. After a first circulation of slides in which only fair agreement was achieved, a second circulation of slides was accompanied by diagnostic criteria and diagrams. In this second circulation, there was a higher level of agreement for overall diagnosis, using the categories benign, melanocytic intraepidermal neoplasia, and melanoma with vertical growth phase ($\kappa = 0.68$). In their conclusions, these authors emphasized the importance of standardized diagnostic criteria to ensure accurate reporting of incidence and correct management of patients (31).

As discussed by Foucar and illustrated in some of the foregoing examples, differences in criteria may result from the use of different assumptions for the development of criteria (22). At the simplest level of diagnosis, an individual pathologist might establish a set of criteria that establish a diagnosis "by definition." Such a definitional diagnosis reduces uncertainty for that individual to a minimum. At a somewhat more advanced level, criteria are used that are considered likely to be acceptable to other pathologists, constituting a "consensus gold standard." At this level of diagnosis, difficulties in communicating a clear definition of the criteria among pathologists introduce uncertainty due to lack of reproducibility, and this uncertainty increases with the number of variables under consideration and the resultant increasing subjectivity of the diagnostic exercise.

The most advanced measure of the level of diagnostic problem solving, according to Foucar, is represented by the attempt to assign a biologically correct label, one that precisely predicts a disease's course (22). Attempts fully to resolve this more difficult level of prediction are likely in many cases, if not most, to be frustrated by the uncertainties enumerated earlier, especially the existence of hidden variables— "host resistance," "virulence," "environmental effects," and so on—that are not evident to the observer of a histologic slide, however expert and diligent he or she may be. Efforts to improve on diagnostic efficacy at this level might, for example, pursue information at the ultrastructural or molecular level. However, the accurate and complete prediction of a particular disease outcome will always prove to be an elusive goal.

Prognostication—the prediction of disease outcome—is an important biological indicator of diagnostic efficacy. In some instances, many of them neoplasms, a histologic diagnosis is predictive of biological behavior, such as the capacity for distant metastasis. Then, follow-up studies of outcome can serve as an appropriate gold standard for validation of diagnostic utility. Indeed, a 100% statistical probability of survival for a given neoplasm could be regarded as equivalent to a diagnosis of benignancy, illustrating a strong relationship between diagnosis and prognosis. Even when such studies are available, however, the prediction of outcome is usually in terms of statistical probabilities, which are not absolute. In addition, the course of the disease is inevitably altered by the diagnostic process; for example, excision of a melanocytic lesion that is diagnosed as a melanoma *in situ* is effective in preventing "malignant" behavior such as persistence, continued growth, and progression to a lesion with capacity for metastasis. The information needed to predict outcome accurately in any given individual case is also frequently not available to the histologic observer. For example, the outcome of a viral infection may depend on the presence or absence of antibodies in the patient's serum, which cannot be determined from observation of histologic sections. Similarly, even the most advanced and seemingly lethal primary malignant

melanoma has a certain probability of survival, even after using the most sophisticated prognostic models (32).

Another advanced measure of the biological relevance of a diagnostic system is through the correlation of traditional diagnostic labels with molecular findings. In the molecular-based studies of Bastian and his colleagues (33–36), nevi have been distinguished from melanomas, a subset of atypical Spitz nevi has been distinguished from among the usual forms of this condition, the acral-lentiginous subset of melanoma has been distinguished from other types, and findings traditionally associated with melanoma classification have been found to relate to underlying genetic abnormalities, all through the use of comparative genomic hybridization or gene sequencing techniques to identify molecular lesions that appear to have specificity for these traditionally defined variants of melanocytic neoplasia (see Chapter 29). In a patient with a suspected infection, a PCR test for "foreign" DNA can be diagnostic of the presence of an infectious agent (see Chapters 20 to 25). These types of correlations can be expected to increase in the future, strengthening the relationship between our present empirically based classification schemas and the underlying biology.

It is likely that the best approximation to the goal of improving diagnostic specificity will be achieved by a detailed correlation of findings at the molecular, histologic, and gross anatomic levels with the physical findings and clinical history, interpreted in the context of the whole patient and his or her environment, with long-term follow-up serving as the gold standard. In the real world of clinical medicine, a histologic description and differential diagnosis for a difficult case is often more likely to be useful than a single "specific" diagnosis that may be correct in its own frame of reference but wrong or misleading in the total clinicopathologic context of a particular patient. The former is the traditional method of clinical practice, which should be aided but not supplanted by the tools of histopathology. The information in this book has been designed to assist in this clinical diagnostic process.

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CHAPTER 2

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Biopsy Techniques

It has been said that more errors are made from failing to biopsy properly than from performing unnecessary biopsies (1). Biopsy is indicated in suspected malignant neoplasms and to clarify a diagnosis when a limited number of conditions are under consideration. Biopsies submitted without a differential diagnosis are likely to be less successful in supporting a more definitive diagnosis, although of course there are exceptions to this rule. The technique used to obtain a specimen for microscopic evaluation may have a significant impact on the ability of the dermatopathologist to arrive at the correct diagnosis. Commonly used skin biopsy techniques are punch biopsy, superficial and deep shave biopsy, deep incisional biopsy, complete excision, and curettage. The choice of technique depends on many factors, including the clinical differential diagnosis and a mental review of the pathology of each disorder; the anatomic site; the morphology of the lesion, particularly its size and shape; the overall physical health of the patient; and cosmetic concerns. Several reviews of biopsy techniques have been published (1–3).

Selection of the appropriate lesion to biopsy when evaluating an inflammatory disorder is crucial. In most instances, histologic examination of a fully developed lesion will give more information than examination of an early or involuting lesion. However, vesicobullous lesions, ulcers, and pustular lesions are exceptions. For their histologic examination, a very early lesion is optimal; otherwise, secondary changes such as regeneration, degeneration, scarring, or secondary infection may obscure essential features and make recognition of the primary pathologic process impossible. The ideal candidate lesion for biopsy has not been scratched or traumatized and is untouched by topical or systemic therapy, especially antiinflammatory agents. If there are lesions in different stages of evolution, multiple biopsy specimens may be helpful. When considering diagnoses such as connective tissue nevus, anetoderma, atrophoderma, and some pigmentation disorders, the dermatopathologist may wish to compare involved and uninvolved skin. In those cases, one can perform a scalpel biopsy incorporating a portion of the lesion and adjacent normal skin.

When performing scalp biopsies for alopecia, many laboratories prefer two specimens: one for transverse (horizontal) sectioning and one for standard "vertical" sections. The punch instrument should be inserted into the skin parallel to the direction of hair growth, and the biopsy should extend well into the subcutis to be certain that the bulbs of terminal follicles are included (4). In scarring alopecia, it is important that a biopsy be performed in an area of erythema with visible hair shafts; a biopsy of a completely scarred area of alopecia will show only end-stage nonspecific changes.

Punch biopsy is the standard procedure for obtaining samples of inflammatory dermatoses but is often used for neoplasms as well. In most instances, a specimen obtained with a 4-mm punch biopsy is adequate for histologic study. A 3-mm punch biopsy may be preferable for small lesions or biopsies from the face or other areas where cosmesis is a concern. Either a 6-mm punch biopsy or a deep incisional biopsy using a scalpel should be performed if panniculitis is suspected to ensure that adequate amounts of subcutaneous fat are obtained. After the skin specimen has been loosened with the biopsy punch, it should be handled very gently and, above all, should not be grasped with forceps except at the very edge. Crush artifact from forceps makes a specimen of an inflammatory process essentially useless, with lymphoma and leukemic infiltrates being particularly susceptible to crush. Often, a punch biopsy specimen can be squeezed gently out of its socket or carefully speared with the syringe needle that was used for injection of the local anesthetic. Sharp scissors can be used to cut through the subcutaneous fat at the base of the specimen. All punch biopsy specimens for inflammatory disease should extend to the subcutaneous fat because in many dermatoses, characteristic histologic features are found in the lower dermis or in the subcutaneous fat.

Shave biopsies may be either superficial or extend more deeply into the skin, but in general they should extend at least into the papillary dermis. Superficial shave biopsies should be used only for lesions in which characteristic histologic changes are expected to be present in the epidermis or the superficial dermis, such as seborrheic keratoses, solar keratoses, verrucae, benign nevi, and basal cell carcinomas. This method has the advantage of leaving the lower portion of the dermis intact so that, immediately afterward, lesions such as basal cell carcinomas can be fully removed by curettage with or without electrodesiccation. In addition, cosmesis is often improved by using the superficial shave biopsy technique. A variant of the deep shave biopsy is the saucerization technique, in which the blade is introduced at roughly a 45-degree angle. To aid in the control of the size of the tissue to be removed, some physicians score

the skin before performing a shave biopsy. Shave biopsies are inadequate for differentiating between squamous cell carcinoma and keratoacanthoma. A superficial shave biopsy without adequate dermis may be suboptimal if melanoma is included in the differential diagnosis due to concerns that a melanoma might be transected at the base. A transected melanoma specimen may be more difficult to diagnose, and accurate assessment of tumor thickness may be more difficult. Because of the thick stratum corneum, a shave biopsy of acral skin may produce a superficial specimen extending only to the midepidermis or papillary dermis. This is especially important when considering a biopsy of an acral pigmented lesion; in this situation, a punch biopsy or small excision is often the best method.

To carry out a shave biopsy, either the skin is raised as a fold and cut with the blade parallel to the skin surface or a curved razor blade is used. Aluminum chloride is recommended for hemostasis; Monsel's solution (ferric subsulfate) and electrocautery are alternatives, but they may affect the interpretation of subsequent biopsies or reexcisions (5).

Deep incisional biopsies using a scalpel may be helpful when evaluating panniculitis or when assessing deep dermal or subcutaneous nodules. Complete excision is often used to obtain an initial specimen for diagnosis when examining atypical pigmented lesions or when evaluation of margins is necessary. Curettage is the least satisfactory of the foregoing methods of obtaining material for histologic examination because the submitted material usually is scanty and superficial; it has lost its architecture, and it may show crush artifact. Even if curettage is performed well, fragmentation and distortion cannot be avoided. Curettage of a melanoma that clinically resembles a seborrheic keratosis or pigmented basal cell carcinoma may prevent accurate diagnosis and may make assessment of microscopic features such as ulceration or regression more difficult.

The biopsy specimen should be placed in fixative immediately on removal from the patient to prevent autolysis. It should not be allowed to dry, and the dermatologist should check the specimen bottle to ensure that the tissue has not adhered to the side of the bottle or remained inside the punch. Patient information should be placed on the bottle itself, not on the lid, which could be accidentally placed on a different bottle. As fixative, 10% buffered formalin can be used in nearly all instances (see Chapter 4). However, if the specimen is mailed in winter, 10% aqueous formalin, which freezes at −11°C, may allow formation of ice crystals in the specimen. This causes damage and distortion in the specimen, particularly in epithelial cells, and makes adequate histologic evaluation impossible. Freezing can be prevented by the addition to the formalin of 95% ethyl alcohol, 10% by volume. An alternative is to let the specimen stand in the formalin solution at room temperature for at least 6 hours before mailing.

Every specimen submitted for histologic diagnosis should be accompanied by detailed clinical information, including a differential diagnosis. The histopathologist's ability to render an accurate diagnosis often depends on the available clinical information, and clinicopathologic correlation is the key to providing optimal patient care. Previous biopsies at the same site, specific requests (e.g., special stains for infectious organisms), and special handling should also be indicated on the requisition sheet sent to the laboratory with the specimen. If, for instance, a stain for lipids is to be carried out, the specimen must not be processed in the automatic processor (see Chapter 4). Handling of biopsies for immunofluorescence is discussed in Chapter 4.

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CHAPTER 3

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Histology of the Skin

OVERVIEW

Understanding the normal histology of skin is central to recognizing cutaneous pathology. The journey to defining the normal histology of human skin is a relatively short one in terms of spatial dimensions. From an en face view of the skin surface, characterized by desquamating scale, furrows, and evidence of adnexal growth, to the normal ultrastructure of key organelles within underlying cellular constituents, we span a magnification range of 10^5 (1). Over this expanse, the histology of the skin is amazingly complex. Divided into two seemingly separate but functionally interdependent layers (epidermis and dermis) (Figs. 3-1 to 3-5), the skin is composed of cells with myriad functions ranging from mechanical and photoprotection, immunosurveillance, and nutrient metabolism to repair. A third layer, the subcutaneous adipose tissue, is not truly a part of the skin, but because of its close anatomic relationship and its tendency to respond together with the skin in many pathologic processes, it is also discussed in this chapter.

The epidermal layer is composed primarily of keratinocytes (greater than 90%), with minority populations of Langerhans cells, melanocytes, neuroendocrine (Merkel) cells, and unmyelinated axons. In addition, the epidermis also contains specialized cuboidal epithelium that forms the spiraling acrosyringia of eccrine sweat ducts, as well as occasional cells putatively programmed for possible adnexal/glandular differentiation (e.g., Toker cells, as found in nipple epidermis in approximately 10% of individuals) (2,3). Architecturally, the epidermal layer has an undulant undersurface in two-dimensional sections, with downward invaginations termed retes and interdigitating mesenchymal cones termed dermal papillae (not to be confused with follicular papillae of the hair bulb). In reality, three-dimensional reconstruction reveals epidermal rete to form a honeycomb of interconnected ridges, with dermal papillae representing rounded conical invaginations not dissimilar to the undersurface of an egg carton. Separated from the epidermis by a structurally and chemically complex basement membrane zone, the dermis consists of endothelial and neural cells and supporting elements, fibroblasts, dendritic and nondendritic monocyte/macrophages, factor XIIIa–expressing dermal dendrocytes, and mast cells enveloped within a matrix of collagen and gylcosaminoglycan. Adnexae extend from the epidermis into the dermis and consist of specialized cells for hair growth, epithelial renewal (stem cells), and temperature regulation. Adnexal epithelium also appears to provide a safe haven for certain precursor cells (e.g., for melanocytes and dendritic cells) in a tissue niche sequestered from deleterious environmental influences at the skin surface. The subcutis is an underlying cushion formed by cells engorged with lipid and nourished by vessels that grow within thin intervening septae. The developmental anatomy of skin is important not only for understanding the basis for mature structural–functional relationships, but also in relation to certain skin tumors that recapitulate embryologic cutaneous structure.

EPIDERMIS

The epidermis comprises the following cell types:

- Keratinocytes
- Melanocytes
- Langerhans cells
- Merkel cells

Keratinocytes

Embryology

The development of *in utero* skin biopsy techniques gives practical importance to understanding the normal evolutionary histology of fetal skin. The epidermis begins as a single layer of ectodermal cells (4,5). By 5 weeks of gestational age, this has differentiated at least focally into two layers—the basal layer or stratum germinativum and the overlying periderm; by 10 weeks, an intervening layer—the stratum intermedium—develops (Fig. 3-1). Cells forming the periderm are large, bulge from the epidermal surface, and are bathed in amniotic fluid. By 19 weeks, there are several layers of intermediate cells, and the periderm has begun to flatten (Figs. 3-1 and 3-2). Keratinization is well developed by 23 weeks within the stratum intermedium in association with small keratohyaline granules. At this juncture, most of the periderm cells have shed, and the keratinizing cells that remain beneath represent the newly formed stratum corneum (5).

By ultrastructure, the histogenesis of the epidermis involves early formation of immature desmosomes and early hemidesmosomes and distinct basement membrane (6 to 7

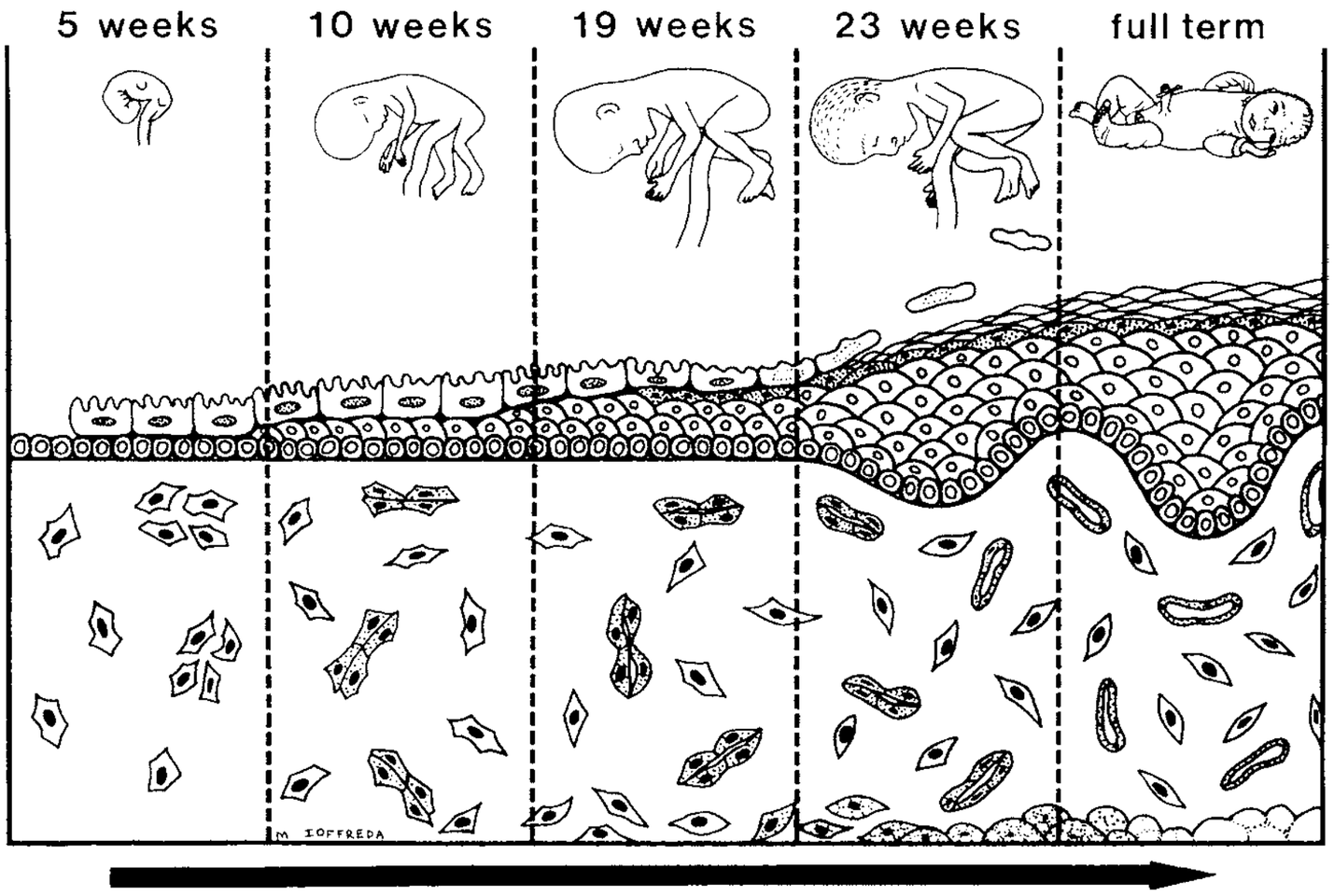


FIGURE 3-1. Schematic overview of embryonic development of human skin. (Courtesy of Dr. Michael Ioffreda).

weeks of gestational age) (6,7). Anchoring filaments are observed several weeks later, and the basement membrane appears structurally mature by the end of the first trimester. The surface cells of the periderm display numerous microvilli and cytoplasmic microvesicles, increasing the area in contact with amniotic fluid and suggesting active interchange between the periderm cells and the amniotic fluid (4). Tonofilaments are sparse until 16 weeks, when dense accumulations are observed in cells of the intermediate layer as evidence of beginning keratinization (5).

Normal Microanatomy

As they differentiate into horny cells, the keratinocytes are arranged in four layers from bottom to top (Figs. 3-6 to 3-12): the basal cell layer (stratum basalis), the squamous cell layer (stratum spinosum), the granular layer (stratum granulosum), and the horny layer (stratum corneum) (Figs. 3-3 and 3-6). An additional layer, the stratum lucidum, can be recognized in

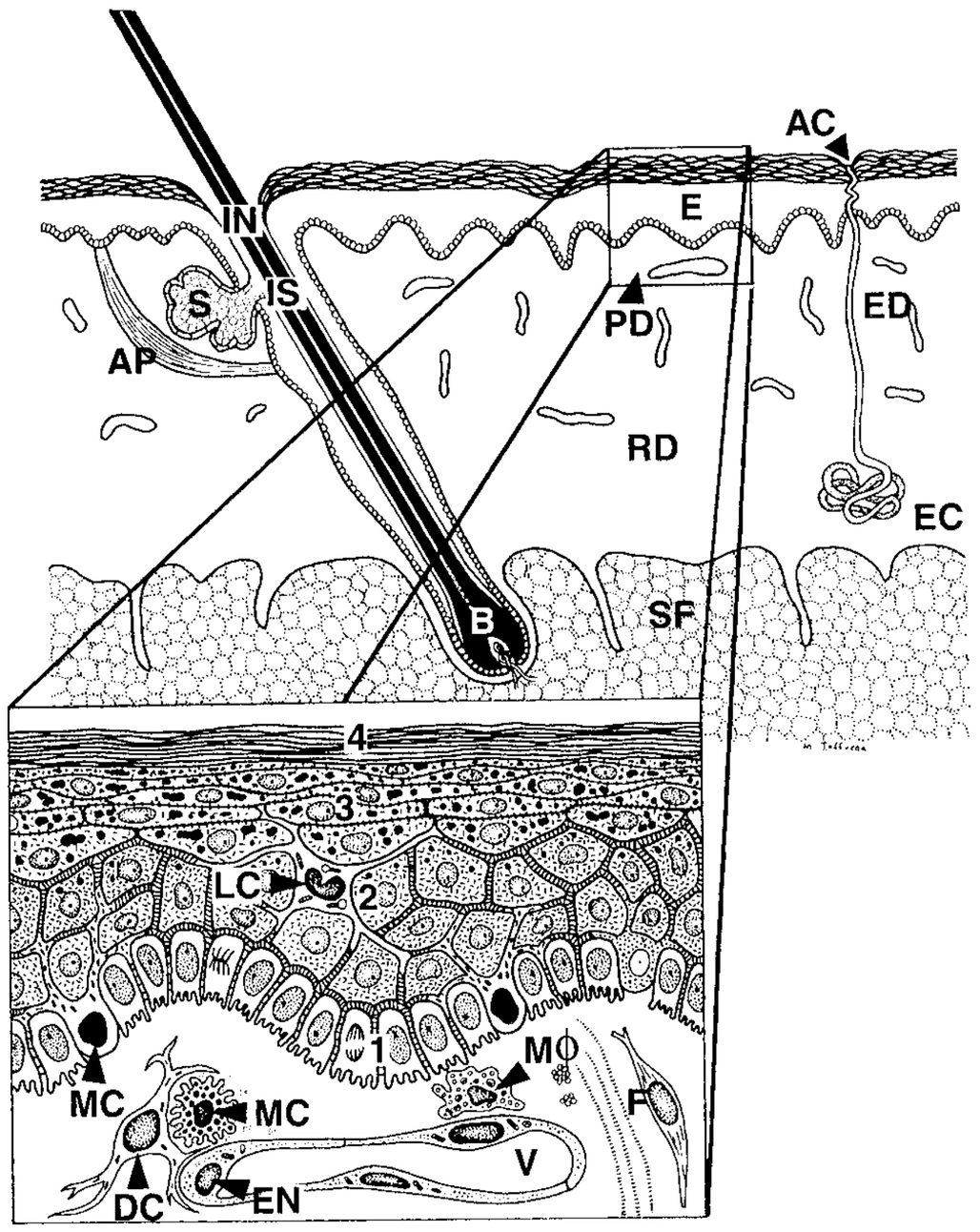


FIGURE 3-3. Schematic overview of the architecture and cytologic constituents of normal human skin. This projection demonstrates the cellular components of the epidermis and superficial dermis in greater detail, with epidermal strata denoted numerically. 1, stratum basalis; 2, stratum spinosum; 3, stratum granulosum; 4, stratum corneum. AC, eccrine acrosyringium; AP, arrector pili muscle; B, follicular bulb; DC, perivascular dendritic cell; E, epidermis; EC, coil of eccrine gland; ED, dermal eccrine duct; EN, endothelial cell; F, fibroblast; IN, follicular infundibulum; IS, follicular isthmus; LC, Langerhans cell; MC, mast cell; Mϕ, macrophage; PD, papillary dermis; RD, reticular dermis; S, sebaceous gland; SF, subcutaneous fat; V, vessel. (Courtesy of Dr. Michael Ioffreda.)

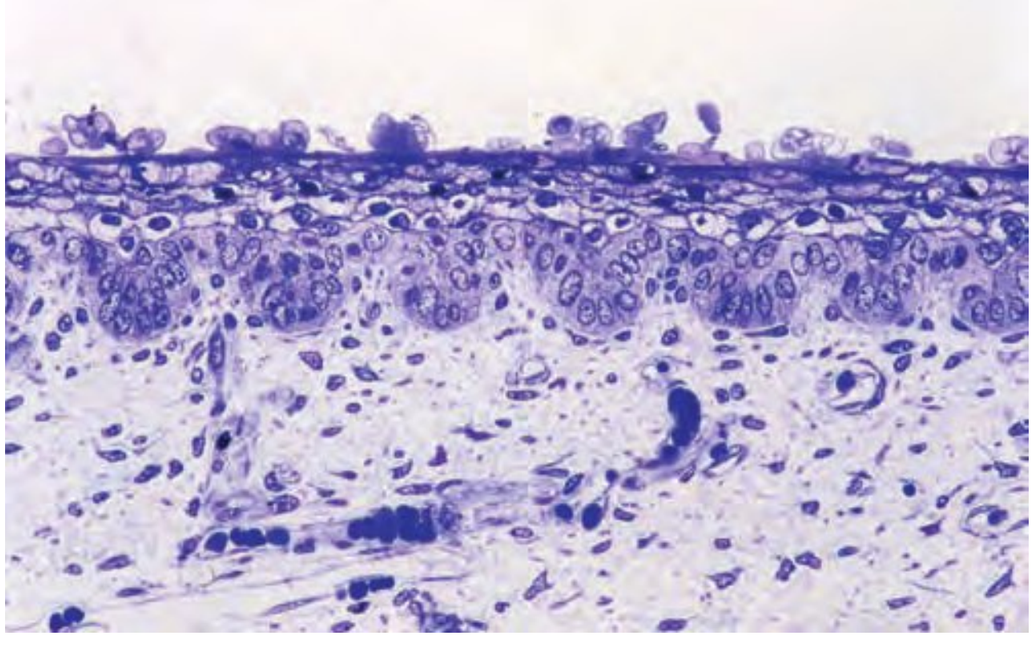


FIGURE 3-2. Histology of epidermis and dermis of 18-week normal human fetal skin (1-μm-thick, plastic-embedded section).

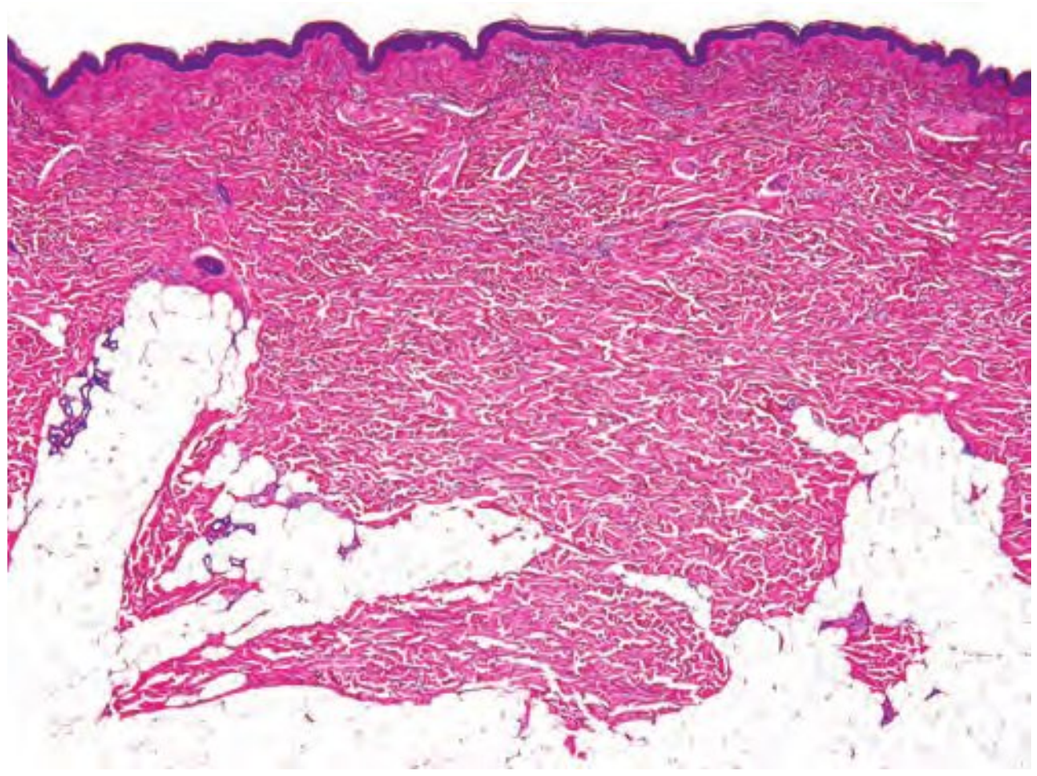


FIGURE 3-4. Histology of normal human skin. From top to bottom: epidermis, dermis, and upper part of the subcutaneous tissue. Note how the adipose tissue from the subcutis follows and surrounds adnexal structures within the dermis.

areas having a thick stratum granulosum and corneum forming the lowest portion of the horny layer, especially on the palms and soles (Fig. 3-7). The keratinocytes differ from the dendritic or clear cells (melanocytes and Langerhans cells) by their larger size, an ample amount of stainable cytoplasm, and the presence of intercellular bridges.

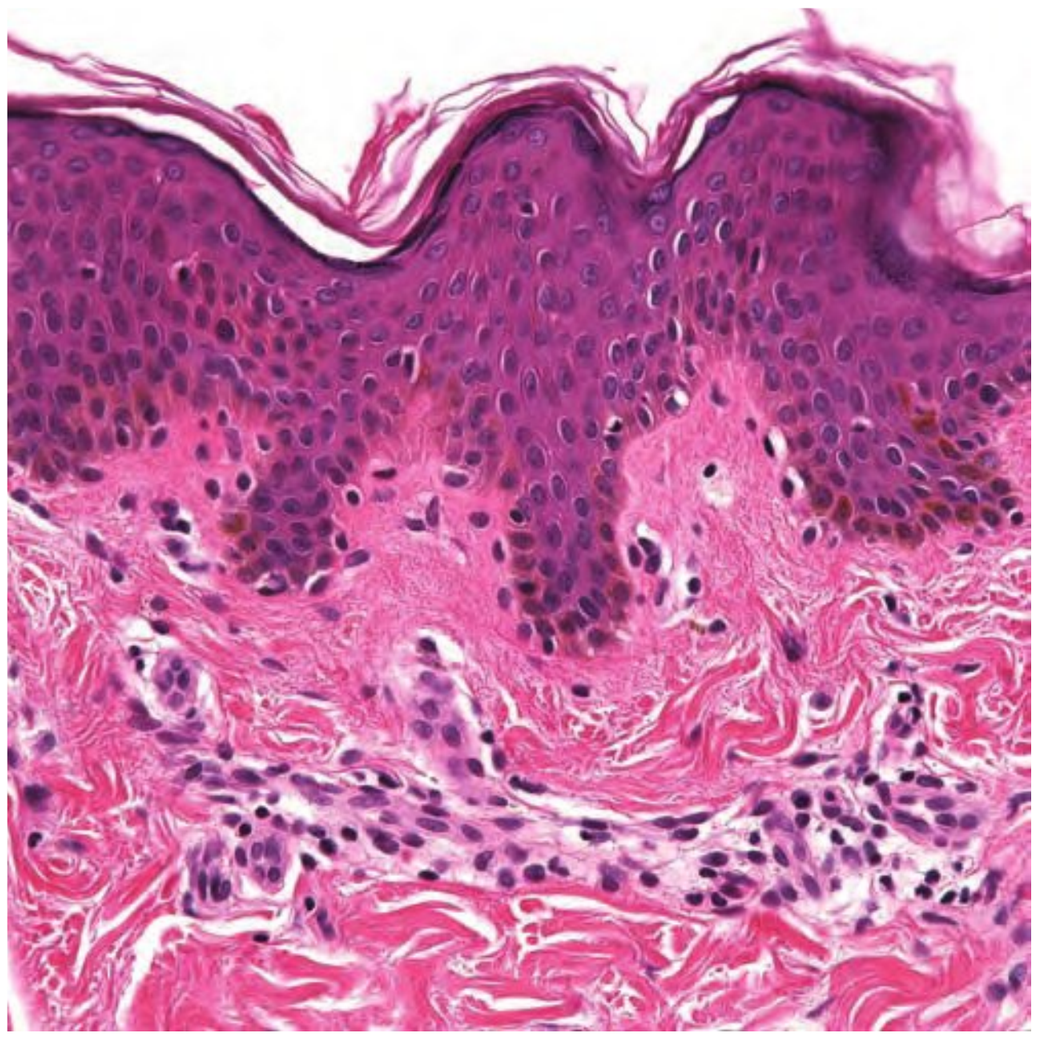


FIGURE 3-5. Histology of normal epidermis and superficial dermis. Note the separation of the delicate papillary dermal collagen from the underlying coarser reticular dermis by the horizontally aligned blood vessel representing a portion of the superficial vascular plexus.

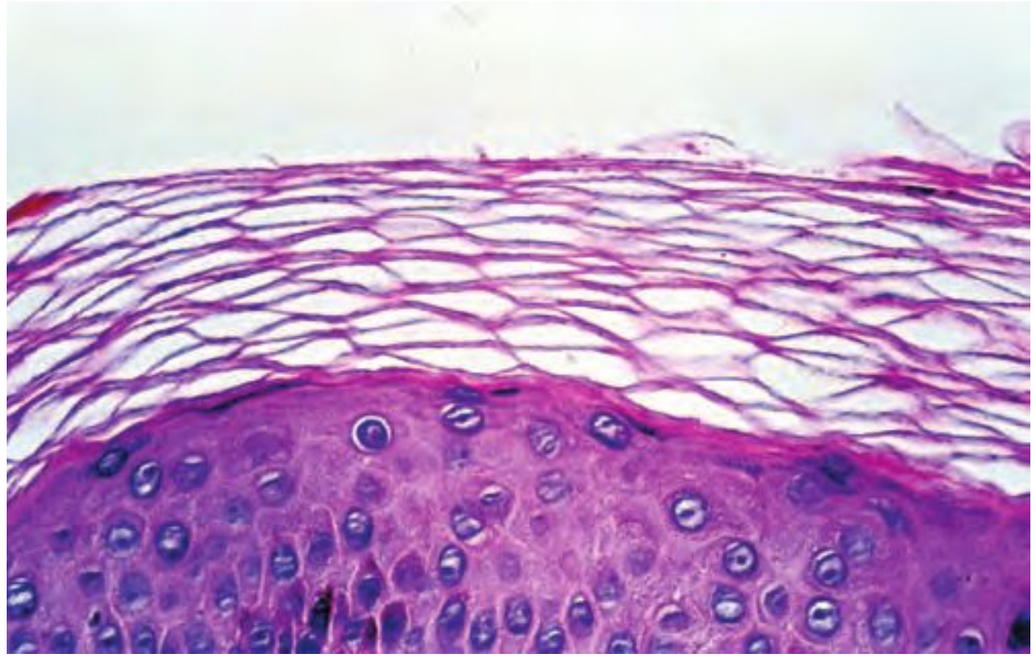


FIGURE 3-6. Histology of normally anucleate stratum corneum, the terminal differentiation product of underlying basal and suprabasal cells. Note the characteristic "basket-weave" architecture typical of nonacral sites.

Stratum Basalis

The basal cells form a single layer, are ovoid in contour, and lie with their long axes perpendicular to the underlying basement membrane. They have a more basophilic cytoplasm than cells of the stratum spinosum, often contain melanin pigment transferred from adjacent melanocytes, and contain dark-staining round to oval nuclei (Fig. 3-5). They are connected with each other and with the overlying squamous cells by intercellular

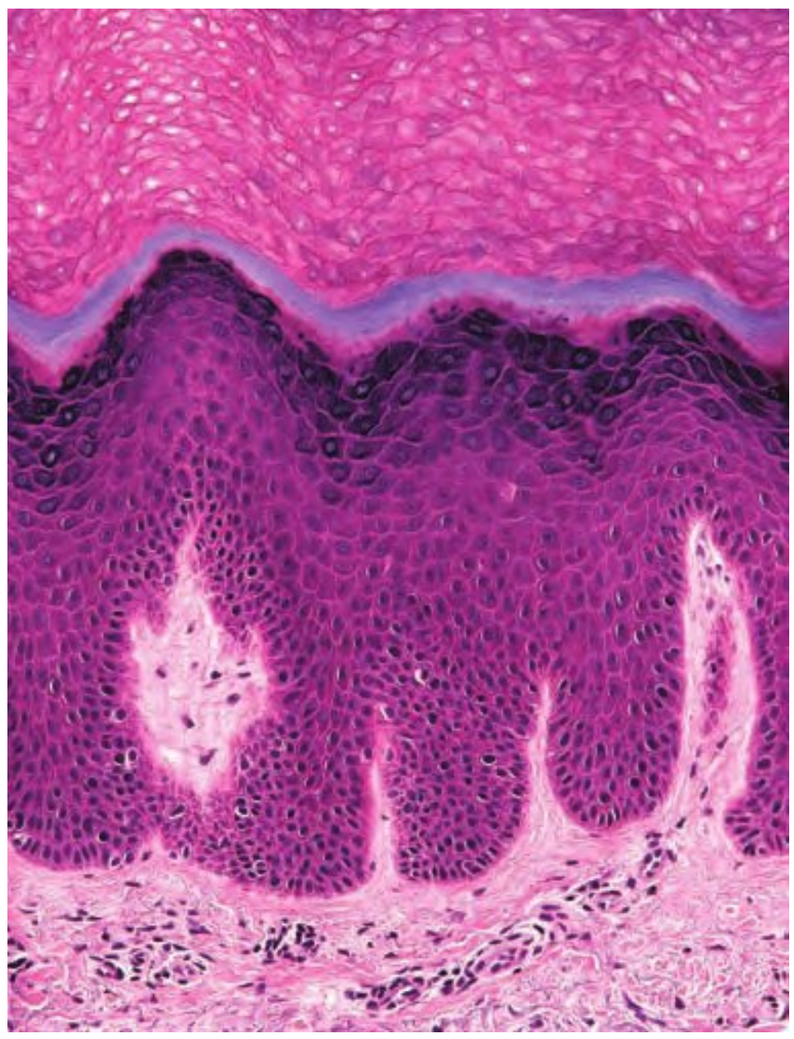


FIGURE 3-7. Histology of normal acral skin illustrating the thick and compact stratum corneum and the presence of a stratum lucidum (gray blue) in the lower portion of the horny layer.



FIGURE 3-8. Ultrastructure of stratum corneum showing transition of intracellular tonofilaments within viable cells to anucleate stratum corneum at the epidermal surface. The darker granules directly beneath the stratum corneum represent keratohyaline granules.

bridges united by desmosomes (discussed in detail later). At their base, the basal cells are attached to the subepidermal basement membrane zone by modified desmosomes, termed hemidesmosomes. Basal cells and overlying squamous cells contain keratin intermediate filaments termed tonofilaments, which form the developing cytoskeleton; these cells and related cytoskeletal proteins ultimately give rise to the anucleate stratum corneum at the epidermal surface (Figs. 3-6 and 3-8).

Most of the mitotic activity in normal human epidermis occurs in the basal cell layer (8). By tritiated-thymidine labeling of cells in the S phase of DNA synthesis, which is approximately seven times longer than the mitotic or M phase, many more tritiated-thymidine–labeled basal cells can be visualized than mitotically active basal cells. Ki-67 labeling is a useful way of determining cycling cells in paraffin sections, and, as with tritiated thymidine, the vast majority of labeled cells in normal skin are within the basal cell layer of the epidermis (Fig. 3-9). Slow-cycling basal cells reside at tips of epidermal rete ridges and have characteristics of stem cells (9). Recent studies have defined similar populations in the bulge region of the hair follicle (10).

Stratum Spinosum

The polyhedral cells of the stratum spinosum overlying the basal cell layer form a mosaic usually 5 to 10 layers thick. They

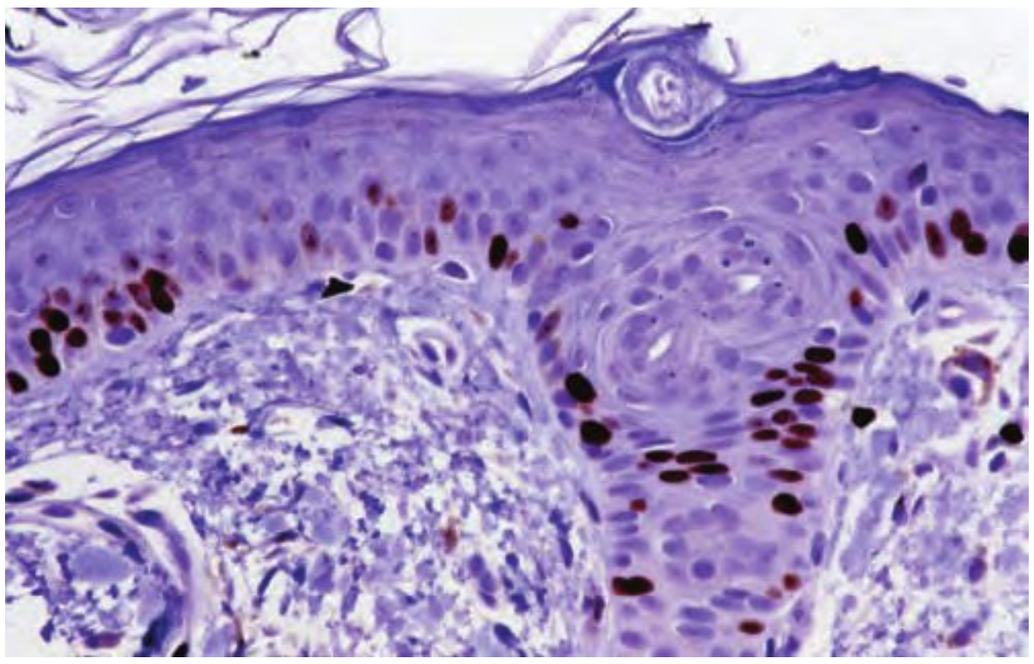


FIGURE 3-9. Evidence of basal cell layer replicative potential by Ki-67 immunostaining. Note the predominance of labeled cells in the basal cell layer of the epidermis and the included portion of a follicular infundibulum.

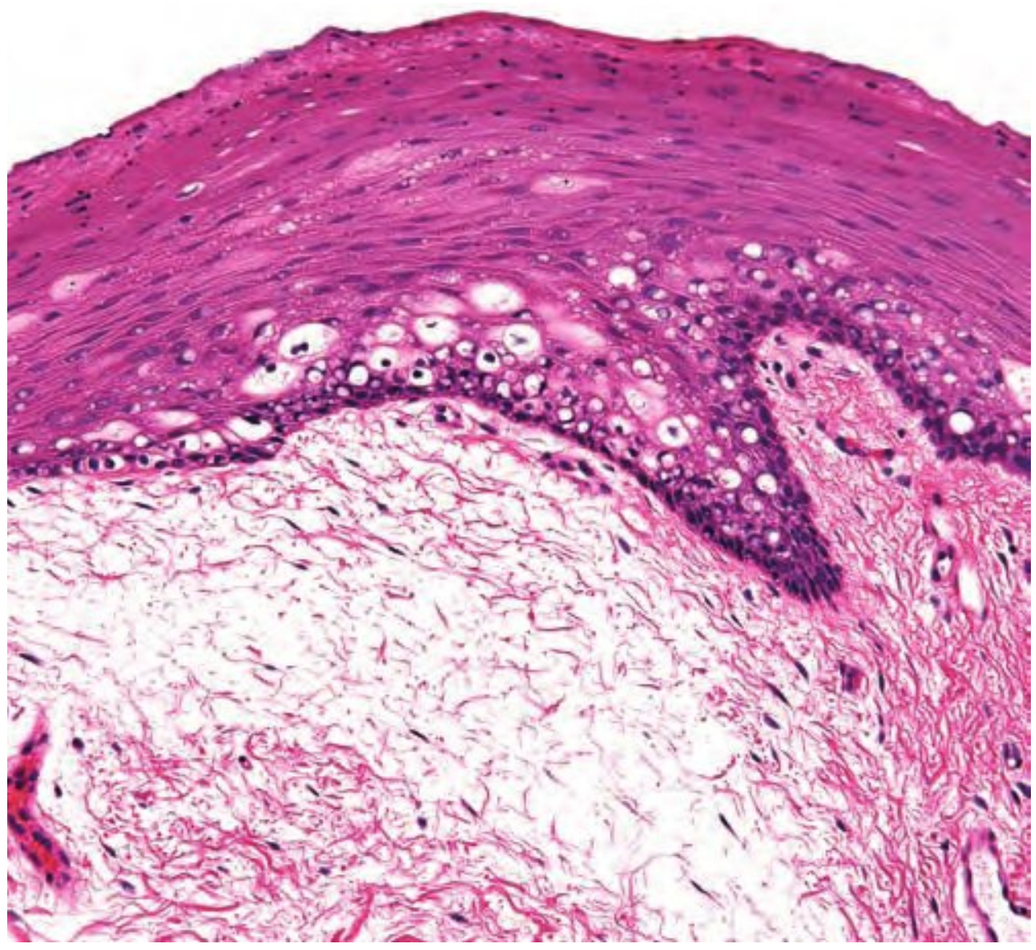


FIGURE 3-10. Mucosal epithelium of the oral cavity showing stratified squamous epithelium without a well-formed granular or cornified layer. Note the cytoplasmic pallor due to glycogenation and delicate underlying connective tissue.

become progressively flattened toward the skin surface (Fig. 3-6). The cells are separated by spaces that are traversed by intercellular bridges united by desmosomes. These intercellular spaces contain neutral mucopolysaccharides and acid mucopolysaccharides (glycosaminoglycans). Hyaluronic acid, an important component of the glycosaminoglycans, is quite abundant in the matrix between keratinocytes, occurring predominantly in the spinous layers but also in the basal layer and the stratum corneum (11). The intercellular cement substance between two adjacent keratinocytes, referred to also as glycocalyx, has a gel-like consistency. On one hand, it provides cohesion between the epidermal cells, and on the other hand, it allows the rapid passage of water-soluble substances through the intercellular spaces; furthermore, it allows the opening up of desmosomes and individual cell movement (12–14).

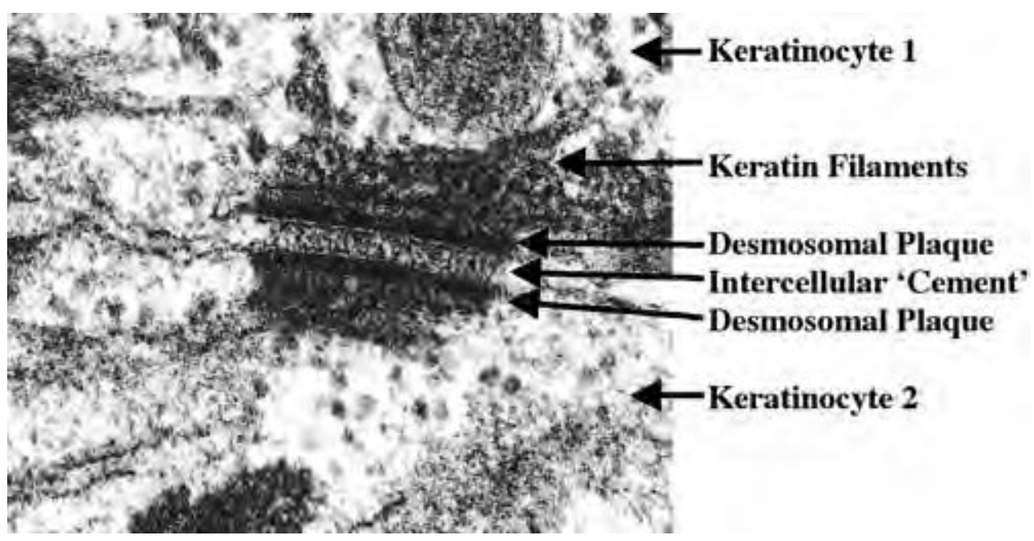


FIGURE 3-11. Ultrastructure of a desmosome. Note the two electron-dense plaques, each located within the cytoplasm of the two keratinocytes that are connected by the desmosome.

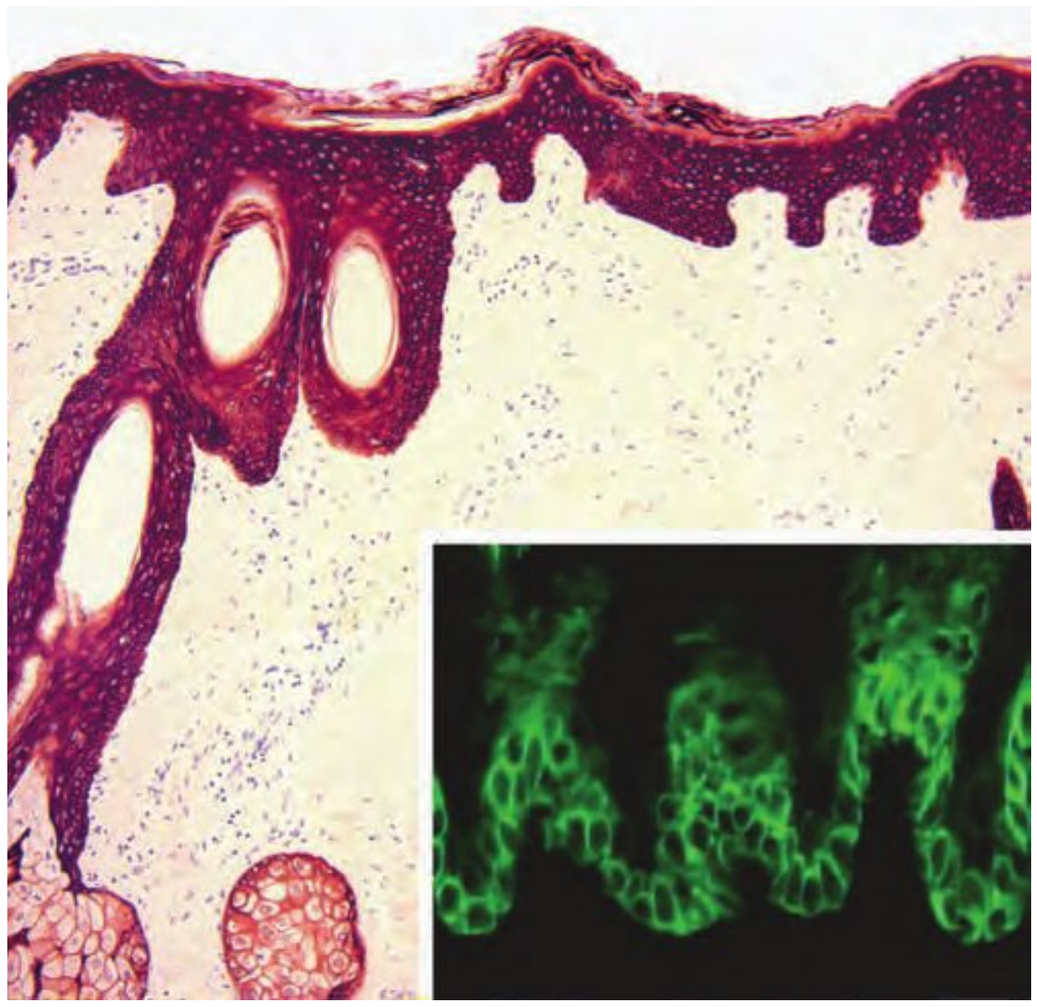


FIGURE 3-12. Immunohistochemistry for a pan-keratin (including low– and high–molecular-weight keratins) showing diffuse expression in the epidermis and adnexal structures. Inset: Preferential expression of keratin 14 by the basal and parabasal layers (immunofluorescence).

The tonofilaments within the cytoplasm of the keratinocytes of the stratum spinosum are loose bundles of electron-dense filaments, each filament measuring 7 to 8 nm in diameter. These structures correlate with keratin proteins, as may be demonstrated by immunohistochemistry (see later discussion on immunohistochemistry) (Fig. 3-12). The tonofilaments at one end are attached to the attachment plaque of a desmosome, and the other ends form the cytoskeleton within the cytoplasm. Electron microscopy shows that the intercellular junctions (desmosomes) consist of two dense plaques 10 to 15 nm thick on adjacent cell membranes. A 30-nm-wide multilayered zone is present between them (Fig. 3-11). The binding of adjacent keratinocytes via interaction of these ultrastructurally complex adjacent desmosomal plaques (12,13) has recently been understood at a molecular level (Fig. 3-11; see also Fig. 3-23). A key family of molecules is the cadherins, derived from multiple genes and representing Ca^{2+}-dependent cell adhesion molecules with a characteristic single-spanning-transmembrane structure (15). Desmosomal cadherins are desmogleins and desmocollins (16) that localize to desmosomes and are linked to intracytoplasmic intermediate filaments by plakoglobin and desmoplakin. Within the desmosome complex, desmogleins within the cell membrane bind to plakoglobin through their cytoplasmic domain. Intermediate keratin filaments anchor at the desmosomal plaque, possibly by way of the carboxy-terminal domain of plakoglobin. The structural importance of these molecules in uniting keratinocyte cytoskeletons within the epidermis is indicated by the disorders pemphigus vulgaris and pemphigus foliaceus, in which autoantibodies to desmoglein 3 and desmoglein 1, respectively, result in clinical blisters due to loss of cell–cell adherence (acantholysis) (see Chapter 9) (17,18). Desmoglein 3 is normally concentrated between immediately suprabasal keratinocytes, whereas desmoglein 1 is distributed preferentially among keratinocytes directly beneath the stratum corneum. Indeed, a remarkable correlation has been established between desmoglein expression in normal skin and pathologic lesions in which specific desmogleins are disrupted with regard to the plane of blister formation due to loss of cell–cell adhesion.

Stratum Granulosum

The cells of the granular cell layer are flattened, and their cytoplasm is filled with keratohyaline granules that are deeply basophilic and irregular in size and shape (Fig. 3-6). The thickness of the granular layer in normal skin is generally proportional to the thickness of the horny layer: It is only 1 to 3 cell layers thick in areas in which the horny layer is thin but measures up to 10 layers in areas with a thick, horny layer, such as the palms and soles (Figs. 3-5 and 3-7). In the process of keratinization, the keratohyaline granules form two structures: the interfibrillary matrix or filaggrin, which cements the keratin filaments together, and the inner lining of the horny cells, the so-called marginal band. Whereas the tonofibrils contain only small amounts of sulfur as sulfhydryl groups, the interfibrillary matrix and the marginal band contain about 10 times the amount of sulfur that is present in the tonofibrils, predominantly as disulfide bonds of cystine (19,20). Consequently, the tonofibrils are soft and flexible, whereas the matrix and marginal band provide necessary strength and stability (20). Thus, the keratin of the epidermis represents "soft" keratin, in contrast to the "hard" keratin of the hair and nails, in which keratohyaline granules are lacking and the tonofibrils themselves harden through the incorporation of disulfide bonds (21). "Soft" keratin desquamates as the result of enzymatic action, but the "hard" keratin of the hair and nails does not and thus requires periodic cutting.

The granular cell layer represents the mature keratin-forming transitional zone of the epidermis, in which the dissolution of the nucleus and other cell organelles is prepared. In contrast to the stratum basalis and stratum spinosum, in which lysosomal enzymes, such as acid phosphatase and aryl sulfatase, are present as only a few granular aggregates, there is diffuse staining for lysosomal enzymes in the granular cell layer. These diffusely staining lysosomal enzymes probably play an important role in the autolytic changes occurring in the granular layer (22).

Stratum Corneum

Unlike the nucleated cells of the other epidermal layers, the cell remnants of the normal stratum corneum are anucleate. Thus the normal horny layer stains eosinophilic. The thickness of the horny layer is often difficult to ascertain in formalin-fixed specimens because the outer cell layers may become

detached. The portion of the horny cytoplasm that contains disulfide bonds of cystine tends to shrink on formalin fixation to form a shell along the cell membrane, resulting in the characteristic basket-weave architecture in routine sections (Fig. 3-6) (23). In contrast, glutaraldehyde fixation used for electron microscopy causes precipitation of the formalin-soluble substances within the horny cells and allows staining of the contents of the horny cells with reagents such as uranyl acetate and lead citrate. With a fluorescent stain it can be shown that the cells of the horny layer are arranged in orderly vertical stacks (24).

Mucosal Epithelium

Skin shows considerable variation among different body sites, and appreciation of such normal differences is critical to accurate diagnostic assessment. Perhaps the most profound differences exist at mucosal and paramucosal sites. For example, with the exception of the dorsum of the tongue and the hard palate, the mucous membrane of the mouth possesses neither a granular nor a horny layer (Fig. 3-10). When these layers are absent, the epithelial cells may appear vacuolated, largely as a result of their glycogen content. Electron microscopic examination reveals that the number of tonofilaments diminishes in the upper layers, and they become dispersed. Large aggregates of glycogen are present in the cells. The epithelial cells of the oral mucosa show only few well-developed desmosomes. Instead, they show numerous microvilli at their borders. They are held together by an amorphous, moderately electron-dense intercellular cement substance, the dissolution of which causes the detachment of the uppermost cells (25).

Specialized Structure and Function

Superficial Cellular Cohesion

The number of tonofilaments in the epidermis increases in the upper portion of the squamous layer. The earliest formation of keratohyaline granules consists of the aggregation of electron-dense ribonucleoprotein particles largely along tonofilaments. The keratohyaline granules increase in size through peripheral aggregation of ribonucleoprotein particles, and they surround more and more tonofilaments (26). By extending along numerous tonofilaments, the keratohyaline granules assume an irregular, often star-shaped outline and may reach a size of 1 to 2 μm. After ultimately ensheathing all tonofilaments, they form in the horny cells the electron-dense interfilamentous protein matrix of mature epidermal keratin. Keratohyaline granules are biochemically complex. One component is a histidine-rich protein called filaggrin precursor (27). When granular cells are converted to cornified cells, filaggrin precursor is broken down into many units of filaggrin. Filaggrin then aggregates with keratin filaments and acts as a "glue" for keratin filaments.

Terminal Differentiation

The transformation of granular cells into horny cells usually is abrupt. By electron microscopy, the cytoplasm of the cells in the lower portion of the horny layer shows relatively electron-lucent tonofilaments, about 8 nm thick, embedded in an interfilamentous substance having the same high degree of electron density as the keratohyaline granules (Fig. 3-8) (28). In the upper portions of the horny layer, however, the cells lose their filamentous structure. Together with the sudden keratinization of the horny cells, an electron-dense, homogeneous marginal band forms in their peripheral cytoplasm in close approximation to the trilaminar plasma membrane. In the lowermost horny layer the trilaminar plasma membrane is preserved outside of the marginal band; in the midportion of the horny layer it becomes discontinuous and then desquamates, so that the marginal band serves as the real cell membrane (25). Immunohistochemistry reveals that involucrin, a structural component of mature squamous epithelium, is incorporated into the marginal band as part of the formation of the protein envelope that characterizes squamous cells immediately prior to terminal differentiation (29). Desmosomal contacts are at first still present in the horny layer but disappear before desquamation of the horny cells.

Barrier Function

Odland bodies, also called membrane-coating, lamellar granules, and keratinosomes are small organelles that are discharged from the granular cells into the intercellular space and have two important functions: They establish a barrier to water loss, and they mediate stratum corneum cell cohesion. Lamellar granules appear first in the perinuclear cytoplasm in the stratum spinosum. Higher up in the epidermis, they rapidly increase in number and size (30). Both within and outside the granular cells, lamellar granules are round or oval, measure approximately 300 to 500 nm in diameter, and possess a trilaminar membrane and a laminated interior. The lamellar granules fuse with the plasma membrane of a granular cell, secreting its contents into the intercellular spaces (31). The lamellar granules fuse and completely fill the intercellular spaces at the level of the granular layer. They contain neutral sugars linked to lipids and/or proteins; hydrolytic enzymes, possibly charged with degrading intercellular materials; and free sterols. The stratum granulosum interstices contain free sterols and sugars; the stratum corneum intercellular spaces stain as a pure neutral lipid mixture with abundant free sterols but no sugars (31). Sugars are cleaved at the granular-cornified layer interface by sugar-specific glycosidases. The lipids formed in these organelles act as hydrophobic material, which is important to the barrier function (32). A similar permeability barrier exists in the oral mucosa. Lamellar granules may also contribute to cohesion between the cells of the lower stratum corneum as a result of the lipids that they contain. The action of enzymes, such as steroid sulfatase, removes the lipids from the upper stratum corneum and brings about desquamation of the cells there (33).

Enzyme Activity

Primary lysosomes that are membrane bound and contain a variety of hydrolytic enzymes, such as acid phosphatase, aryl sulfatase, and β-galactosidase, are seen in small numbers within keratinocytes, largely but not exclusively in the basal cell layer and lower squamous cell layer (14). A great number of

lysosomal enzymes, primarily located free within the cytoplasm, are demonstrable in the granular layer and in the lowermost horny layer. Lysosomal enzymes are found also in the lamellar granules and are located within granular cells and after their discharge into the intercellular space (34). Secondary lysosomes, also called phagolysosomes, are present in the lower epidermis, especially in the basal cells, where they digest phagocytized melanosomes, usually as melanosome complexes (see later discussion). In cases of epidermal injury, such as sunburn or interface dermatitis, numerous phagosomes are observed that contain remnants of organelles from damaged cells (34).

Immune Functions of Keratinocytes

In recent years, the epidermal keratinocyte has been recognized as a potent source of immunogenic molecules. Keratinocytes are capable of producing interleukins (ILs) (IL-1α, IL-1β, IL-6, IL-8); colony-stimulating factors (CSFs) (IL-3, granulocyte-macrophage-CSF, granulocyte-CSF, macrophage-CSF); interferons (IFNs) (IFNα, IFNβ); tumor necrosis factors (TNFs); transforming growth factors (TGFs) (TGFα, TGFβ); and growth factors (platelet-derived growth factor, fibroblast growth factor, melanocyte-stimulating hormone) (35). Some of these substances are expressed constitutively, whereas others are synthesized only after signal transduction initiated by external or systemic cues (36). Accordingly, keratinocytes may play an active role in elaboration of molecular signals that facilitate lymphocyte homing and local activation, enabling certain dermal cells to mature and regulating synthesis of extracellular matrix molecules.

Immunohistochemistry

Immunohistochemical techniques have become an important part of the diagnostic arsenal of pathologists, and the expression of keratin by poorly differentiated tumor cells is considered an important marker of epithelial differentiation. Keratins consist of two families of intermediate filament proteins, with type I and type II members always occurring as pairs (37,38). In humans, keratin genes are clustered as families in two regions of the genome, the type I genes on chromosome 17q21.2 and those encoding type II keratins on chromosome 12q13.13. There are 54 functional keratin genes, 27 in each of these domains (38). Different epithelia express different keratins. In addition, different keratins are expressed by the different layers of the human epidermis, reflecting the variable degree of differentiation in keratinocytes. Keratin 5 (K5) and keratin 14 (K14) are predominantly expressed by basal cells (39) (Fig. 3-12). When these cells differentiate, they downregulate expression of mRNAs encoding these two keratins and induce expression of new sets of keratins specific for individual programs of epithelial differentiation (Fig. 3-12). Moreover, unlike other basal cells that express K14, basal cells in the general region where stem cells reside also express keratin 15, indicating that biosynthetic heterogeneity exists within the basal layer with regard to expression of cytoskeletal elements (40,41). Suprabasal keratinocytes predominantly express keratin 1 and keratin 10. Keratin 2 is expressed by terminally differentiated keratinocytes. Keratin 9 is expressed by suprabasal keratinocytes in palmar and plantar epidermis. The pattern and type of keratin expression is different in the epidermis and adnexal structures. It is important to be familiar with the expression of keratin by normal structures because specific mutations are associated with different conditions (e.g., epidermolysis bullosa simplex variants are associated with mutations in keratin 5 and 14 genes, whereas mutations for keratin 1 and 10 genes are associated with bullous ichthyosiform erythroderma; mutations in the keratin 2 gene result in bullous ichthyosis of Seimens, and mutations of keratin 9 genes are responsible for epidermolytic palmoplantar keratoderma).

A more novel epithelial immunohistochemical marker is p63, a member of the p53 gene family implicated in both the development and maintenance of stratified epithelial tissues, including the epidermis. Increasing data support p63 function in the regenerative capacity of basal keratinocytes by maintaining cell proliferation (42) as well as inducing epidermal commitment of embryonic stem cells (43,44). The critical contribution of p63 to embryonic development is underscored by the severe abnormalities seen at birth in mice null for p63, including lack of epidermis. Mutations in p63 have been linked to ectodermal dysplasia syndromes with a skin phenotype, indicating the relevance of p63 to normal epidermal development in humans (45). In normal human epidermis, in hair follicles, and in stratified epidermal cultures, p63 protein is principally restricted to cells with high proliferative potential and is absent from the cells that are undergoing terminal differentiation. Accordingly, p63 expression is seen in basal/suprabasal cells of the epidermis, outer root sheath, and hair matrix cells of the hair follicle, basal cells situated in the outermost layer of sebaceous glands, and outer layer cells of the ductal portion and myoepithelial cells of the secretory portion of the sweat glands (Fig. 3-13). p63 is overexpressed in the vast majority of squamous

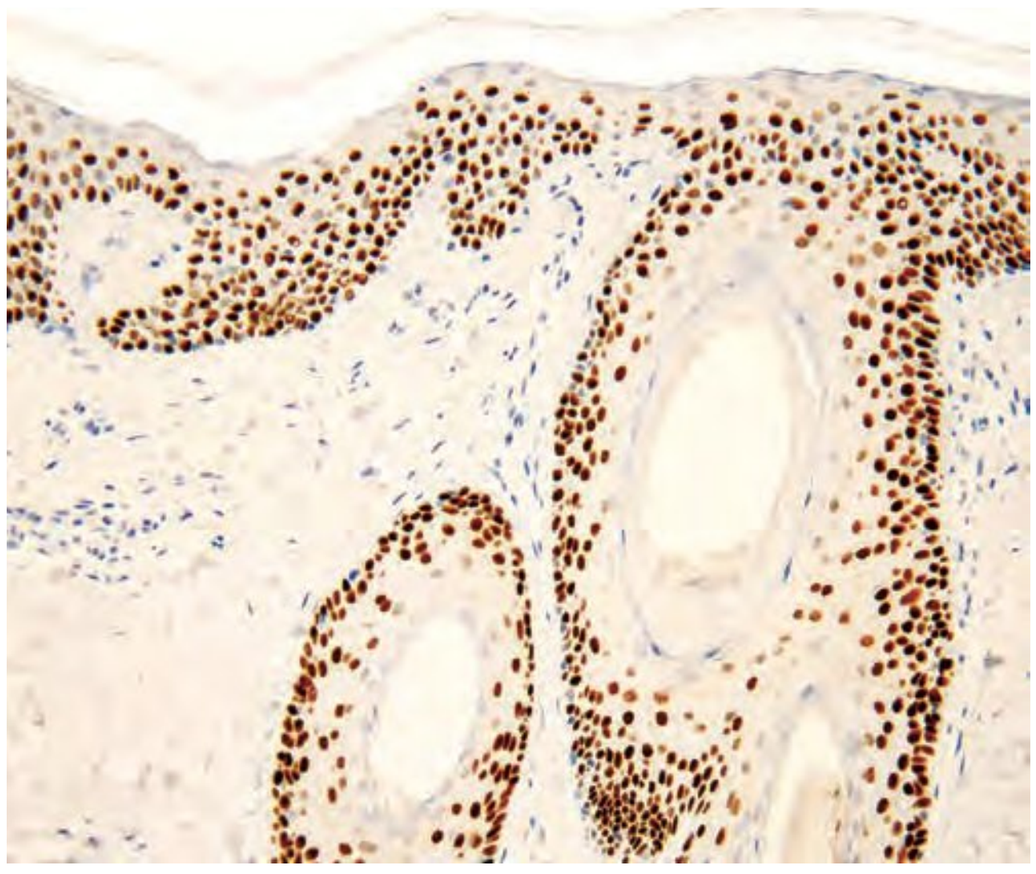


FIGURE 3-13. p63 immunostain shows intense nuclear positivity in all epithelial compartments, including the epidermis and adnexal structures. The staining is more intense in basal and parabasal areas.

cell carcinomas and basal cell carcinomas and appears to be an especially helpful marker for poorly differentiated squamous cell carcinomas, including the sarcomatoid variant (46).

Melanocytes

Embryology

The appearance of melanocytes in the epidermis takes place in a craniocaudal direction, in accordance with the development of the neural crest, from which the melanocytes are derived. By enzyme histochemistry, melanocytes can be identified in the epidermis of the head region during the latter part of the third fetal month; in the more caudal body regions, the earliest-formed melanin can be observed only in the latter part of the fourth month. Because melanocytes are functionally immature during their migration through the fetal dermis, they cannot be identified by histochemical methods until they have reached the epidermis (47). Electron microscopy and immunohistochemical approaches (e.g., stain for HMB-45 protein) allow for an earlier recognition of melanocytes in the epidermis than is possible by light microscopy (48,49).

The tyrosine kinase receptor KIT and its ligand stem cell factor play a critical role in melanocyte physiology, influencing migration, proliferation, differentiation, and survival (50–52). Piebaldism, a genetic disorder, results from KIT receptor defects secondary to mutations of the c-kit proto-oncogene. Patients with piebaldism present at birth with white patches of skin and hair that lack melanocytes, supporting the major role of KIT in melanocyte migration from the neural crest to the skin (53).

Microphthalmia transcription factor (MITF) is a nuclear protein involved in the embryonic development of melanocytes and the regulation of transcription of genes involved in melanin synthesis, such as tyrosinase. The microphthalmia (*mi*) gene is located on chromosome 3p. Since its discovery as a mutant allele producing mice devoid of viable melanocytes, *mi* has emerged as the gene whose mutation is responsible for the human pigmentation condition Waardenburg's syndrome IIa, as well as a variety of cellular defects involving retinal pigment epithelium, osteoclasts, and mast cells (54).

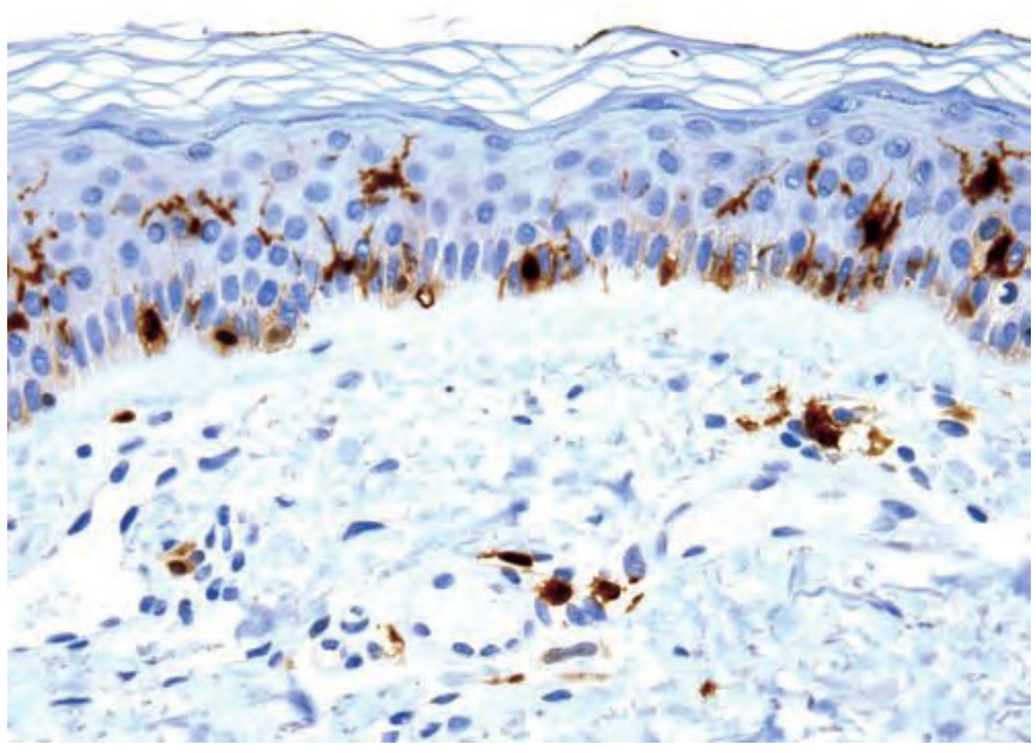


FIGURE 3-14. S100 immunostain is expressed by junctional melanocytes and also by Langerhans cells in the mid epidermis and dermis.

Normal Microanatomy

Mature melanocytes are melanin-synthesizing dendritic cells located within the basal layer of the epidermis, hair bulb, and outer root sheath of hair follicles (Figs. 3-14 to 3-17). In sections stained with hematoxylin-eosin, the dendrites of epidermal melanocytes are usually not seen, and the cells bodies are randomly dispersed within the basal cell layer. They contain round to oval, dark-stained nuclei that are generally smaller than those of basal keratinocytes and what may appear as a clear halo of surrounding cytoplasm, largely as the result of shrinkage during tissue processing. Although the number of

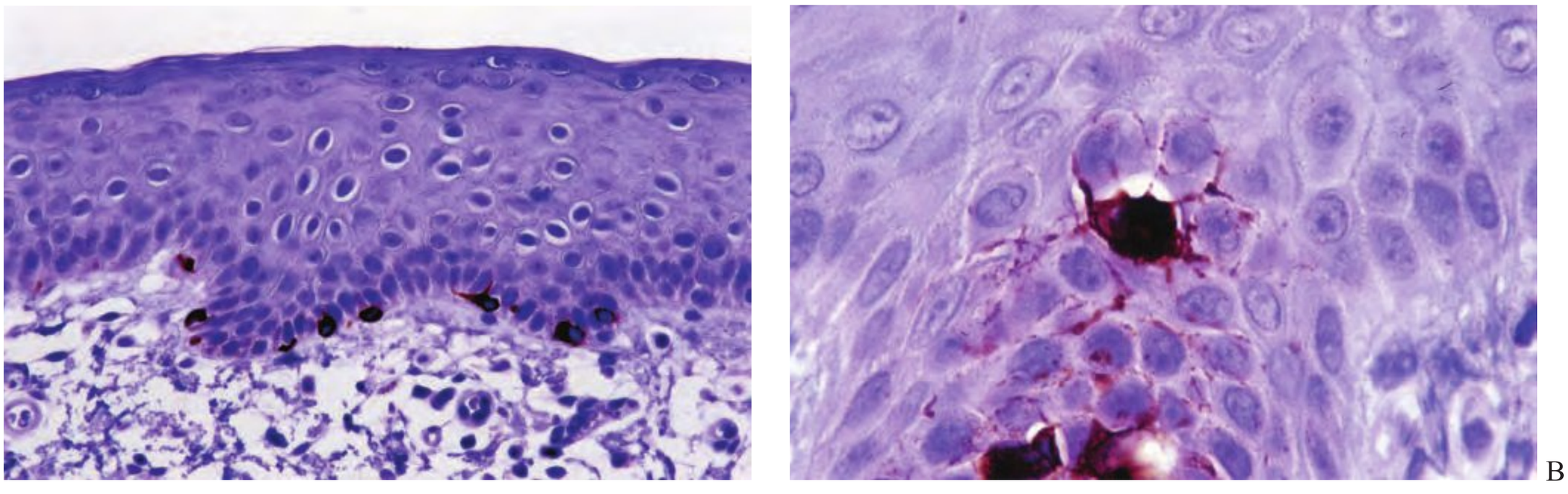


FIGURE 3-15. Melan-A/MART-1 immunostain demonstrates normal melanocytes within the epidermal basal layer. This is a more specific melanocytic marker compared to S100 (A). Note the dendritic extension at higher magnification (B). This melanocyte appears to be suprabasal as a result of the tangential plane of the section.

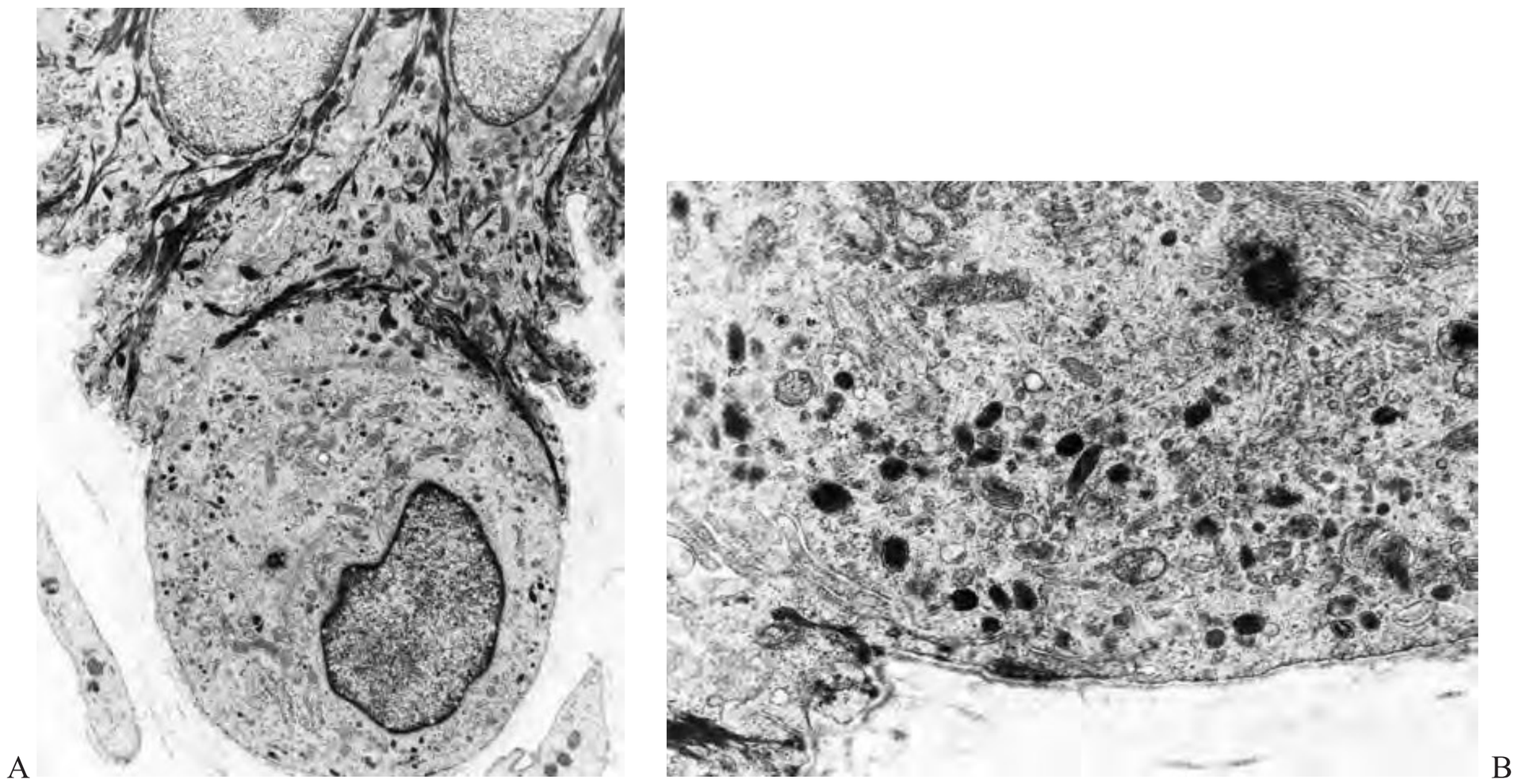


FIGURE 3-16. Ultrastructure of melanocytes. These cells characteristically "hang down" from the basal cell layer and are devoid of tonofilaments of desmosomes (A). They contain characteristic melanosomes in varying stages of melanization (B).

melanocytes in relation to basal cells varies with the body region and increases with repeated exposure to ultraviolet light, the average number of clear cells in hematoxylin-eosin–stained vertical sections is 1 of 10 cells in the basal layer, and a similar ratio was found with immunohistochemical studies (55,56). Melanin is transferred by means of the dendritic processes (Figs. 3-14 and 3-15A, B) from the melanocytes to the basal keratinocytes, where it is first stored and later degraded. As a rule, a greater amount of melanin is present in the basal keratinocytes than in the melanocytes, and often basal cells at the tips of rete ridges are preferentially more melanized. Because only about 10% of the cells in the basal layer are melanocytes, each melanocyte supplies several keratinocytes with melanin, forming with them an epidermal-melanin unit (57).

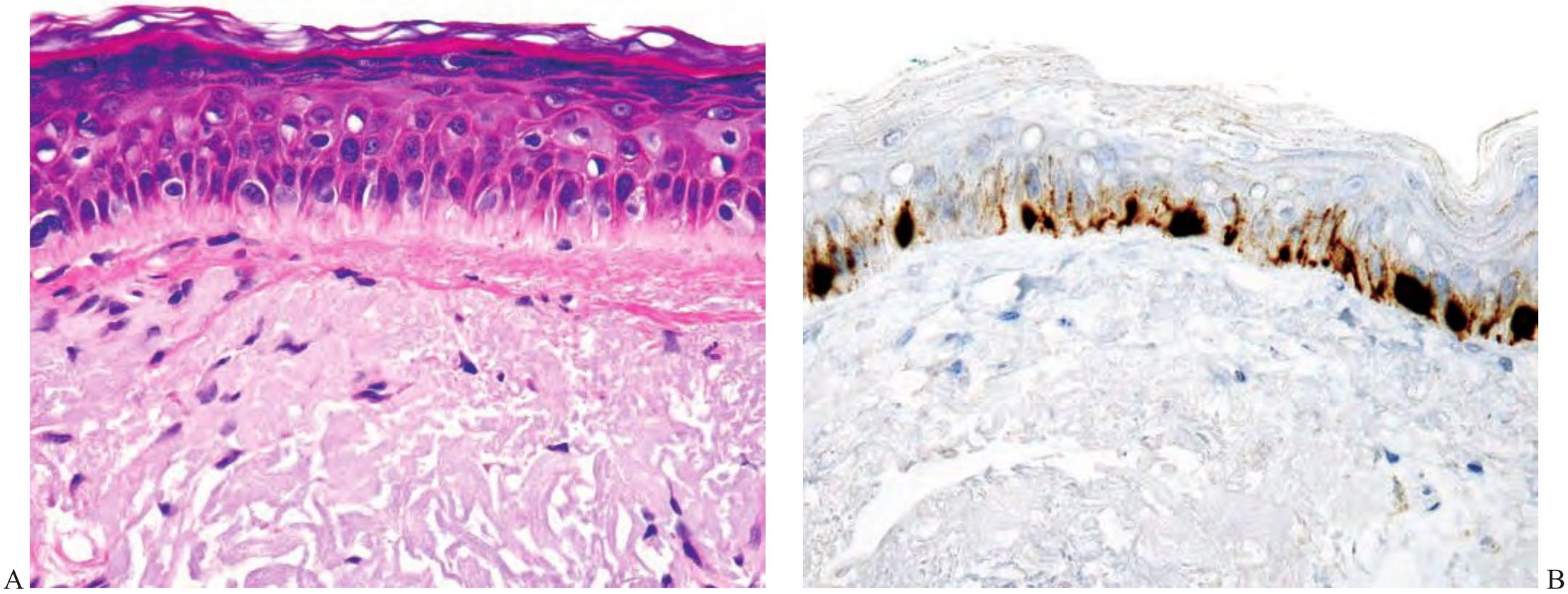


FIGURE 3-17. A: Melanocytes in sun-damaged skin may be increased in number and size as depicted in this microphotograph. Note the marked dermal solar elastosis. B: MART-1 immunostain highlights an increase in melanocyte density in sun-damaged skin.

In persons with a light skin color, staining with hematoxylin-eosin may reveal few or no melanin granules in the basal cell layer. In persons with a dark skin color, especially individuals of African heritage, melanin granules are present in the basal cell layer, as well as throughout the epidermis, including the horny layer, and in some instances in the upper dermis within macrophages, called melanophages. Accordingly, ethnic background and body site are critical in separating normal variations from true pathology.

Special Stains

Melanocytes may be difficult to appreciate on hematoxylin-eosin–stained sections, and there are several special stains that can facilitate their detection by light microscopy. Silver stains indicate the presence of melanin, which is both argyrophilic and argentaffin. Argyrophilia is based on the ability of melanin to be impregnated with silver nitrate solutions, which, on reduction with hydroquinone to silver, stain black. Because melanin is argentaffin, ammoniated silver nitrate may be reduced by phenolic groups in the melanin, forming black silver precipitate (e.g., the Fontana-Masson method). Neither of these methods is entirely specific for melanin, however. Melanin may be bleached by a strong oxidizing agent, such as hydrogen peroxide or potassium permanganate, a method that permits more specific identification (58) and is used in heavily melanized tumors, where pigment may obscure nuclear detail. The dihydroxyphenylalanine (dopa) reaction, which stains melanocytes dark brown to black, imitates physiologic melanin formation, which begins by tyrosinase-dependent hydroxylation of tyrosine to dopa and the oxidation of dopa to dopa-quinone, which is subsequently polymerized into melanin. Thus, the dopa reaction is in essence an assay for tyrosinase activity in melanosomes (58).

The use of immunohistochemical techniques for labeling melanocytes is becoming increasingly important, and several melanocytic markers that work in paraffin-embedded tissues are available (see Table 3-1). Immunohistochemical detection of melanocytes has been classically and most commonly accomplished by polyclonal antibodies to S100 protein. The antigen S100, a family of calcium-binding proteins (molecular weight 21,000), originally isolated from bovine brain extract (59), is present in the cytoplasm and nucleus of a variety of cells, including those of neural melanocytic lineage (60). The function of S100 within melanocytes is unclear, although different subtypes of S100 appear to have different functions in different cell types. The member of the S100 family predominantly expressed in normal melanocytes is S100B (61), whereas S100A subtypes have been reported in various skin lesions. In the skin, in addition to melanocytes, S100 labels Langerhans cells, specialized macrophages, Schwann cells, sweat glands, and adipocytes, and therefore, although it is a sensitive marker, it lacks specificity (Fig. 3-14; see also Figs 3-35F, 3-52C, 3-53A, and 3-54B).

The search for new targets for immunotherapy in patients with melanoma has generated several novel reagents valuable for diagnostic pathology. By using cytotoxic T-cell assays, various antigens that are recognized by autologous cytotoxic T lymphocytes were identified (62). A group of these antigens is referred to as melanocyte differentiation antigens because their expression is restricted to cells of melanocytic lineage. A number of reagents to melanocyte differentiation antigens suitable for analysis of paraffin-embedded material have become available, including the classically used monoclonal antibody HMB-45 and more novel reagents such as monoclonal antibodies to Melan-A/MART-1 (63,64) (Fig. 3-15), tyrosinase, and PNL2. HMB-45 antibody reacts with a cytoplasmic epitope, the premelanosome glycoprotein gp100 (75 to 100 kD), in cells of most but not all melanomas and in a minority of nevi (65,66). HMB-45 is negative in normal epidermal melanocytes in adults; however, it is expressed by melanocytes in fetal skin and stimulated adult melanocytes and is considered a highly specific antibody for the immunocytochemical substantiation of the diagnosis of malignant melanoma.

The advantage of the newer melanocyte differentiation antigens (e.g., Melan-A/MART-1) is a stronger sensitivity

TABLE 3-1 Immunohistochemical Expression of S100 and Most Common Melanocytic Differentiation Markers in Normal Skin

Antigen	Antibody	Positive cells	Antigen location
S100 protein	Anti-S100 protein	Melanocytes, Langerhans cells, macrophages, Schwann cells, adipocytes, myoepithelial cells of sweat glands	Nuclear and cytoplasmic
gp100	HMB-45	Fetal melanocytes, activated melanocytes	Cytoplasmic
Melan-A/MART-1	A103/M2-7C10	Melanocytes	Cytoplasmic
Tyrosinase	T311	Melanocytes	Cytoplasmic
PNL2 Antigen	PNL2 Antibody	Melanocytes, neutrophils	Cytoplasmic
MITF	D5	Melanocytes, macrophages, Schwann cells, smooth muscle cells	Nuclear

MITF, microphthalmia transcription factor.

when dealing with melanocytic neoplasms compared to HMB-45 and stronger specificity when compared with S100. The gene for Melan-A/MART-1 was independently cloned by two groups of scientists, which explains the two different designations (67). This melanocytic differentiation antigen is a small cytoplasmic protein (22 kD) with distinctive nucleotide sequences and genetic organization that is believed to be a melanosomal component. Tyrosinase is a key enzyme in melanin biosynthesis and represents a marker of melanocytic differentiation. T311, a murine monoclonal antibody to tyrosinase, is a reliable marker of melanocytes in paraffin-embedded sections (68). PNL2 is a relatively new monoclonal antibody directed against a fixative-resistant melanocyte antigen. The exact nature of the antigen recognized by PNL2 remains to be defined. The analysis of PNL2 immunostaining on a broad range of normal or malignant human tissues and on various melanocytic lesions revealed its high specificity (69). Despite the advent of these new markers, S100 and HMB-45 remain very important tools when dealing with tumors, and S100 remains the more sensitive (although not very specific marker) for neoplastic melanocytes, especially spindle cell lesions (e.g., desmoplastic melanoma).

Microphthalmia transcription factor, another novel melanocyte differentiation marker, was shown to be less sensitive and not restricted to melanocytes. D5 (monoclonal antibody to microphthalmia transcription factor) was generated from the consensus region shared by various isoforms of MITF. Only one isoform, MITF-M, is melanocyte specific. Other isoforms that are recognized by D5 can be found in various nonmelanocytic cell types (see Table 3-1) (70).

Ultrastructure

Melanocytes differ from keratinocytes by possessing no tonofilaments or desmosomes (Fig. 3-16A). At their base, where they lie in close apposition to the lamina densa, melanocytes show structures resembling, yet smaller than, hemidesmosomes of basal keratinocytes (71). Melanosomes are the most characteristic organelles of the melanocyte, and identification of various stages of their formation within a cell assists in its ultrastructural identification as a melanocyte (in contrast to keratinocytes that contain via transfer only fully melanized organelles) (Fig. 3-16B). Melanosomes are membrane-bound organelles that in their development from stage I to stage IV gradually move from the cytoplasm of the melanocyte into the dendritic processes. As melanosomes mature, their content of melanin increases, and their concentration of melanogenic enzyme decreases (72).

Stage I melanosomes are round, 0.3 μm in diameter, and contain no melanin (73). Stage II-IV melanosomes are ellipsoid and measure approximately 0.5 μm in length. They contain longitudinal filaments that are cross-linked with one another. Enzyme activity is present both on the enveloping membrane and on the filaments. Melanin deposition on the cross-linked filaments begins at stage II. Stage III melanosomes have only little tyrosinase activity but show continued melanin deposition, partially through nonenzymatic polymerization. Stage IV melanosomes are fully melanized and no longer possess tyrosinase activity. Melanin, which is homogeneous and electron dense, fills the entire organelle at this stage, obscuring its internal structure.

Regional and Racial Variation

The highest concentration of melanocytes is found on the face and the male genitals, about 2,000/mm^2, and the lowest on the trunk, about 800/mm^2 (74–76). No significant difference in the density of distribution of melanocytes for any given area of the skin exists between African-American and Caucasoid skin. In the former, the melanocytes are uniformly highly enzymatically reactive, whereas the melanocytes of Caucasoids, when not exposed to sunlight, are highly variable in dopa reactivity (77). In addition, African-American skin contains larger and more highly dendritic melanocytes than does Caucasoid skin (75,76). Finally, transferred melanosomes within keratinocytes of people of African descent tend to be individually distributed, whereas those in keratinocytes of Caucasians are packaged in membrane-enclosed aggregates (78–81).

Melanocytes in Sun-Exposed Areas

Regional variation of melanocyte number and morphology may also be influenced by environmental factors, such as sun exposure. After a single exposure to ultraviolet light *in vivo*, the skin of Caucasoids, when examined with the dopa reaction, shows no increase in the density of the melanocyte population but does show an increase in the size and functional activity of the existing melanocytes (82). Repeated exposure to ultraviolet light, however, causes an increase in the concentration of dopa-positive melanocytes, as well as an increase in their size and functional activity (77,83). Thus, examination of habitually exposed and of unexposed skin from adjacent anatomic sites, such as the lateral and medial aspects of the upper arm, has shown a twofold-higher concentration of melanocytes in the former, and the melanocyte concentration is even higher in areas such as head and neck (84).

Surgical pathologists and dermatopathologists often face the difficulty of having to distinguish melanocyte hyperplasia of sun-damaged skin from melanoma *in situ* (e.g., when evaluating surgical margins in melanoma excisions). It is known that melanocytes increase in number and size in sun-damaged skin (Fig. 3-17A,B). On immunohistochemical studies, long-standing sun-exposed skin has been reported to have an average of 15 to 20 melanocytes per high-power field (in 0.5 mm of skin) (84,85), some degree of contiguous growth (up to nine adjacent melanocytes), and melanocytes extending to hair follicles but not reaching the level of the uppermost portion of sebaceous glands. However, there should not be significant confluence, deep follicular penetration, nesting, or pagetoid spread.

Specialized Structure and Function

Melanogenesis

Enzymatic melanogenesis involves tyrosinase as the melanogenic enzyme (76,86). Tyrosinase is a copper-containing enzyme that

catalyzes the hydroxylation of tyrosine to dopa and the oxidation of dopa to dopa-quinone. However, before tyrosinase can act on tyrosine, two cupric atoms present in tyrosinase must be reduced to cuprous atoms. It is believed that, in addition to being a substrate, dopa activates this reduction, thereby acting as a cofactor in the reaction. The conversion of tyrosine to melanin by tyrosinase is characterized by a variable lag period. When tyrosinase is present in low concentrations, as in epidermal melanocytes of nonirradiated skin, this lag period is markedly prolonged, and no use of tyrosine by tyrosinase is detectable. In contrast, in skin exposed *in vivo* to ultraviolet light, as well as in epidermal sheets and in hair bulbs, tyrosinase activity is detectable with tyrosine as substrate (57,76,87). Because there is no lag period with dopa as substrate, tyrosinase in epidermal melanocytes can be readily demonstrated even in nonirradiated skin when skin sections are incubated in dopa rather than in tyrosine. The enzyme acting on dopa is therefore thought to be tyrosinase rather than dopa-oxidase.

The melanogenic enzyme tyrosinase is synthesized in the Golgi-associated endoplasmic reticulum, in which tyrosinase condenses in membrane-limited vesicles. This process has been observed by electron microscopy in epidermal melanocytes after *in vivo* ultraviolet irradiation with either dopa or tyrosine as substrate (88). Subsequently, these tyrosinase units are transferred to dilated tubules of the smooth endoplasmic reticulum. There, tyrosinase is incorporated into a structural protein matrix containing filaments that have a distinctive periodicity. This then represents a stage I melanosome (89). Few stage I and II melanosomes have acid phosphatase activity, but the proportion of acid phosphatase–positive melanosomes increases in stage III, reaching a maximum in stage IV (90). This enzyme may play a role in the degradation or transfer of melanosomes. Detailed analysis of nonmelanosomal regulatory factors in melanogenesis has revealed coated vesicles to be richest in tyrosinase and catalase, whereas premelanosomes have the highest concentrations of peroxidase (91). Among relevant metal ions, premelanosomes contain higher amounts of copper, zinc, and iron than do coated vesicles.

Melanin Transfer

The transfer of melanosomes from melanocytes to epidermal keratinocytes and to hair cortex cells is the result of active phagocytosis of the tips of melanocytic dendrites by keratinocytes and hair cortex cells as demonstrated in tissue cultures (92) and in epidermal reconstructs seeded with melanocytes (93). Once incorporated into keratinocytes, melanosomes aggregate to form protective parasoles above the keratinocyte nuclei. As previously noted, melanin in Caucasoids is concentrated in basal keratinocytes, whereas in people of African ancestry, distribution is more diffuse within the epidermis (94,95). Both melanin formation and melanin transfer are enhanced by various stimuli, notably by skin exposure to ultraviolet (UV) light. Recent data suggest a central role for p53 in UV-induced skin melanization and potentially certain forms of pathologic hyperpigmentation (96). UV-induced melanization, or sun tanning, requires the induction of α-melanocyte-stimulating hormone (α-MSH) secretion by epidermal keratinocytes. This phenomenon requires α-MSH generation as a cleavage product of pro-opiomelanocortin (POMC). p53 is believed to stimulate the POMC promoter in response to UV exposure, and mice genetically deficient in p53 fail to exhibit the normal tanning response. Accordingly, it is possible that p53 may function as, in addition to an inducer of apoptosis in UV-damaged cells, a sensor/effector of the tanning response, and even potentially as a trigger for certain pathologic forms of melanization.

Merkel Cells

Embryology

Although the origin of Merkel cells is unclear, it seems likely that they are differentiated from stem cells in the epidermis (97,98). The alternative hypothesis is that Merkel cells derive from the neural crest (97,99,100). The favored hypothesis, however, is that they arise between weeks 8 and 12 of gestational age from precursor stages of epithelial cells of early fetal epidermis that still express simple epithelial cytokeratins. *In situ* differentiation from epidermal ectoderm versus immigration of cells from the neural crest is supported by studies of fetal skin without Merkel cells transplanted to nude mice and subsequently found to contain mature Merkel cells within the engrafted tissue (101). Some Merkel cells detach from the epidermis and migrate temporarily into the upper dermis, where some of them associate with small nerves.

Normal Microanatomy

Merkel cells are present within the basal cell layer of the epidermis, oral mucosa, and the bulge region of hair follicles (102). They are quite scarce, irregularly distributed, and occasionally arranged in groups, often at tips of rete ridges (Fig. 3-18A), in eccrine glandular ridges of glabrous skin, in "Haarscheiben" of hairy skin, within beltlike clusters of hair follicles, and in certain mucosal tissues (103). It is assumed that the Merkel cell may represent a rudimentary touch receptor, more important in lower vertebrates (e.g., particularly in relationship to vibrissa hairs). The Merkel cell cannot be recognized in light microscopic sections; however, in silver-impregnated sections, the meniscoid neural terminal that covers the basal portion of each Merkel cell can be seen as a Merkel disk (104). A sensory nerve fiber may terminate at the disk. Immunohistochemistry for low–molecular-weight cytokeratins (CKs) such as CK8, 18, 19, and 20 more typical of simple epithelial cells than keratinocytes permits differential identification of Merkel cells in tissue sections (77). The most useful of these filamentous proteins is CK20, which has been shown to be a highly specific marker for Merkel cells because in human skin no other cell type expressing CK20 exists (103) (Fig. 3-18A).

By electron microscopic examination, Merkel cells usually are located directly above the basement membrane (105). They possess small, electron-dense, membrane-bound neurosecretory-type granules, strands of perinuclear intermediate

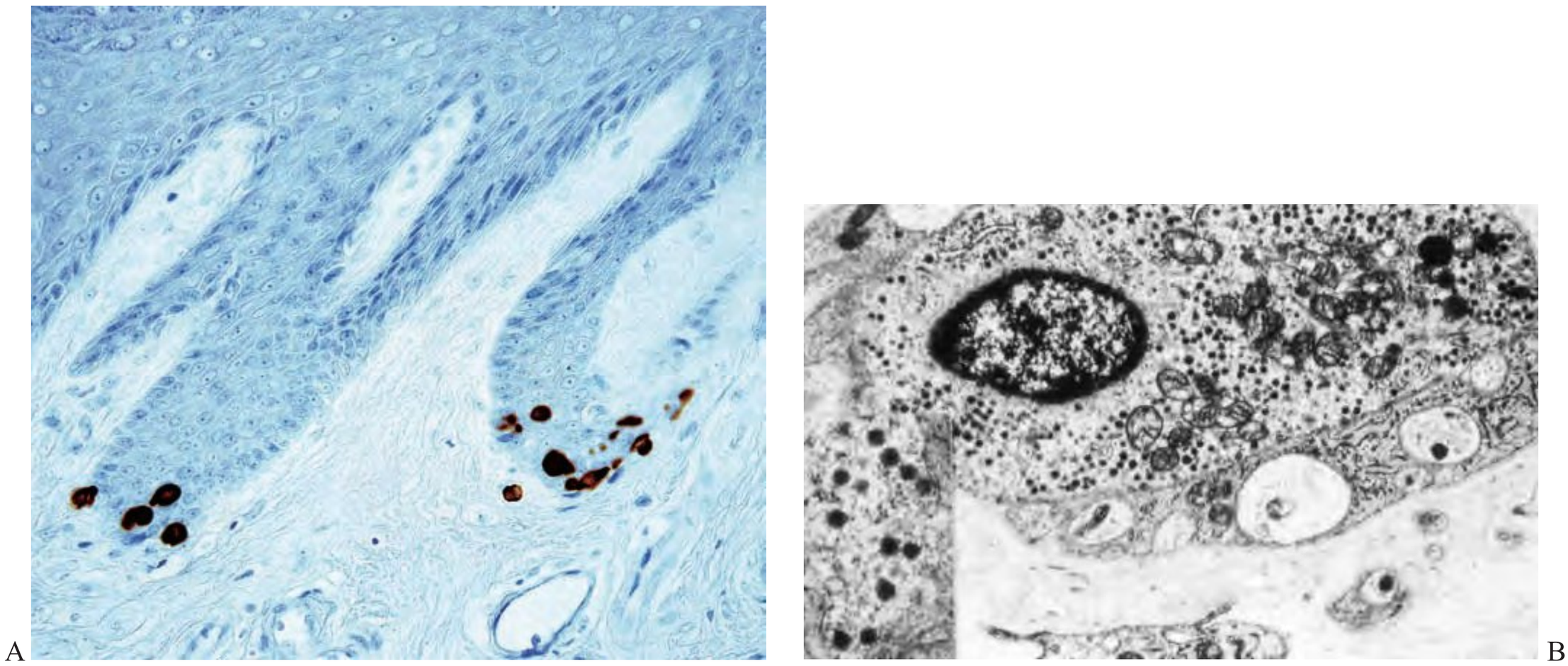


FIGURE 3-18. A: Immunohistochemistry with cytokeratin 20 highlights Merkel cells in the glabrous epithelium of the digit. They are often distributed, forming small groups at the tip of the rete ridges. B: By electron microscopy, Merkel cells contain characteristic neurosecretory granules.

filaments, and occasional desmosomes on their cell membranes connecting them with neighboring keratinocytes (Fig. 3-18B). The electron-dense granules vary in size between 80 and 200 nm and tend to be located at the side of cytoplasm in contact with axon terminals. Intermediate-type junctions are noted between axon terminals and Merkel cells.

Regional Variation

Merkel cells are most heavily concentrated in skin with high hair density and in glabrous epithelium of the digits, lips, regions of the oral cavity, and the outer root sheath of the hair follicle. These cells are present in mammals as so-called "touch-domes," also known as "Haarscheiben," a form of type I mechanoreceptor that surrounds tylotrich (large touch-sensitive) hairs and the rete ridge collars about external root sheaths of hair follicles.

An increase in Merkel cells is seen after chronic sun exposure and has also been described in the epidermal basal layer adjacent to prurigo nodularis, actinic keratoses, and tumors such as basal cell carcinomas (103).

Specialized Structure and Function

Merkel cells are specialized epithelial cells that react with the intermediate filament cytokeratin and desmosomal proteins (106,107). Of note, Merkel cells also express neuroendocrine markers such as chromogranin A, the matrix substance of the dense-core granules, as well as synaptophysin, supporting the view that they are epithelial neuroendocrine cells and that they may possess a neurosecretory function (103,108). Merkel cells also contain neuron-specific enolase and neurofilaments in their cytoplasm (109,110). The characteristic presence of specific cytokeratins (CK20) and neuroendocrine markers in Merkel cells is relevant to the diagnosis of Merkel cell carcinoma (primary neuroendocrine tumor of the skin), perhaps the only practical reason for the diagnostician to know about this mysterious cell type.

In addition to the expression of neuroendocrine markers, a variety of neurosecretory substances, in particular neuropeptides, that are stored within the dense-core granules have been demonstrated in Merkel cells. These neuropeptides include vasoactive intestinal polypeptide, calcitonin gene–related peptide (CGRP), serotonin, and substance P (103). Although some of these neurosecretory substances work as neurotransmitters, others have been demonstrated to promote growth and differentiation of various cutaneous cell types (103). However, any functional significance to their presence in human Merkel cells is unproven.

Langerhans Cells

Embryology

Langerhans cells are bone marrow–derived, dendritic, antigen-presenting cells that appear in the epidermis by 7 weeks of gestation, as documented by their positive staining for adenosine triphosphatase (ATPase) (Fig. 3-19). Although all Langerhans cells at this stage are ATPase positive, they are negative for their more characteristic and specific cell surface glycoprotein CD1a. At a gestational stage of 60 days, Langerhans cells begin to express CD1a reactivity. By 80 to 90 days, the number of CD1a-positive cells increases abruptly, and after 90 days, the expression of CD1a is approximately equivalent to the number of ATPase-positive Langerhans cells (111) (Fig. 3-20A,B).

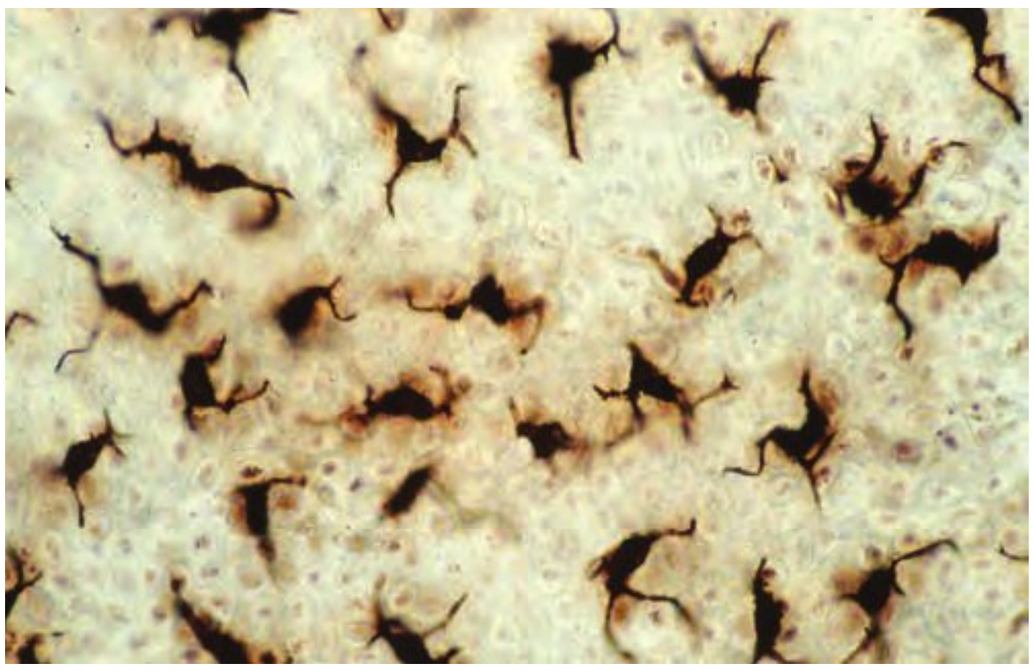


FIGURE 3-19. An epidermal sheet, removed and viewed en face, after adenosine triphosphatase enzyme histochemical staining. Note numerous, evenly distributed dendritic Langerhans cells.

S100 protein is not found in the Langerhans cells of fetal epidermis, but it can be demonstrated within 1 day after delivery (112). By electron microscopy, Langerhans cells can be identified by 10 to 11 weeks of gestation on the basis of the presence of Langerhans granules (Fig. 3-20 C).

Normal Microanatomy

Langerhans cells may be presumptively observed in histologic sections stained with hematoxylin-eosin as clear cells in the suprabasal epidermis. However, they cannot be reliably distinguished from occasional intraepidermal T lymphocytes and macrophages, and their dendritic cytoplasmic processes cannot be resolved. Because Langerhans cell detection is difficult in conventional sections, special stains are generally required for their detection and enumeration. Several enzyme histochemical stains have historically been used to identify Langerhans cells and to differentiate them from melanocytes. These

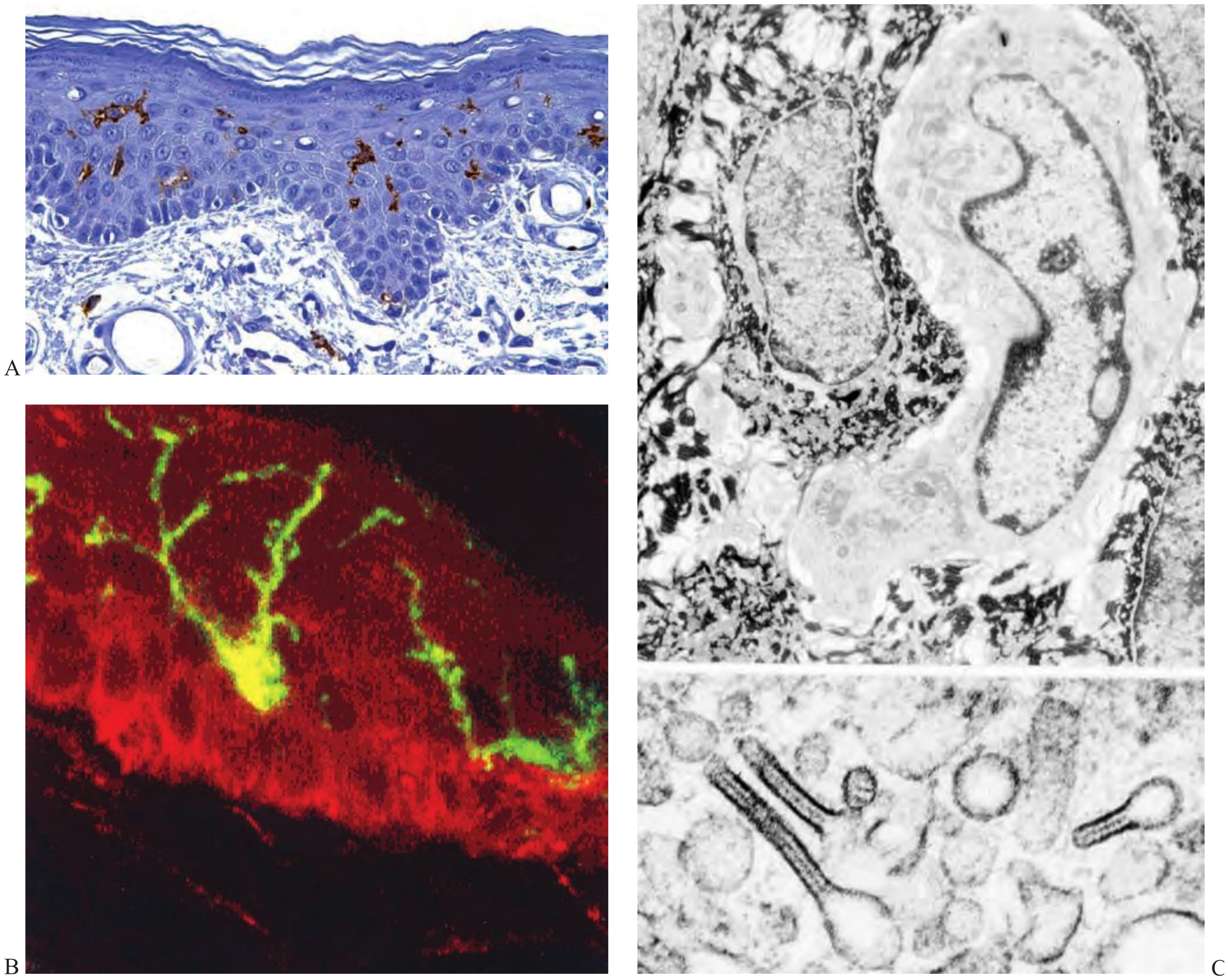


FIGURE 3-20. A: Anatomy of a human Langerhans cell. B: Typical dendritic morphology seen with immunohistochemical stain for CD1a and immunofluorescence detection of CD1a glycoprotein by confocal scanning laser microscopy. C: Transmission electron micrograph of Langerhans cell (top) and characteristic cytoplasmic granules (Birbeck granules) (bottom).

include ATPase (Fig. 3-19) and aminopeptidase (113). Langerhans cells are also positive for HLA-DR antigen and S100 protein, although the former also reacts with cells forming the acrosyringium (114), and the latter is found in melanocytes (Fig. 3-14). Langerhans cells can be demonstrated more specifically with monoclonal antibody to the prothymocyte differentiation cell surface glycoprotein CD1a when the antibody is labeled with either peroxidase or fluorescein (115–117) (Fig. 3-20A, B).

By electron microscopic examination, Langerhans cells show a markedly folded nucleus and no tonofilaments or desmosomes. Melanosomes are only rarely found in them, and, if they are, they always are located within lysosomes, indicating that they have been phagocytized (118). Of great interest is the regular presence of an organelle called the Langerhans or Birbeck granule in the cytoplasm of Langerhans cells (Fig. 3-20 C). The size of these granules varies considerably, from 100 nm to 1 μm (119). The granule has the three-dimensional shape of a disk and often shows a vesicle at one end and occasionally at both ends. A cross section of the disk portion has the appearance of a rod, and, if a vesicle is attached to the rod at one end, the Langerhans granule has the highly characteristic appearance of a tennis racquet. The rod-shaped cross section has a central lamella showing cross striation with a periodicity of 6 nm (119). Langerhans cell granules form as a consequence of endocytotic, clathrin-associated invaginations of the cell membrane of Langerhans cells. This was first recognized on the basis of the presence of intradermally injected peroxidase within the granules of Langerhans cells, even though the peroxidase molecule cannot cross the cell membrane (120). In addition, on incubating Langerhans cells with a gold-labeled antibody directed against the CD1a glycoprotein of the cell membrane of the Langerhans cell it was found that the labeled CD1a was internalized and appeared within Langerhans granules (121). The histiocytes present in the cutaneous and visceral lesions of histiocytosis X contain Langerhans granules. These granules are indistinguishable in their electron microscopic appearance from those seen in epidermal Langerhans cells (122,123). Cells that have the ultrastructural features of Langerhans cells but lack the Langerhans granule have been called indeterminate cells. They react specifically with the monoclonal antibody to CD1a (124,125).

Regional Variation

Langerhans cells are present in the epidermis in a concentration similar to that of melanocytes, between 460/mm^2 and 1,000/mm^2. In contrast to melanocytes, their number does not increase but instead may decrease with repeated exposure to ultraviolet light (113). CD1a-positive Langerhans cells have been found to be less plentiful in trunk skin than extremity skin (126). However, there appears to be considerable site variation among individuals, and the best comparison for determination of site-matched normal Langerhans cell numbers may be uninvolved skin directly adjacent to the lesion under study (126). Langerhans cells are present not only in the skin but also in the oral mucosa, the vagina, lymph nodes, and the thymus; occasionally, they are seen in the dermis (127). Their numbers may vary significantly in pathologic processes, in part as a result of local accumulation or their tendency actually to migrate on stimulation (128).

Specialized Structure and Function

Langerhans cells originate in the bone marrow and are functionally and immunologically related to the monocyte-macrophage-histiocyte series (129). Langerhans cells constitute 2% to 4% of the total epidermal cell population, and they tend to be evenly distributed such that their dendrites extend toward the epidermal surface in a uniform manner (130). A few Langerhans cells are present in the dermis of normal skin. Langerhans cells express immune response–associated antigens class II (HLA-DR in humans, Ia in mice) (131,132), leukocyte common antigen (133) Fc and C3 receptors, CD1a antigen (116–118), CD1c (M241) antigen (134), a membrane-bound ATPase (130), S100 protein, and actin-like and vimentin filaments. These markers are compatible with an active role in cutaneous immunity.

Langerhans cells have antigen-processing and antigen-presenting capacity. The recognition of a soluble protein and haptenized antigens by T lymphocytes requires the initial uptake and processing by an HLA-DR–positive cell like the Langerhans cell, which then presents immunologically relevant signals to the T lymphocytes. This often involves active migration of the antigen-bearing Langerhans cell from the epidermis into the dermis, where transit to draining lymph nodes occurs via lymphatic channels. In the lymph node, naive T cells are plentiful for receipt of the antigenic signals communicated by the Langerhans cells in a class II (HLA-DR)–dependent manner. Such T-cell sensitization results in the formation of memory T cells with the ability to recall and respond to the specific antigenic peptide on reexposure or challenge. This mechanism is believed to provide an important component to normal cutaneous immunosurveillance, as well as the underpinning of the contact hypersensitivity reaction.

Ultraviolet radiation interferes with the antigen-presenting capacity of Langerhans cells. After UV irradiation fewer Langerhans cells could be demonstrated in the skin (135). It is likely that this initial decrease of Langerhans cells is due to a temporary loss of membrane markers rather than to a destruction of the cells. Chronic repeated exposure to UV light may result in actual depletion of cells, contributing to potential for carcinogenesis as a result of impaired immunosurveillance. Similar depletion of Langerhans cells may result from application of potent topical corticosteroids (136) and in the setting of acquired immunodeficiency syndrome (137). With respect to the latter, viral particles have been identified in Langerhans cells (138), which, it is interesting to note, express one of the HIV receptors, CD4 (139). Replenishment of Langerhans cells after depletion has been accomplished by application of topical retinoids (140).

Basement Membrane Zone

Normal Microanatomy, Ultrastructure, and Molecular Structure

The basement membrane is an inconspicuous structure of enormous junctional significance, bonding together the protective epidermal layer and adnexal structures with the adjacent dermis.

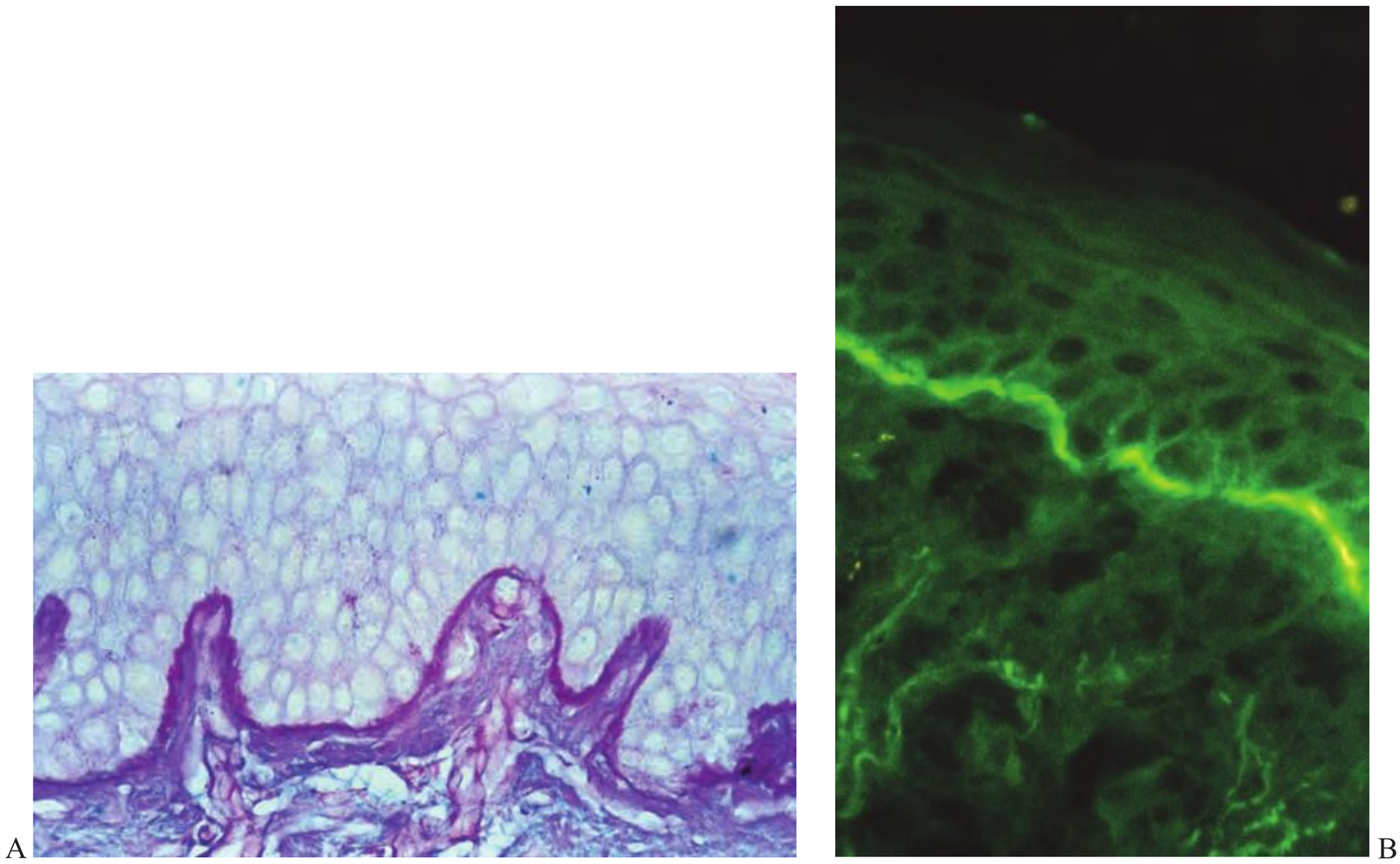
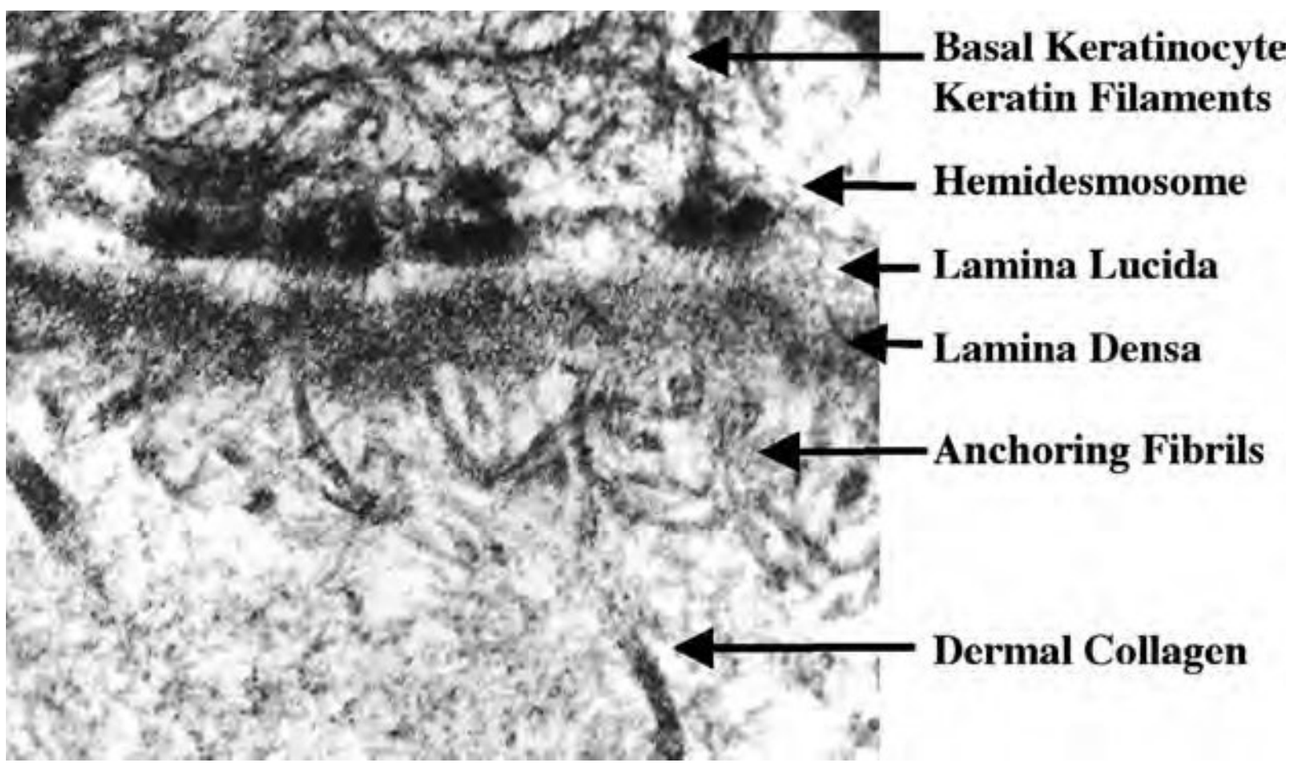


FIGURE 3-21. A: Demonstration of normal basement membrane zone separating epidermal and dermal layers by periodic acid Schiff stain. B: By direct immunofluorescence staining for the basement membrane–associated structural protein bullous pemphigoid antigen, a linear band is observed along the dermal–epidermal junction.

A subepidermal basement membrane zone not visible in sections stained with hematoxylin-eosin is seen on staining with the periodic acid Schiff (PAS) stain or by immunofluorescence as a 0.5- to 1.0-μm-thick homogeneous band (141) (Fig. 3-21). Its positive PAS reaction indicates a relatively large number of neutral mucopolysaccharides in this zone. Furthermore, impregnation with silver nitrate reveals a meshwork of reticulum fibers in the uppermost dermis. Staining with alcian blue, which identifies the band of polysaccharides and the reticulum meshwork, reveals that the band of polysaccharides is located above the reticulum layer (142). The light microscopic PAS-positive subepidermal basement membrane zone appears heterogeneous on electron microscopy (Fig. 3-22). The plasma membrane at the undersurface of basal cells shows hemidesmosomes ("half-desmosomes") possessing only one intracytoplasmic attachment plaque, to which tonofilaments from the interior of the basal cell are attached (Fig. 3-22). The cytoskeletal intermediate filaments within basal keratinocytes that insert into hemidesmosomes are composed predominantly of keratins 14 and 5 (143,144) (Fig. 3-23).

FIGURE 3-22. Transmission electron microscopy of the basement membrane separating the epidermis and dermis. Hemidesmosomes, lamina lucida, lamina densa, and anchoring fibrils can all be seen in this image.



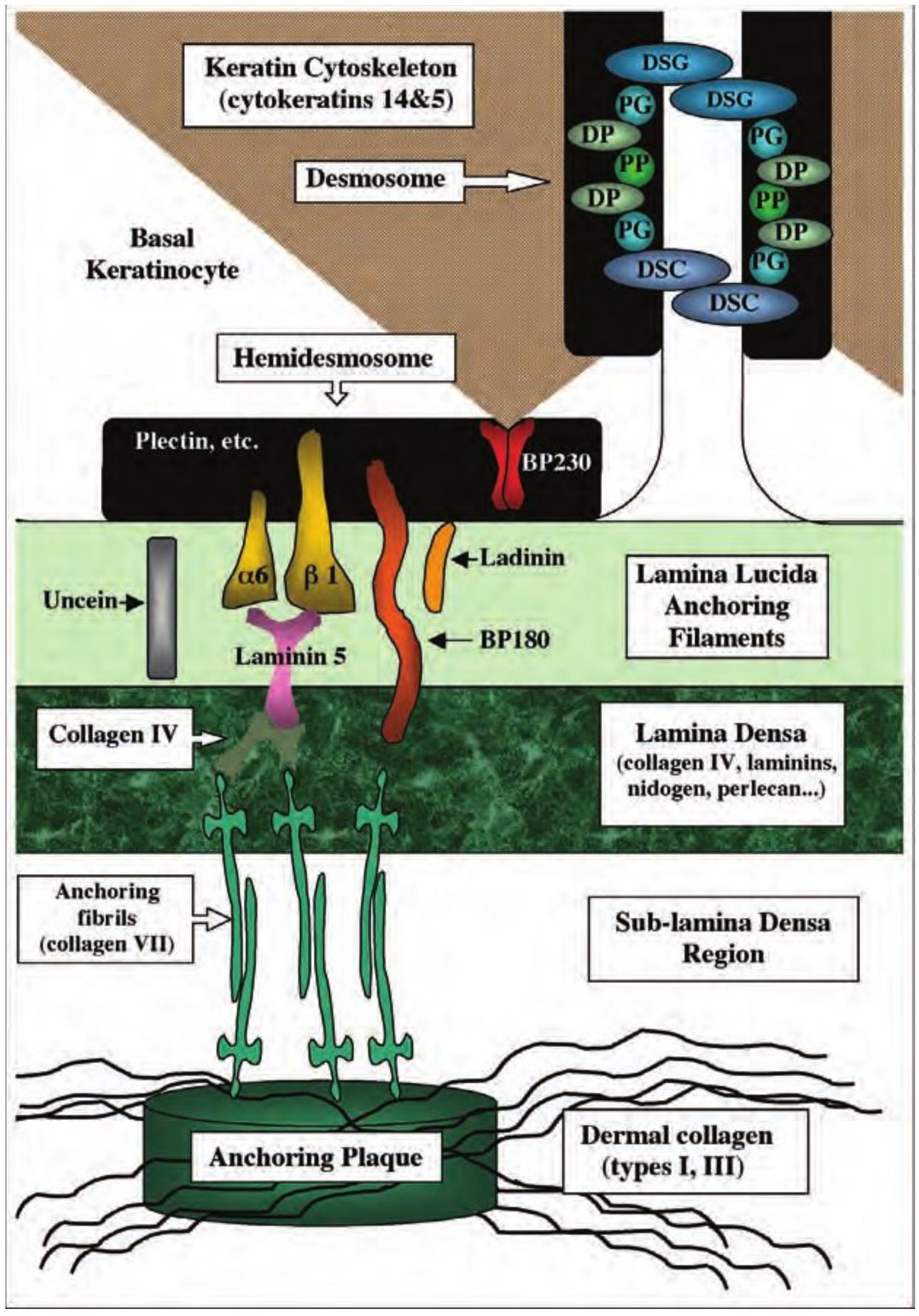


FIGURE 3-23. Diagram illustrating the different components of the desmosome and basement membrane zone. DP, desmoplakin; DSC, desmocollin; DSG, desmoglein; PG, plakoglobin; PP, plakophilin.

Hemidesmosomes contain plaque proteins involved in intermediate filament anchorage including bullous pemphigoid antigen 1 (BPAG1; 230 kD) and plectin, transmembranous proteins including bullous pemphigoid antigen 2 (BPAG2; 180 kD), and integrin α6β4. Additional components of the hemidesmosomes include IFAP300, p200, and other molecules not yet fully characterized. Bullous pemphigoid antigens are easily demonstrated by immunofluorescence as a smooth linear band that separates the epidermal and dermal layers (Fig. 3-21B). Beneath the plasma membrane of the basal cells, a rather electron-lucent zone called the lamina lucida separates the trilaminar plasma membrane, about 8 nm wide, from the more electron-dense component of the basement membrane, or lamina densa (141). Anchoring filaments extend from the basal cell plasma membrane to the lamina densa, traversing the lamina lucida (Fig. 3-23). Anchoring filament components include BPAG2 and α6β4 integrin, which extend from the basal cell membrane into the lamina lucida. BPAG2 exhibits features of a collagen molecule, and it is also referred to as collagen XVII. The 97-kD/120-kD protein ladinin, an important antigen in linear immunoglobulin A (IgA) dermatosis (lamina lucida type), is considered to represent a degradation product of the 180-kD bullous pemphigoid antigen (BPAG2) (145). Other proteins in the lamina lucida that are associated with these anchoring filaments include laminin 5 (also called kalinin, nicein, or epiligrin), uncein (defects in uncein are known to be involved in the recessive junctional type of epidermolysis bullosa), laminin 1, and nidogen (entactin). Although the molecular binding interactions are undoubtedly complex, it is known that α6β4 integrin is a receptor for laminin 1 and 5, and that laminin 5 (epiligrin) is a ligand for α3β1 integrin, which is also expressed by basal keratinocytes. Such adhesive interactions are likely to contribute to the anchoring of basal cells to underlying lamina lucida. Nidogen within the lamina lucida is a 150-kD protein that facilitates adhesion between specific domains of laminin and type IV collagen within the

adjacent lamina densa. Anchoring fibrils are short, curved structures with an irregularly spaced cross-banding of their central portions (146). They fan out at either end, the distal part inserting into the lamina densa and the proximal part terminating in the papillary dermis or looping around and merging in the lamina densa. They insert into amorphous patches containing type IV collagen, which is the main component of the lamina densa (146). The lamina densa itself is anchored to the underlying dermis in part by anchoring fibrils. The anchoring fibrils derive, at least in part, from the dermis and contain type VII collagen (147). The anchoring fibrils connect with islet-like anchoring plaques in the subjacent dermis. These anchoring plaques have a basement membrane–like composition (144). These anchoring structures are interwoven with the dermal interstitial type I and type III collagen fibers, resulting in the adhesion of the basement membrane to the dermis. In addition to anchoring fibrils, elastic fibers consisting of microfibril bundles and individual microfibrils approximately 10 nm in diameter are attached to the undersurface of the lamina densa. Three varieties of elastic tissue exist: oxytalan, elaunin, and elastic fibers (148). The oxytalan fibers consisting of microfibrils form a thin, superficial network perpendicular to the dermoepidermal junction. They originate from a plexus of elaunin fibers located parallel to the dermoepidermal junction in the upper dermis. The elaunin fibers are connected with the thicker elastic fibers of the middle and deep dermis. Effective anchoring of the epidermis to the dermis is a function largely of the anchoring fibrils; anchoring of the basement membrane by oxytalan fibers is quite sparse (149). Defects in basement membrane zone adhesive molecules due to autoantibodies or gene defects may result in disorders characterized by dermal–epidermal separation, as in bullous pemphigoid (BPAG1 and 2 = targets), cicatricial pemphigoid and Herlitz-type junctional epidermolysis bullosa (laminin 5 and uncein = target), and epidermolysis bullosa acquisita, dystrophic epidermolysis bullosa, bullous systemic lupus erythematosus, and some cases of linear IgA disease (type VII collagen = target), discussed further in Chapters 6 and 9.

In addition to their critical adhesive junctions, basement membrane related proteins have recently been shown to subserve other important functions. Certain protein components of the hemidesmosomes have more than just a structural role; for example, integrin $\alpha 6\beta 4$ is able to transduce signals from the extracellular matrix to the interior of the basal cells modulating the organization of their cytoskeleton and their proliferation, apoptosis, and differentiation (150).

Hair Follicles

Embryology

Hair germs, or primary epithelial germs, are first observed in embryos in the eyebrow region and the scalp during the third month of gestation (151). The general development of hair begins in the fourth fetal month in the face and scalp and gradually extends in a cephalocaudal direction. Thus, during the fourth month, while some hair follicles on the head are already well matured and are producing hair, most of those on the trunk are barely differentiated (152). In addition, new primary epithelial germs continue to form adjacent to more-established ones so that, in any section obtained from the beginning of the fifth month up to birth, hair structures in different stages of development are found (153).

Hair germs, or primary epithelial germs, in their earliest stage of development consist of a cluster of tightly aggregated, deeply basophilic cells in the basal cell layer of the epidermis. Subsequently, these develop into buds that protrude into the dermis (Figs. 3-24 and 3-25). Beneath each bud lies a zone of plump mesenchymal cells from which the dermal hair papilla

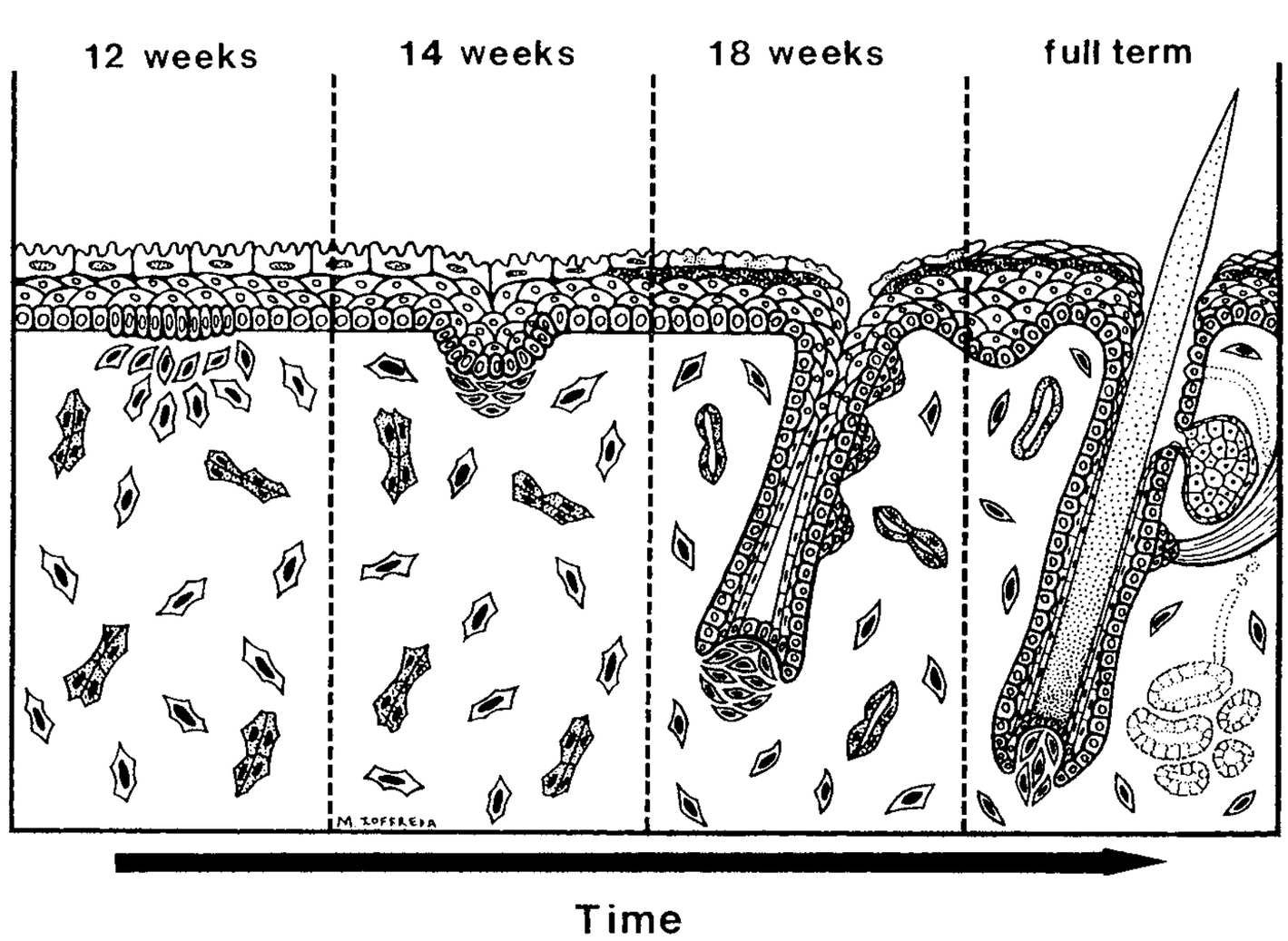


FIGURE 3-24. Schematic overview of embryonic trichogenesis in human skin. (Courtesy of Dr. Michael Ioffreda.)

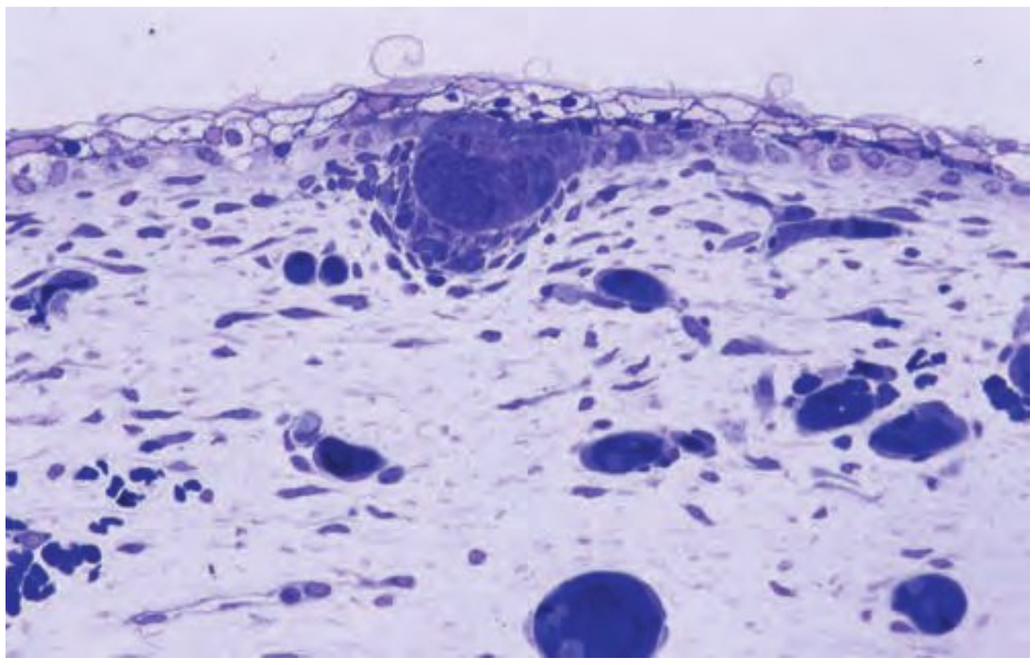


FIGURE 3-25. Histology of early trichogenesis, showing the formation of a primary epithelial germ with associated underlying mesenchymal condensation (1-μm-thick, plastic-embedded section).

is later formed. As the primary epithelial germ grows deeper into the dermis under the inductive influence of the underlying mesenchymal cells, it forms first the hair peg and then, as the hair matrix cells and the dermal hair papilla develop, the bulbous hair peg (154). Ultrastructural observations suggest that the "hair germ mesenchymal cells" pull down the hair germ as they move deeper in the dermal mesenchyme (151).

As the bulbous peg stage is reached, differentiation occurs in the lower and upper portions of the hair follicle and in the overlying epidermis. Differentiation in the lower portion of the follicle leads to the formation of the hair cone and subsequently to the formation of the hair, the cuticle, and the two inner root sheaths. The hair canal in the upper portion of the hair follicle, located at the level of the upper dermis, is formed by the premature death of the central core cells before they have become keratinized. In contrast, the intraepidermal portion of the hair canal is produced by means of premature keratinization and subsequent dissolution of the matrix cells of the cordlike hair canal extending obliquely through the epidermis. By the time the hair cone has reached the upper portion of the hair follicle, the hair canal is already open within the dermis and epidermis (155).

The hair follicles grow at a slant and, in the late hair peg or early bulbous stage, develop two or three bulges on their undersurface. The lowest of the three bulges develops into the attachment for the arrector pili muscle and is associated with the follicular stem cell niche; the middle bulge differentiates into the sebaceous gland. The uppermost bulge, if present, either involutes or develops into an apocrine gland. Apocrine glands develop only in certain regions (156). The intraepidermal portion of the hair canal seems to form by lysosomal digestion of cellular cytoplasm analogous to the formation of the intraepidermal eccrine duct and of the intrafollicular apocrine duct (155).

In sections treated with the dopa reaction or stained with ammoniated silver nitrate, melanocytes are distributed at random in primary epithelial germs and in hair pegs. During the bulbous peg stage, the melanocytes concentrate in the so-called pigment matrix region (the basal cell layer lying on top of the dermal hair papilla) and to a lesser degree in the lower hair bulb located lateral to the dermal hair papilla (153).

Normal Microanatomy

General Anatomic Features

The hair follicle, with its hair in longitudinal sections, consists of three parts: the lower portion, extending from the base of the follicle to the insertion of the arrector pili muscle; the middle portion, or isthmus, a rather short section, extending from the insertion of the arrector pili to the entrance of the sebaceous duct; and the upper portion, or infundibulum, extending from the entrance of the sebaceous duct to the follicular orifice (Figs. 3-26 to 3-33). The lower portion of the hair follicle is composed of five major portions: the dermal hair papilla; the hair matrix; the hair, consisting inward to outward of medulla, cortex, and hair cuticle; the inner root sheath, consisting inward to outward of inner root sheath cuticle, Huxley layer, and Henle layer; and the outer root sheath (Figs. 3-27

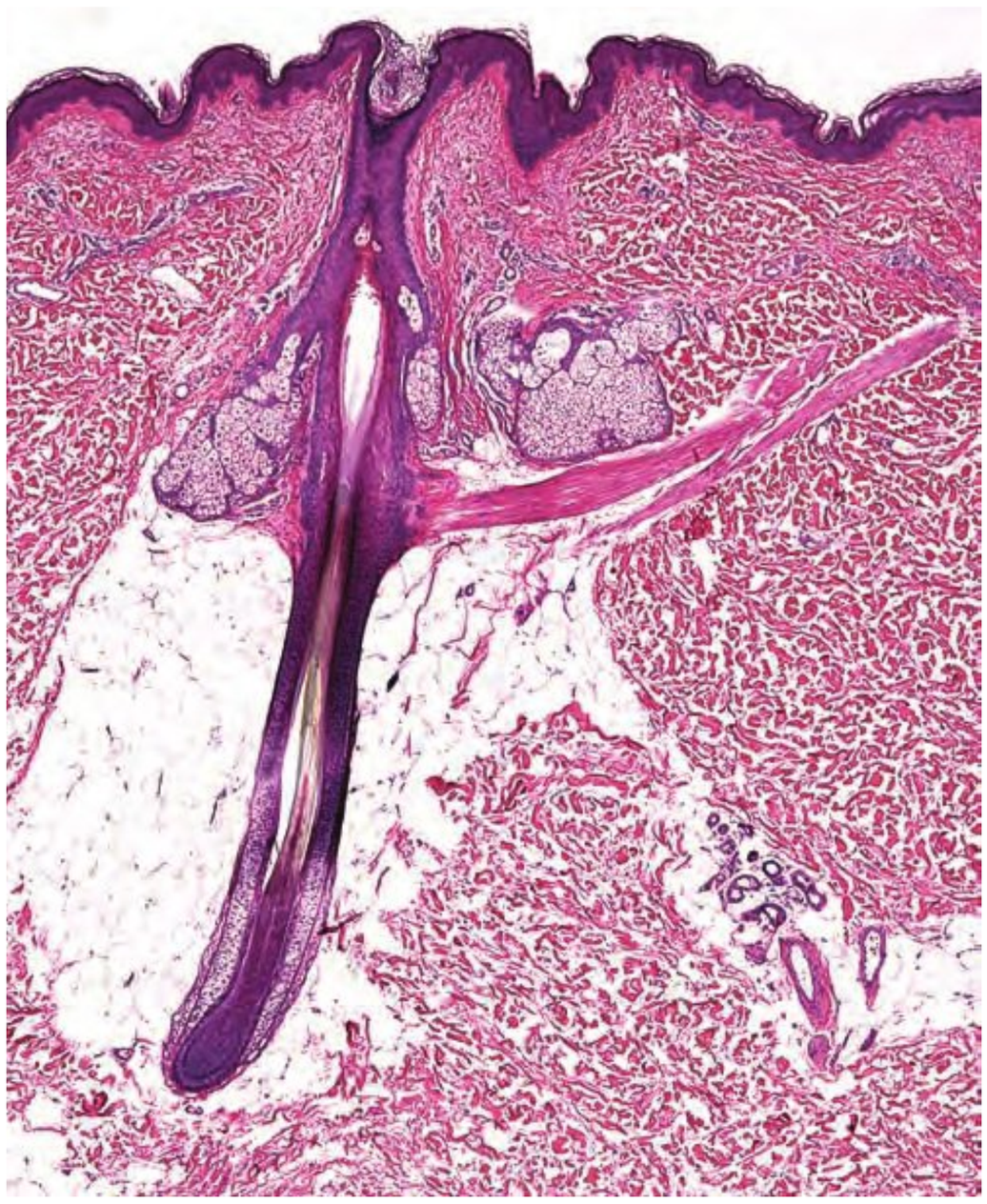


FIGURE 3-26. Low-power view of a hair follicle to illustrate its four zones. From bottom to top: the hair bulb, the suprabulbar zone (at which point the various layers of the follicle start to differentiate), the isthmus (located between the arrector pili muscle and entrance of the sebaceous duct), and the infundibulum (the uppermost zone of the follicle, whose inferior boundary is represented by the entrance of the sebaceous duct).

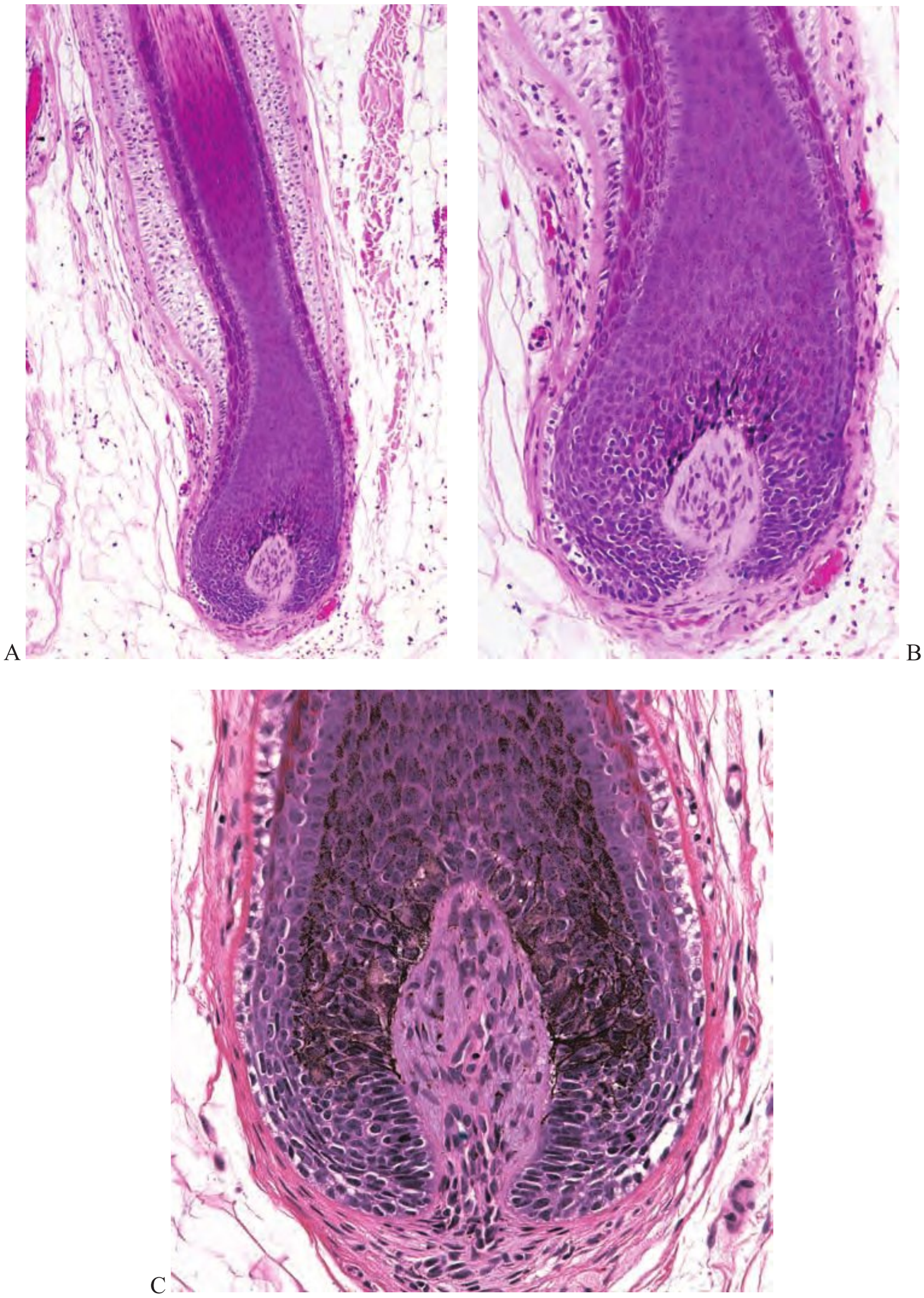


FIGURE 3-27. Histology of the lower portion of the human hair follicle. A: The terminal anagen hair bulb is usually located in the deep dermis or superficial subcutaneous tissue. B: The basophilic hair matrix surrounds the dermal papillae. C: Note the pigmented and dendritic melanocytes in the suprapapillary matrix. The typically mucinous inferior portion of the follicular papilla (stalk) is continuous with the fibrous root sheath.

and 3-28). This bulb region gives rise to the formation of the hair shaft that occupies the overlying follicular canal (Figs. 3-27 and 3-28). The hair shaft is predominantly composed of keratin. The large keratin multigene family comprises the epithelial keratins and the hair keratins, the latter involved in the formation of hard keratinized structures such as hair and nail. Recent studies have found that the human hair keratin family consists of nine type I and six type II members, whose genes are organized as distinct clusters within the type I and type II epithelial keratin gene domains (157,158).

Cycles of Hair Growth

The size of the hair follicles varies from long and thick terminal hairs with their bulbs in the fat to thin, short, and often hypopigmented vellus hairs with bulbs located in the upper dermis (Fig. 3-31). Regardless of size, every follicle goes through the three phases of the "hair cycle." The histologic appearance of the hair follicle changes considerably during the hair cycle, which causes the hair to turn from an anagen hair into a catagen hair, then into a telogen hair, and finally into a new anagen hair (Chapter 18). In the adult scalp, the anagen stage—the

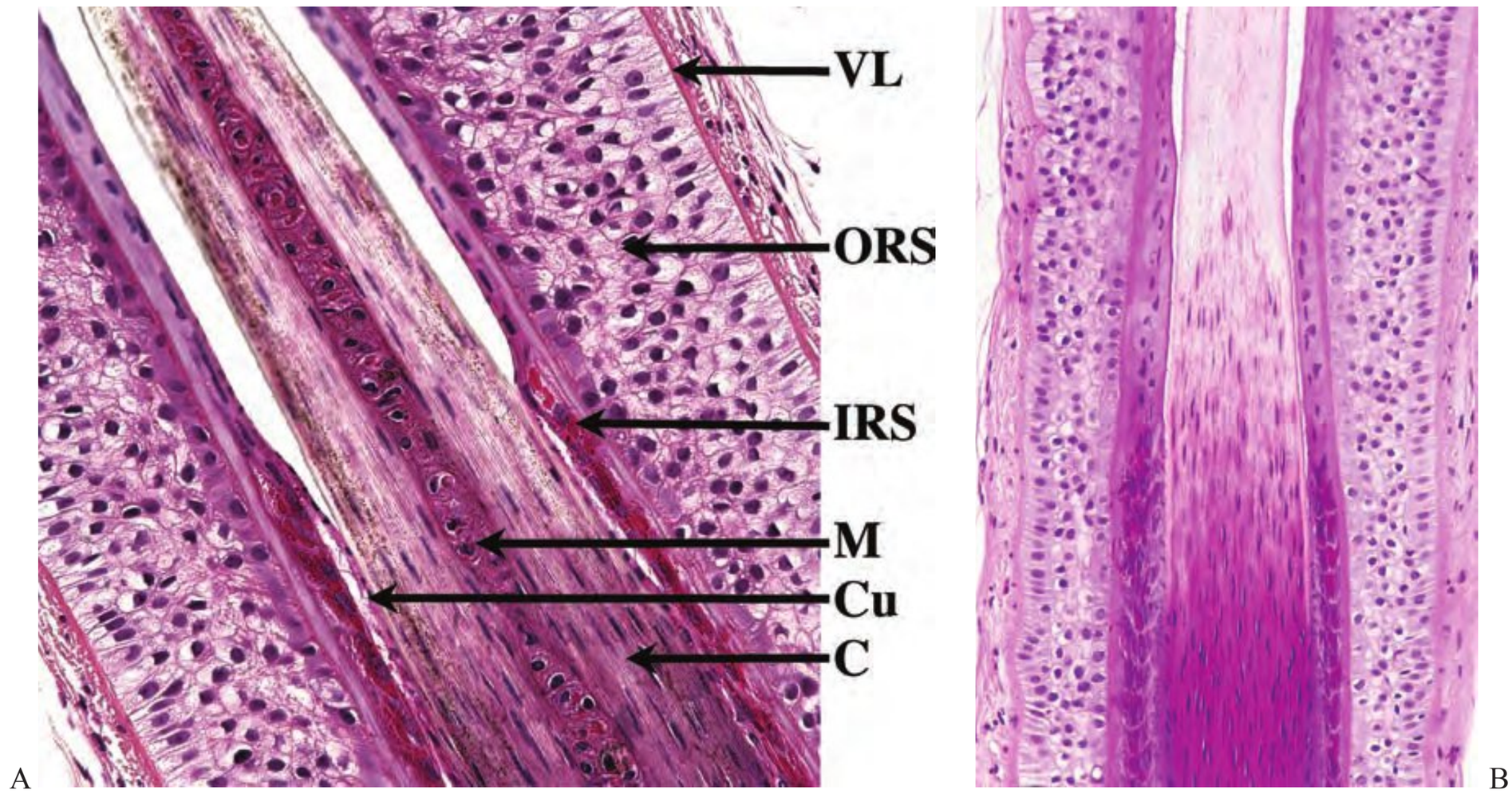


FIGURE 3-28. A: Suprabulbar portion (lower segment) of the hair follicle. The various layers of the anagen hair can be recognized. From the inside to the periphery: the medulla (M) when present, the cortex (C), the cuticle (Cu) that includes the hair shaft cuticle and the cuticle of the inner root sheath (IRS), the Huxley and Henley layers of the IRS, the highly glycogenated outer root sheath (ORS), and the glassy vitreous layer (VL). B: Note the loss of nuclei in the hair shaft and inner root sheath.

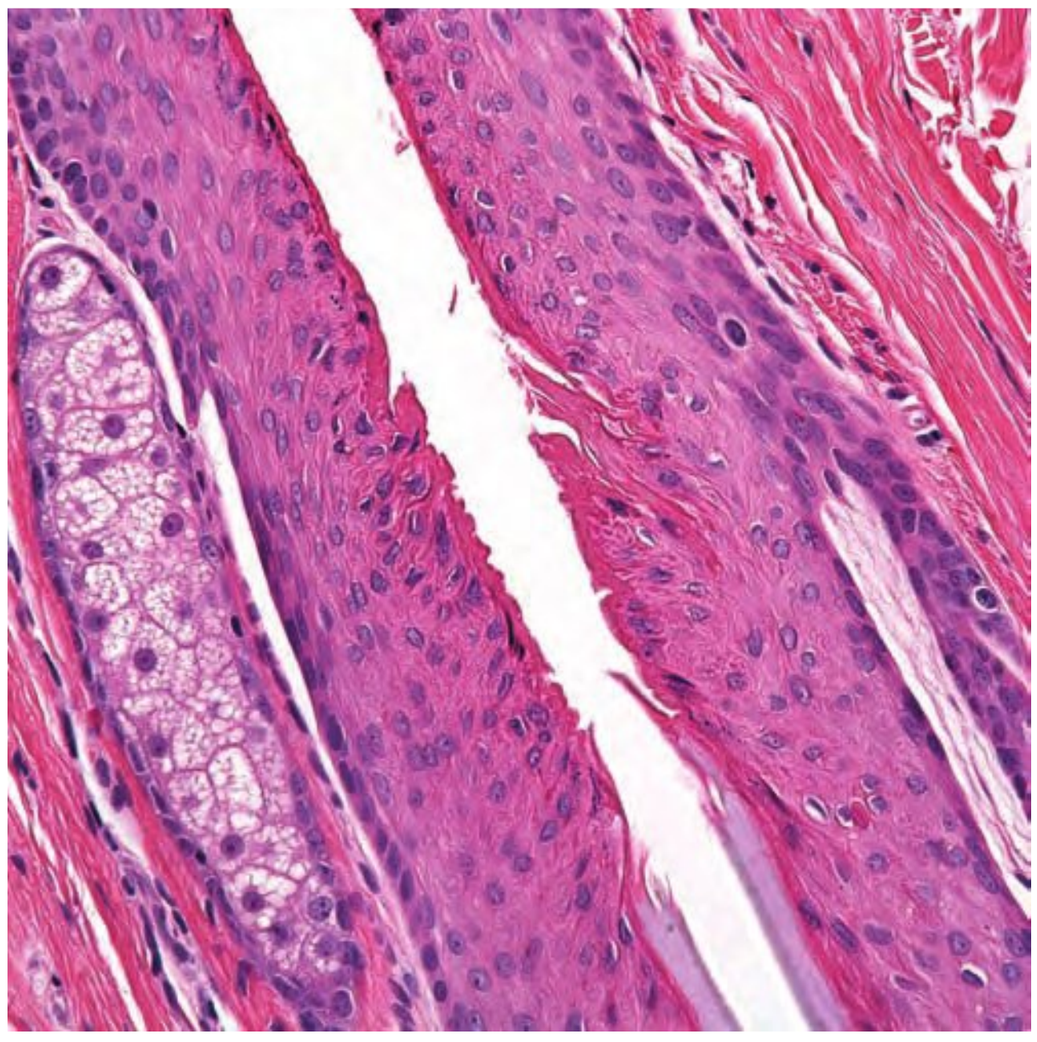
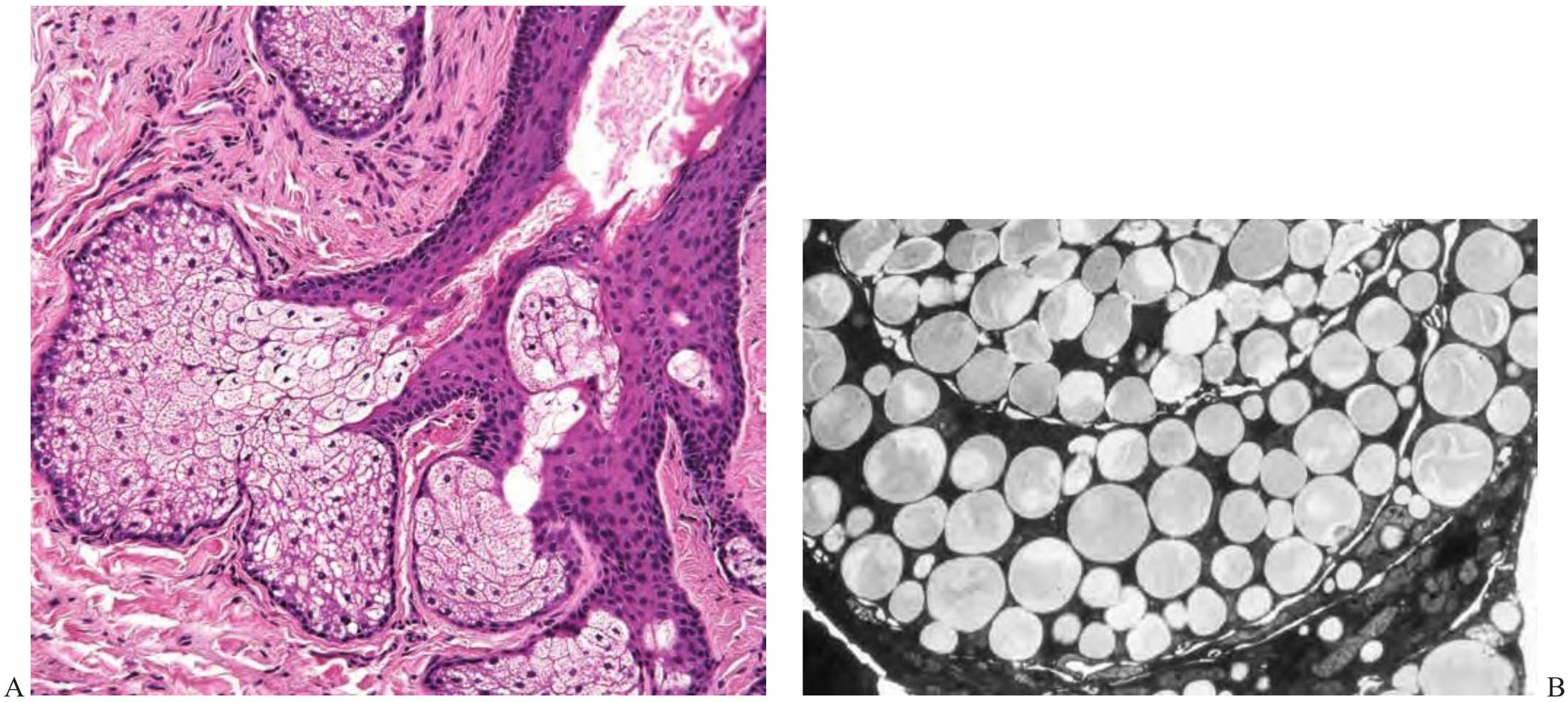


FIGURE 3-29. Isthmus of a hair follicle. Its upper limit is marked by the sebaceous gland opening. In the mid portion of the isthmus, the abrupt desquamation of the inner root sheath (gray blue) takes place. Above it, the outer root sheath cornifies (dark pink) without formation of a granular layer (trichilemmal keratinization).

phase of active growth—lasts at least 3 years; catagen—the phase of regression—lasts about 3 weeks; and telogen—the resting period—lasts about 3 months. At any one time, approximately 84% of scalp hairs are in anagen stage, 2% in catagen, and 14% in telogen (159). These ratios are important in evaluating abnormalities in the hair cycle in biopsies of partially alopecic scalp. The daily hair growth rate averages about 0.4 mm on the scalp.

During its active growth, or anagen, stage the hair follicle shows at its lower pole a knoblike expansion, the hair bulb, composed of matrix cells and melanocytes. A small, egg-shaped dermal structure, the dermal hair papilla, protrudes into the hair bulb (Fig. 3-27). The papilla induces and maintains the growth of the hair follicle (160). Because of the presence of large amounts of acid mucopolysaccharides in its ground substance, the dermal hair papilla stains positively with alcian blue and metachromatically with toluidine blue. Because positive staining with alcian blue takes place at pH 2.5 and 0.5, it can be concluded that the ground substance of the hair papilla contains nonsulfated acid mucopolysaccharides, such as hyaluronic acid, and sulfated acid mucopolysaccharides, such as chondroitin sulfate (161). In addition, there is considerable alkaline phosphatase activity in the hair papilla during the anagen stage as a result of the presence of large numbers of capillary loops (162,163). In persons with dark hair, large amounts of melanin can be seen in the dermal hair papilla situated within melanophages.



A B

FIGURE 3-30 A: Sebaceous gland and sebaceous duct opening into a hair follicle. B: Transmission electron microscopy of a sebaceous lobule. Lipid is visible as rounded, homogeneous bodies filling the cytoplasm of mature sebocytes.

Bulb and Lowermost Portion of the Hair Follicle

The pluripotential cells of the hair matrix present in the hair bulb give rise to the hair and to the inner root sheath. In contrast, the outer root sheath represents a downward extension of the epidermis. The cells of the hair matrix have large vesicular nuclei and a deeply basophilic cytoplasm. Dopa-positive melanocytes are interspersed mainly between the basal cells of the hair matrix lying on top of the dermal hair papilla and, to a lesser degree, between the basal cells of the hair matrix located lateral to the hair papilla (153). Melanin, varying in quantity in accordance with the color of the hair, is produced in these melanocytes and is incorporated into the future cells of the hair through phagocytosis of the distal portion of dendritic processes by future hair cells. This transfer of melanin is analogous to that observed from epidermal melanocytes to keratinocytes.

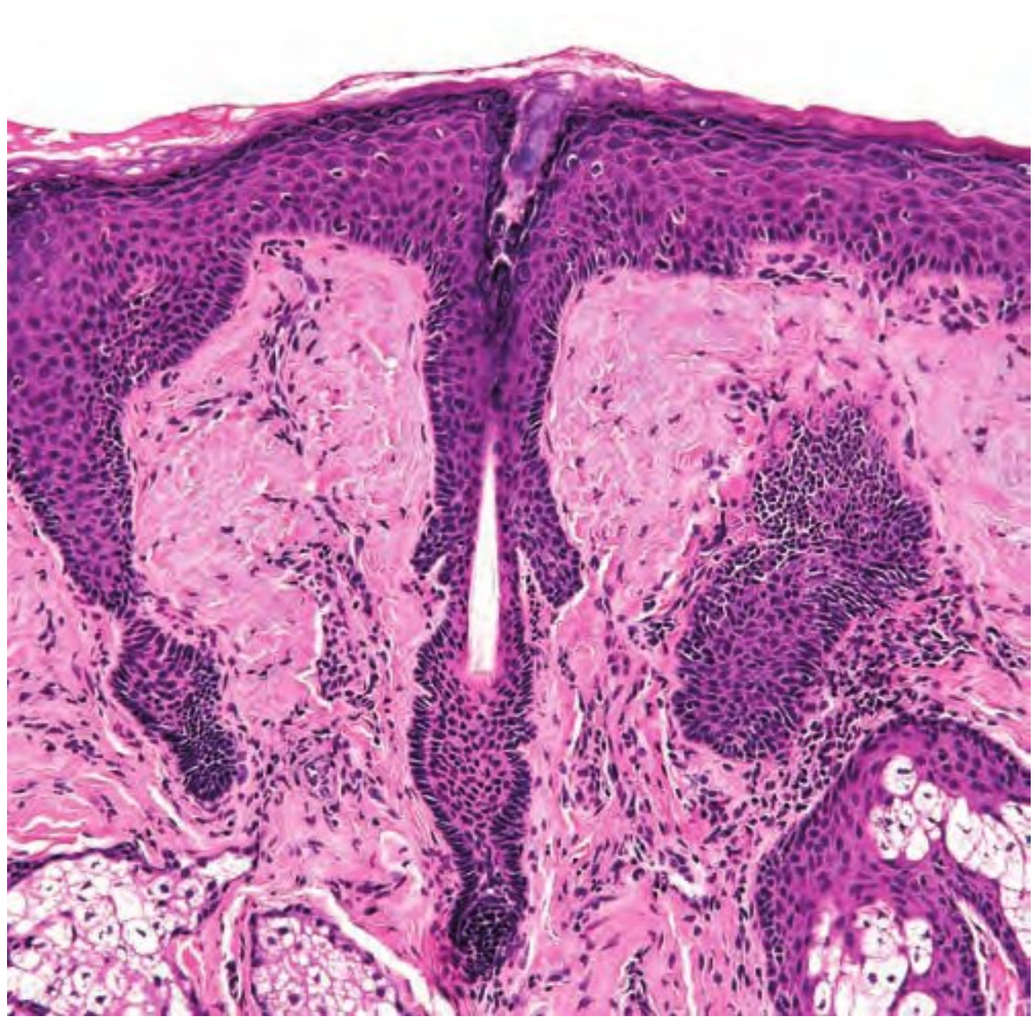


FIGURE 3-31. Vellus hair. The bulb of these small hair follicles is located in the upper dermis. As terminal hairs, vellus hairs go through the entire hair cycle.

As they move upward, the cells arising from the hair matrix differentiate into six different types of cells, each of which keratinizes at a different level. The outermost layer of the inner root sheath, the Henle layer, keratinizes first, thus establishing a firm coat around the soft central parts. The two apposed cuticles covering the inside of the inner root sheath and the outside of the hair keratinize next, followed by Huxley's layer. The hair cortex then follows, and the medulla is last (164).

The hair medulla of human hair is often difficult to find by routine light microscopy because it may be discontinuous or even absent. It is more readily recognizable by polariscopic examination because, unlike the cortex, the only partially keratinized medulla contains hardly any doubly refractile structures (165). If the medulla is seen by light microscopy in human hairs, it appears amorphous because of only partial keratinization.

The hair cortex consists of cells that, during their upward growth from the hair matrix, keratinize gradually by losing their nuclei and become filled with keratin fibrils. The process of keratinization takes place without the formation of keratohyaline granules, as seen in the keratinizing epidermis, or of trichohyaline granules, as seen in the inner root sheath. Thus,

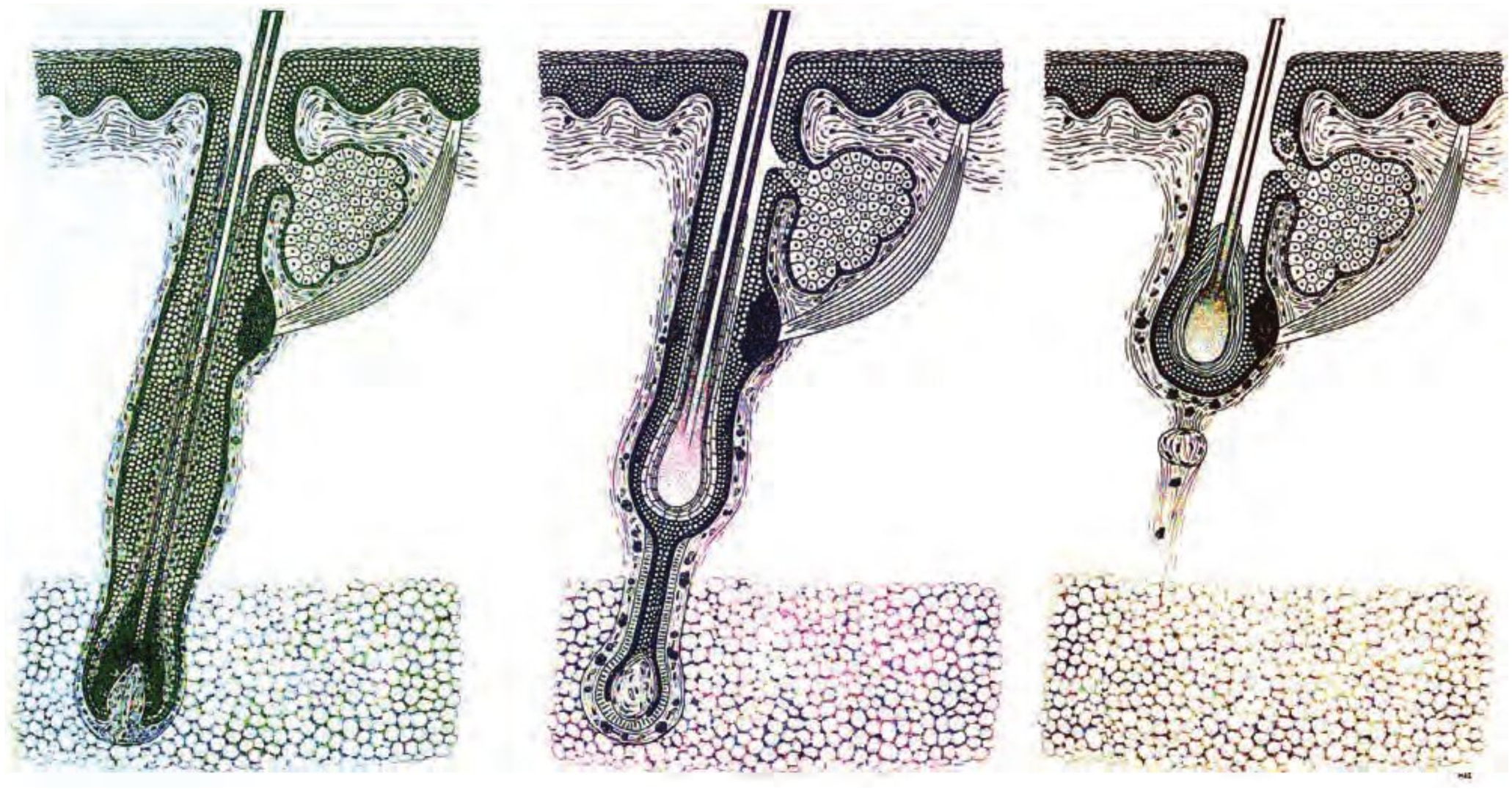


FIGURE 3-32. Diagram of the hair cycle. From left to right: anagen hair, catagen hair, and telogen hair.

the keratin of the hair cortex represents hard keratin, in contrast to the keratin of the inner root sheath, which, like that of the epidermis, represents soft keratin (166).

The hair cuticle (Fig. 3-28), located peripheral to the hair cortex, consists of overlapping cells arranged like shingles and pointing upward with their peripheral portion. The cells of the hair cuticle are tightly interlocked with the cells of the inner root sheath cuticle, resulting in the firm attachment of the hair to its inner root sheath. The hair and the inner root sheath move upward in unison (167).

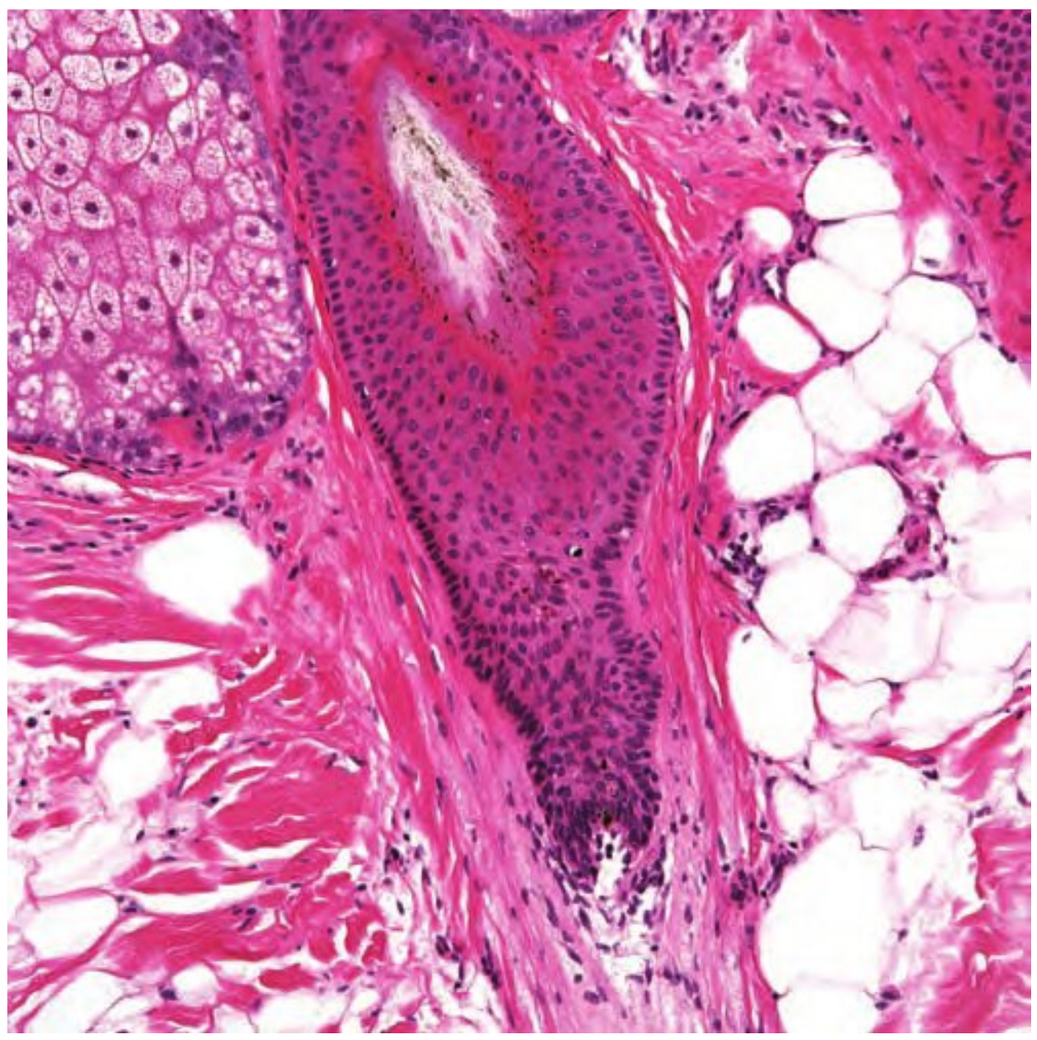


FIGURE 3-33. Section of a catagen/telogen hair. Note the club-shaped cornifying hair shaft with serrated borders. There are numerous apoptotic nuclei in the hair epithelium.

The inner root sheath is composed of three concentric layers; from the inside to the outside, these are the inner root sheath cuticle, the Huxley layer, and the Henle layer (Fig. 3-28). None of these three layers contains melanin. All three layers keratinize, unlike the cells of the hair cortex and of the hair cuticle, by means of trichohyaline granules. These granules resemble the keratohyaline granules of the epidermis, although they stain eosinophilic, in contrast to the basophilic-staining keratohyaline granules of the epidermis. Similar granules may be noted in the pathologic process of epidermolytic hyperkeratosis. Closest to the hair is the single-layered inner root sheath cuticle, consisting of flattened overlapping cells that point downward in the direction of the hair bulb. Because the cells of the hair cuticle point upward, these two types of cells interlock tightly. Trichohyaline granules are few in the inner root sheath cuticle cells. The Huxley layer, which usually consists of two rows of cells, develops numerous trichohyaline granules at the level of the keratogenous zone of the hair. The Henle layer, which is only one cell layer thick and the first layer to undergo keratinization, already has many trichohyaline granules at its emergence from the hair matrix (168) (Fig. 3-27). After having become fully keratinized, the cells of all three layers composing the inner root sheath disintegrate when they reach the isthmus of the hair follicle, which extends from the area of attachment of the arrector pili muscle to the entrance of the sebaceous duct. The cells of the inner root sheath thus do not contribute to the emerging hair (169).

The outer root sheath extends upward from the matrix cells at the lower end of the hair bulb to the entrance of the sebaceous duct, where it changes into surface epidermis, which lines the upper portion, or infundibulum, of the hair follicle. The outer root sheath is thinnest at the level of the hair bulb, gradually increases in thickness, and is thickest in the middle portion of the hair follicle, the isthmus. In its lower portion, below the isthmus, the outer root sheath is covered by the inner root sheath and does not undergo keratinization. The outer root sheath cells have a clear, vacuolated cytoplasm because of the presence of considerable amounts of glycogen (Fig. 3-28). In contrast to the surface epidermis lining the infundibulum, which contains active, melanin-producing melanocytes in its basal layer, the basal layer of the outer root sheath contains only inactive, amelanotic melanocytes demonstrable with toluidine blue. However, these inactive melanocytes can become melanin-producing cells after skin injuries, such as dermabrasion, when they increase in number and migrate upward into the regenerating upper portion of the outer root sheath and into the regenerating epidermis (170).

Follicular Isthmus and Infundibulum

In the middle portion of the hair follicle, the so-called isthmus, which extends upward from the attachment of the arrector pili muscle (so-called bulge region) (Fig. 3-29) to the entrance of the sebaceous duct, the outer root sheath is no longer covered by the inner root sheath, which by then has keratinized and disintegrated. The outer root sheath therefore undergoes keratinization. This type of keratinization, referred to as trichilemmal keratinization, produces large, homogeneous keratinized cells without the formation of keratohyaline granules (Fig. 3-29). Trichilemmal keratinization is found also in catagen and telogen hairs and in trichilemmal cysts and trichilemmal tumors. The bulge region at the site of the arrector pili muscle insertion is poorly defined in human follicles and difficult to detect in routine sections. When it is visualized, it consists of several knobby protuberances and ridges composed of relatively undifferentiated follicular keratinocytes with putative stem cell capability (10).

The upper portion of the hair follicle above the entrance of the sebaceous duct, the infundibulum, is lined by surface epidermis, which, like the sebaceous duct, undergoes keratinization with the formation of keratohyaline granules. The infundibulum contains a number of dendritic nonkeratinocytes on ultrastructural examination, and immunohistochemistry reveals numerous CD1a-positive Langerhans cells within the infundibula of normal adult anagen hairs.

The glassy or vitreous layer forms a homogeneous, eosinophilic zone peripheral to the outer root sheath (Fig. 3-28). Like the subepidermal basement membrane zone, it is PAS positive and diastase resistant, but it differs from the subepidermal basement membrane zone by being thicker and visible with routine stains. It is thickest around the lower one third of the hair follicle. Peripheral to the vitreous layer lies the fibrous root sheath, which is composed of thick collagen bundles.

Sebaceous Glands

The sebaceous glands are well developed at the time of birth, most likely because of maternal hormones. After a few months, they undergo considerable involution. At puberty, as a result of increased androgen output, the sebaceous glands become greatly enlarged (171). This normal cycle may also occur in certain pathologic conditions, such as nevus sebaceus.

A sebaceous gland may consist of only one lobule but often has several lobules leading into a common excretory duct composed of stratified squamous epithelium (Fig. 3-30A). Sebaceous glands, being holocrine glands, form their secretion by decomposition of their cells. In sebaceous glands of the skin, the pilosebaceous follicle into which the sebaceous duct leads may possess a large hair or a vellus hair that may be too small to reach the skin surface. There is no relationship between the size of the sebaceous gland and the size of the associated hair. For example, in the center of the face and on the forehead, where the sebaceous glands are very large, the associated hairs are of the vellus type.

Each sebaceous lobule possesses a peripheral layer of cuboidal, deeply basophilic cells that usually contain no lipid droplets (Fig. 3-30B). The more centrally located cells contain lipid droplets, which can be detected if lipid stains are used on formalin-fixed frozen sections, but in routinely processed sections in which the lipid has been extracted, the cytoplasm of these cells appears as a delicate network of fine cytoplasmic vacuoles. The nucleus is centrally located. In the portion of the lobule located closest to the duct, the cells disintegrate.

The composition of lipids in the sebaceous glands is not uniform. Thus, under polarized light, doubly refractile lipids may be present in small to moderate amounts or may be absent (172). Histochemical examination reveals the presence of triglycerides and small amounts of phospholipids. Esterified cholesterol is present, but there is no free cholesterol. Waxes are also present, but they are not identifiable by histochemical means (172). Evidence of active lipid synthesis and storage may be observed by electron microscopy (173,174).

Lysosomal enzymes bring about the physiologic autolysis that occurs in the holocrine secretion. Histochemical staining of electron microscopic sections for lysosomal enzymes, such as acid phosphatase and aryl sulfatase, reveals an increasing number of lysosomes as the sebaceous cells become more lipidized. In the disintegrating cells located in the preductal region, the acid phosphatase and aryl sulfatase activity is most pronounced, but this activity is largely outside of lysosomes because the lysosomes have released their contents in their function as "suicide bags" (175). Prior to the sudden disintegration of the sebaceous cells an abrupt conversion of –SH to S–S linkages of proteins occurs in sebaceous glands just as in epidermis and hair (176).

Regional Variation

Hair follicles vary considerably in different anatomic regions and according to age and sex. In adults, deep anagen hairs (extending into subcutaneous fat) are typically found on the scalp (see Fig. 3-59) and male beard area, whereas vellus hairs typify the female face and nonbeard-area facial regions of men.

Hair of extremities and trunk generally can be differentiated from scalp by the more superficial location of the bulbs and diminished density. Sebaceous glands are present everywhere on the skin except on the palms and soles. On the skin, they are found in association with hair structures. In addition, free sebaceous glands that are not associated with hair structures occur in some areas of modified skin, such as the nipple and areola of both the male and female breasts. There, they occur over the entire surface of the nipple and in Montgomery's areolar tubercles, each of which contains several sebaceous lobules in association with a lactiferous duct. Free sebaceous glands also may be found on the labia minora and the inner aspect of the prepuce. Modified sebaceous glands called Tyson's glands have been reported to occur on the coronal sulcus of the penis (177). The not infrequent presence of free sebaceous glands on the vermilion border of the lips and on the buccal mucosa is known as Fordyce's condition. The meibomian glands of the eyelids are modified sebaceous glands (see Fig. 3-62A).

Specialized Structure and Function

Hair Cycle

The hair cycle ensures that periodically, entirely new hair shafts are produced, and it also serves as an intrinsic regulator of maximum hair length The hair cycle consists of the involutionary stage (catagen) and the end stage (telogen) of the old hair and its replacement by a young, new hair (early anagen) (Fig. 3-32). At the onset of the catagen stage, mitotic activity and melanin production in the hair bulb cease. Next, the bulb shrinks and becomes separate from the dermal hair papilla (168). As the hair moves upward, the lower portion of the follicle involutes (Fig. 3-33). The reduction in follicle size results from cell deletion by apoptosis, or programmed cell death (178). The lower follicle thus becomes a thin cord of epithelial cells surrounded by the fibrous root sheath, which is wrinkled in thick folds. In addition, as the hair moves upward, growth of the inner root sheath ceases, so that the lower end of the hair shaft becomes surrounded by dense keratin, referred to as trichilemmal keratin, that is formed by the outer root sheath without the interposition of keratohyaline granules. This then represents the club hair of the catagen stage.

Next, the thin cord of epithelial cells retracts upward, faithfully followed by the underlying dermal hair papilla, which also moves upward. The cord of epithelial cells shortens until it forms only a small, nipple-like downward protrusion from the club hair, called the secondary hair germ. Under it lies the dermal hair papilla. With the hair follicle decreased to about one third of its former length, the lowest portion of the hair follicle lies at the level of the attachment of the arrector pili. The lower portion of the hair is encased in trichilemmal keratin and completely surrounded by the outer root sheath. Folds of the fibrous root sheath extend downward from the hair follicle. At this point, the hair has reached the telogen stage (179).

When regrowth of the hair begins, the secondary hair germ where the stem cell cluster is believed to be preserved begins to elongate by cell division and grows down as an epithelial column together with the dermal hair papilla inside of the old, collapsed fibrous root sheath of the previous hair (so-called "bulge activation" stage). As it is growing down, the lower end of the epithelial column becomes invaginated by the dermal hair papilla. A new hair bulb is formed, representing the early anagen stage. By subsequent differentiation, a new hair arises. Thus, the formation of an active hair follicle from the secondary germ recapitulates the embryonic pattern of development of the hair from the primary hair germ (179). Recent experimental data in rodents suggest that the primary site that gives rise to new hair germ during follicular regrowth is the bulge region of the follicle, where a population of normally slow-cycling, relatively undifferentiated cells with features of stem cells reside (10). Stimulation of the bulge region, which persists throughout telogen, then gives rise to new hair germ and the developing anagen follicle (bulge activation hypothesis).

Hair Color

Three types of melanosomes are present in hair. Erythromelanin granules, seen in red hair, are polymorphous and have an irregular internal structure. The other two types of granules, homogeneous eumelanin granules and lamellated pheomelanin granules, are found in varying proportions in blond and dark hair and are round to oval. Dark hair contains more melanosomes than light hair, and the melanosomes are largely of the homogeneous eumelanin type; in light hair, lamellated pheomelanin melanosomes predominate (180).

In gray and white hair, the melanocytes in the basal layer of the hair matrix are greatly reduced in number or are absent. The melanocytes that are present show degenerative changes, especially of their melanosomes (181). Such changes appear to affect melanocyte stem cells, resulting in permanent hair graying (182). The hair shafts contain only detritus of melanin or none at all (180).

Follicular Immunity

The number of CD1a-positive Langerhans cells in normal follicular infundibula raises questions concerning their role in follicular immunity. Such populations could be appropriately sequestered from harmful environmental agents, such as ultraviolet light, and thus serve as a reservoir of antigen-presenting cells, as well as an evolutionary rationale for preservation of hair follicles in *Homo sapiens* no longer in need of the thermal or protective benefits of hair shafts. Such follicle-associated immune tissue has been evidenced in clinical settings of primarily follicular pathology in contact dermatitis, as well as in sequential studies of human, experimentally induced contact allergy, where the first sentinel lymphocytes selectively home to follicular infundibula (183). Chronic UV exposure may deplete epidermal Langerhans cells, whereas follicular Langerhans cells remain intact, resulting in a protected niche that may be stimulated to replenish sun-damaged skin (140).

Eccrine and Apocrine Glands

The apocrine glands differ from eccrine glands in origin, distribution, size, and mode of secretion. The eccrine glands primarily

serve in the regulation of heat, and the apocrine glands represent scent glands. More recently, a third type of sweat gland called the apoeccrine gland has been described in the axillae (184).

Embryology

Eccrine glands are present in mammals, with the exception of anthropoid apes, only on the soles. Their presence in other parts of the skin in humans is a late development from the phylogenetic point of view. Accordingly, the eccrine glands develop in humans earlier on the palms and soles than elsewhere. On the palms and soles, eccrine gland germs are first seen early in the fourth gestational month (185). In the early part of the fifth fetal month, they develop in the axillae, and near the end of the fifth month, they begin to appear over the remainder of the body (152). The eccrine gland germs begin as areas of crowding of deeply basophilic cells in the basal layer of the epidermis. They differ from primary epithelial germs only slightly by being narrower and by showing fewer mesenchymal cells at their base. Like hair follicles, eccrine glands may be seen at one time in different stages of development. In embryos 16 weeks old, some eccrine glands are already beginning to form coils on the palms and soles, while new eccrine gland germs are still forming in the epidermis (186).

At the time of lumen formation, the intradermal duct and the secretory segment show a wall composed of two layers of cells—an inner layer of luminal cells and an outer layer of basal cells. Although the dermal duct continues to consist of these two layers of cells throughout life, the two layers in the secretory segment undergo differentiation: The luminal cells differentiate into tall, columnar secretory cells extending from the basement membrane to the luminal border, and the basal cells differentiate into secretory cells or into myoepithelial cells, which appear as pyramidal, relatively small cells wedged at the base between secretory cells (185). The differentiation into secretory and myoepithelial cells in the secretory segment is well advanced on the palms and soles of embryos 22 weeks old. At the time of birth, the appearance of the eccrine glands resembles that of adult eccrine glands.

In contrast to eccrine glands, apocrine glands develop only in certain areas. Wherever they form, they develop from the upper bulge of hair follicles that are in the early bulbous peg stage and show a hair cone. The formation of apocrine glands begins late in the fourth month and continues until late in embryonic life, as long as new hair follicles develop. In the earliest stage, a solid epithelial cord projects into the perifollicular mesenchyme at a right angle to the long axis of the hair follicle and then grows downward past the developing sebaceous gland and arrector pili bulge. By the time the tip of the epithelial cord has reached the level of the sebaceous gland, the intradermal ductal lumen begins to form, as does the intrafollicular lumen (156). At the time of birth, there is no recognizable myoepithelial layer of cells around the secretory portion of the apocrine glands (152).

Eccrine glands apparently give rise to apoeccrine axillary glands during puberty (184).

Normal Microanatomy

Eccrine glands are composed of three segments: the intraepidermal duct, the intradermal duct, and the secretory portion (Fig. 3-34). The secretory portion makes up about one half of the basal coil, the other half being composed of duct. The basal coil lies either at the border between the dermis and the subcutaneous fat or in the lower one third of the dermis. When located in the lower dermis, it is surrounded by fatty tissue that connects with the subcutaneous fat. Eccrine glands are highlighted by immunohistochemical stains for S100 protein and carcinoembryonic antigen (Fig. 3-35).

The intraepidermal eccrine duct extends from the base of a rete ridge to the surface and follows a spiral course (Fig. 3-34A). The cells composing the duct are different from the cells of the surrounding epidermis in that they are derived from dermal duct cells through mitosis and upward migration (187). For this reason, the intraepidermal eccrine duct has been referred to as acrosyringium or the epidermal sweat duct unit. The intraepidermal eccrine duct consists of a single layer of inner or luminal cells and two or three rows of outer cells. The ductal cells begin to keratinize, as evidenced by the presence of keratohyaline granules, at a lower level than the cells of the surrounding epidermis, in the middle squamous layer, and are fully keratinized at the level of the stratum granulosum of the surrounding epidermis (188). Before keratinization, the intraepidermal lumen is lined by an eosinophilic cuticle.

The intradermal eccrine duct is composed of two layers of small, cuboidal, deeply basophilic epithelial cells (Fig. 3-34B). Unlike the secretory portion of the eccrine gland, the eccrine duct has no peripheral hyaline basement membrane zone, but the lumen of the duct is lined with a deeply eosinophilic, homogeneous cuticle that is PAS positive and diastase resistant.

The secretory portion of the eccrine gland shows only one distinct layer composed of secretory cells (Fig. 3-34C). The presence of only one distinct layer is due to the fact that the cells of the outer layer have become differentiated into either secretory or myoepithelial cells during the sixth to eighth months of embryonic life. The secretory cells lining the lumen consist equally of two types—clear cells and dark cells. The clear cells generally are broader at the base than they are near the lumen, appear somewhat larger than the dark cells, and contain very faint, small granules. The dark cells are broadest near the lumen and contain numerous basophilic granules (189). The clear cells contain PAS-positive, diastase-labile glycogen, and the dark cells contain PAS-positive, diastase-resistant mucopolysaccharides. The clear cells secrete abundant amounts of aqueous material together with glycogen; the dark cells secrete sialomucin. This substance contains both neutral and nonsulfated acid mucopolysaccharides, is positive for PAS and for alcian blue at pH 2.4, and is resistant to diastase and hyaluronidase. Prolonged sweating leads to a depletion of glycogen in the clear cells (190). The myoepithelial cells possess a small spindle-shaped nucleus and long contractile fibrils. The fibrils run in a spiral, their long axes aligned obliquely to the direction of the secretory tubule. Delivery of sweat to the

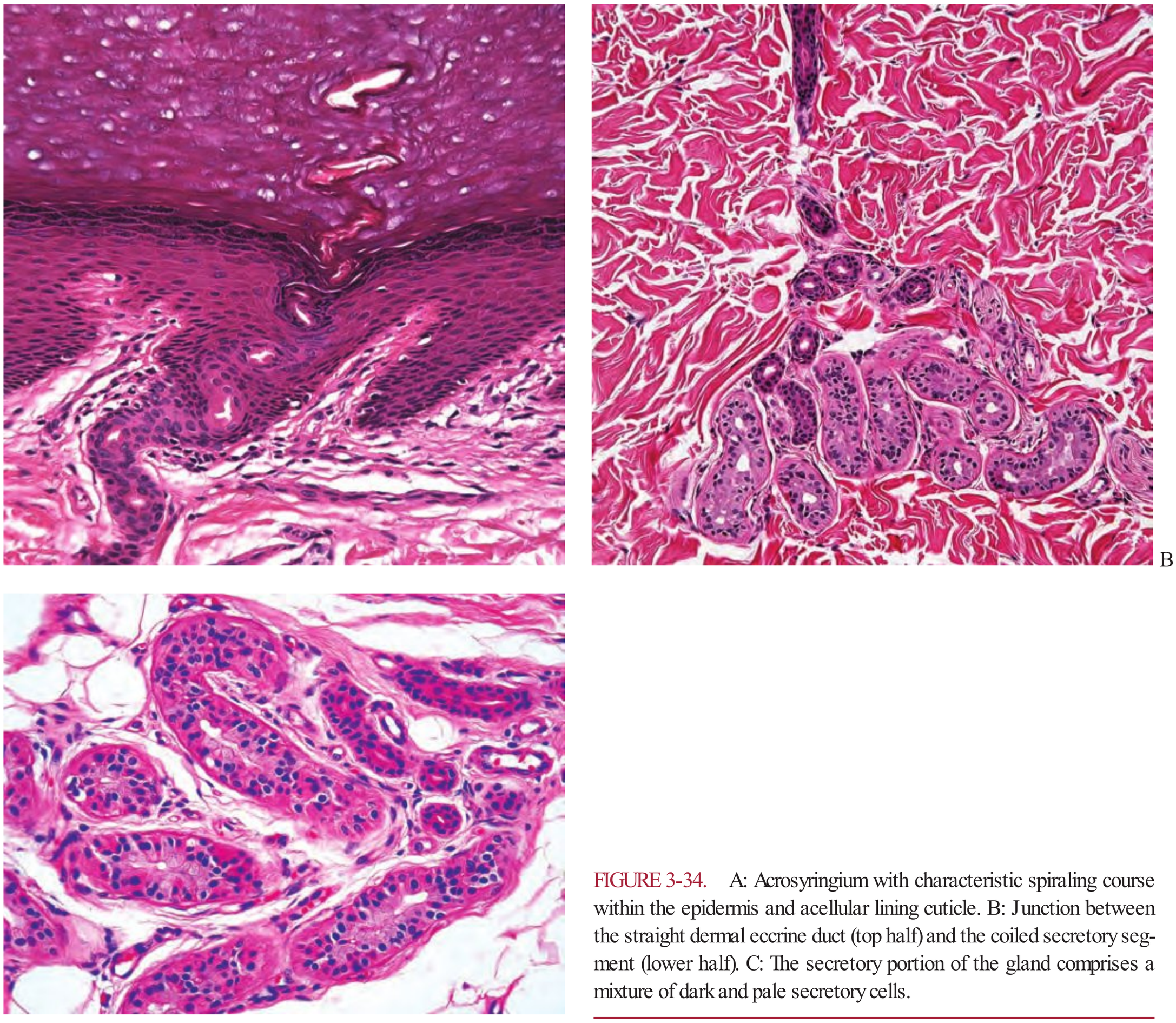


FIGURE 3-34. A: Acrosyringium with characteristic spiraling course within the epidermis and acellular lining cuticle. B: Junction between the straight dermal eccrine duct (top half) and the coiled secretory segment (lower half). C: The secretory portion of the gland comprises a mixture of dark and pale secretory cells.

skin surface is greatly aided by myoepithelial contraction (191). Peripheral to the myoepithelial cells lies a hyaline basement membrane zone containing collagen fibers. The transition from the secretory to the ductal epithelium is abrupt (Fig. 3-34B). The lumen of the secretory portion of the eccrine gland, measuring approximately 20 μm in diameter, is small in comparison with that of the apocrine gland (compare Figs. 3-34C and 3-36). The lumen of the eccrine duct measures about 15 μm across.

Apocrine glands are tubular glands, the secretory cells of which pass through various stages. Schiefferdecker, who in 1917 first described these glands, observed that, during secretion, part of the cell was pinched off and released into the lumen (192). He referred to this process as decapitation secretion. He chose the name apocrine for these glands to indicate that part of the cytoplasm of the secretory cells was pinched off ("apo" = "off").

Apocrine glands, like eccrine glands, are composed of three segments: the intraepidermal duct, the intradermal duct, and the secretory portion. Because apocrine glands originate from the hair germ, or primary epithelial germ, the duct of an apocrine gland usually leads to a pilosebaceous follicle, entering it in the infundibulum, above the entrance of the sebaceous duct. An occasional apocrine duct, however, opens directly on the skin surface close to a pilosebaceous follicle. In contrast to eccrine glands, the basal coil of apocrine glands, which is located in the subcutaneous fat, is composed entirely of secretory cells and contains no ductal cells.

The ductal portion of the apocrine glands has the same histologic appearance as the eccrine duct, showing a double layer of basophilic cells and a periluminal eosinophilic cuticle (Fig. 3-36). The intrafollicular or intraepidermal portion of the apocrine duct is straight and not spiral in appearance, as is the intraepidermal eccrine duct.

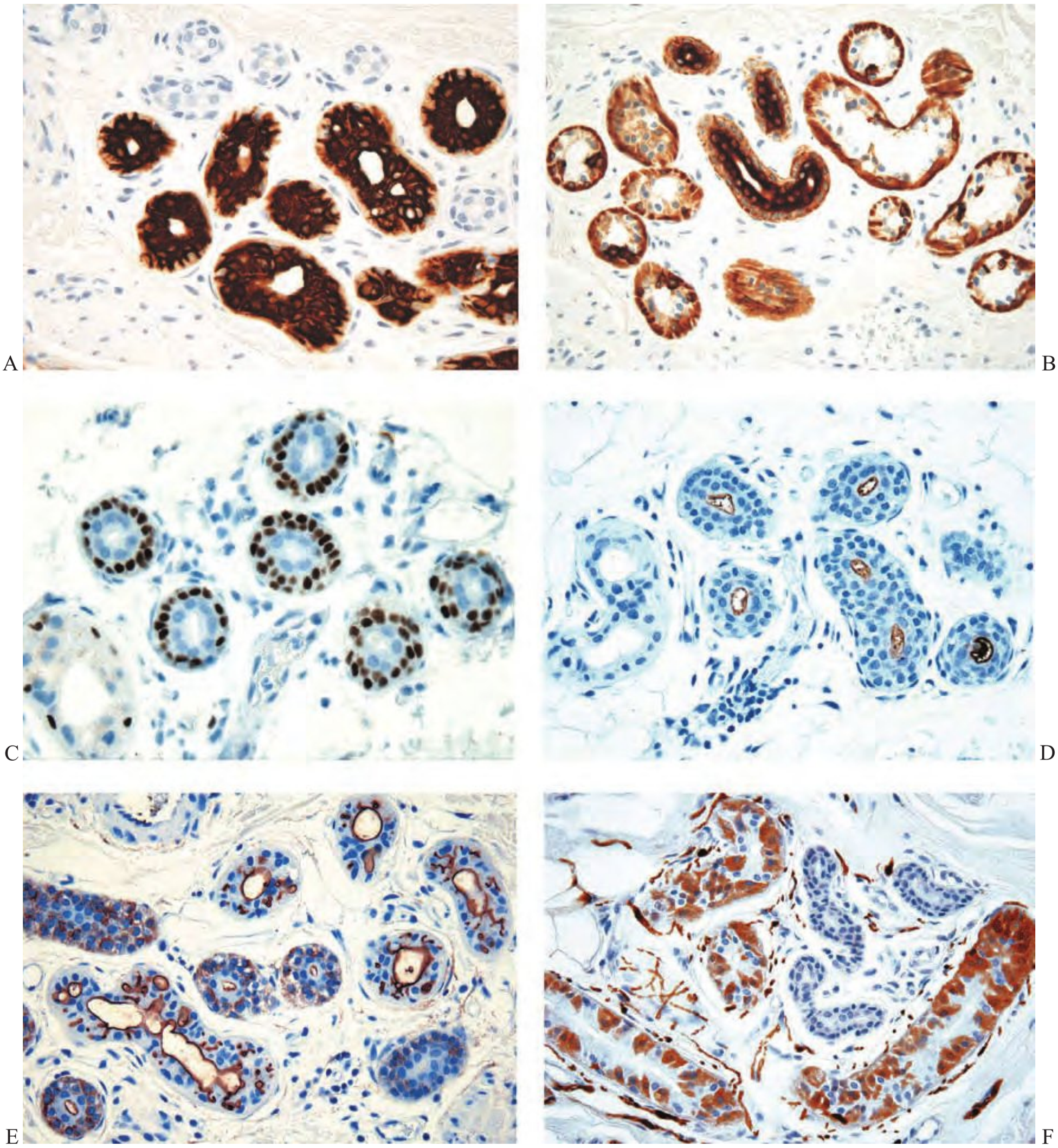


FIGURE 3-35. Immunohistochemistry of eccrine glands. A: Cytokeratin 7 shows strong immunopositivity of the secretory portion, whereas the ductal portion is negative. B: With cytokeratin 34 β E12, there is a preferential staining of the most basally located cells in the secretory portion. The ductal cells are strongly positive. C: p63 immunostain shows strong expression by the most basally located cells in the ductal portion, scattered positive nuclei in the secretory portion of the eccrine glands. D: Carcinoembryonic antigen immunostain shows a classical luminal expression pattern. E: Epithelial membrane antigen immunohistochemistry. Characteristic canalicular pattern. F: S100 protein is expressed by some of the secretory cells. The surrounding stroma contains delicate S100-positive nerves.

The secretory portion of the apocrine gland shows a single layer of secretory cells because the outer layer of cells consists of myoepithelial cells, just as in the eccrine gland. The secretory cells vary greatly in height, depending on the stage of secretion. Variation in height may be seen even in the cross section of the same secretory tubule (193). The secretory cells possess an eosinophilic cytoplasm. Except in the apical portion, they contain in their cytoplasm fairly large, PAS-positive, diastase-resistant granules, which appear much larger than similar granules seen in the dark secretory cells of eccrine glands. In addition, the apocrine

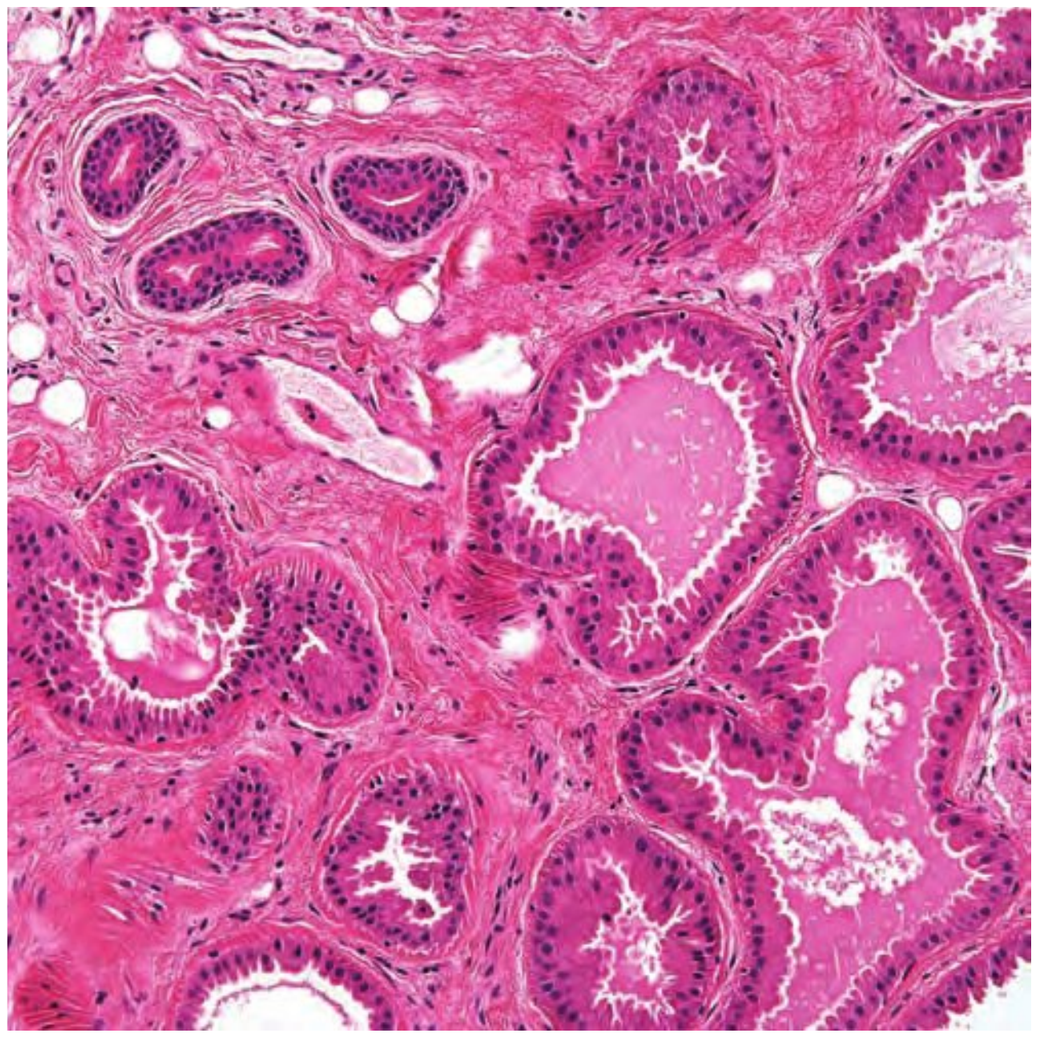


FIGURE 3-36. Apocrine glands. The secretory portion shows typical decapitation-type secretion. The ductal portion is indistinguishable from the ductal portion of the eccrine glands.

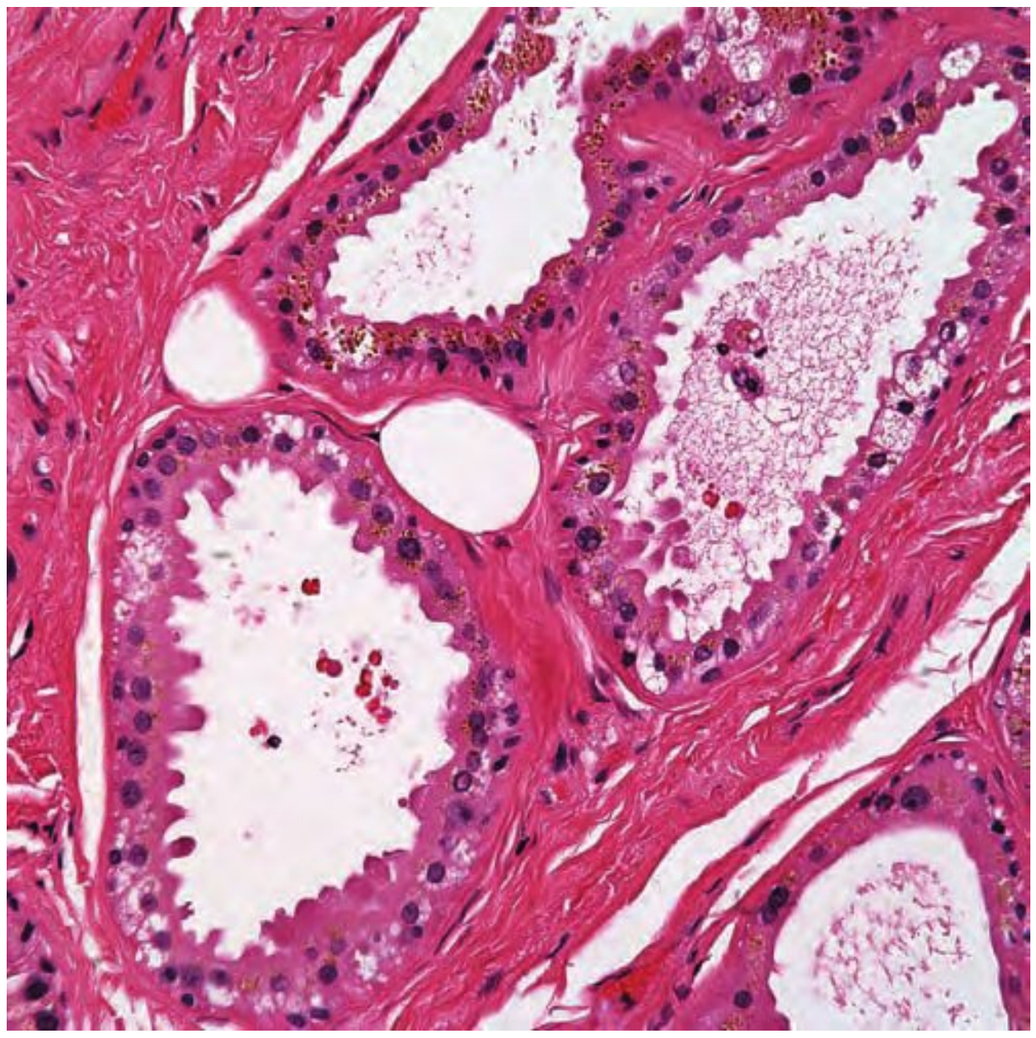


FIGURE 3-37. Ceruminous glands are modified apocrine glands found in the external ear canal. Note the lipofuscin pigment in the cytoplasm of apocrine cells.

granules frequently contain iron. Maturation of the secretory cells is indicated by the formation of a dome-shaped apical cap (Fig. 3-36). The type of secretion occurring in apocrine glands consists of the release of portions of cytoplasm into the lumen. Because of the cytoplasm in the secretion, apocrine secretion, in contrast to eccrine secretion, is visible in histologic sections stained with hematoxylin-eosin. The apocrine secretion contains amorphous, PAS-positive, diastase-resistant material originating from the granules that have dissolved in the apical portion of the secretory cells (194). This PAS-positive material, like the secretion of the dark cells in eccrine glands, consists of sialomucin.

The third type of sweat gland designated as the apoeccrine sweat gland shows a segmental or diffuse, apocrine-like dilation of its secretory tubule but has a long and thin duct that does not open into a hair follicle. The electron microscopy of its dilated segment is often indistinguishable from that of the classical apocrine gland. The less remarkably dilated segment of the apoeccrine gland tends to retain intercellular canaliculi and/or dark cells (184).

Regional Variation

Eccrine glands are present everywhere in the human skin; however, they are absent in areas of modified skin that lack all cutaneous appendages, that is, the vermilion border of the lips, the nail beds, the labia minora, the glans penis, and the inner aspect of the prepuce. They are found in greatest abundance on the palms and soles and in the axillae.

Apocrine glands are encountered in only a few areas: in the axillae, in the anogenital region, and as modified glands in the external ear canal (ceruminous glands) (Fig. 3-37), in the eyelid (Moll's glands) (see Fig. 3-62D), and in the breast (mammary glands). Occasionally, a few apocrine glands are found on the face, in the scalp, and on the abdomen; they usually are small and nonfunctional (195). Apocrine glands develop their secretory portion and become functional only at puberty. Each of the multiple protuberances present in the areola of the female breast and referred to as Montgomery's areolar tubercles contains a lactiferous duct and several superficially located sebaceous lobules whose ducts lead into the lactiferous duct (196,197).

Specialized Structure and Function

The eccrine sweat gland is engineered for temperature regulation (198). With approximately 3 million glands in the human integument weighing 35 μg/gland, the average human boasts about 100 g of eccrine glands capable of producing a maximum of approximately 1.8 L of sweat/hour! The eccrine secretory coil is richly invested in a stroma rich in unmyelinated nerve fibers, which are believed to play an important role in regulation of sweat production. Cholinergic stimulation of eccrine clear cells has been shown to increase cytosolic Ca^{2+} in a biphasic manner. This results in stimulation of both K^+ and Cl^- membrane channels, resulting in a net efflux of KCl along with Na^+ from the cell. Such electrolyte shifts, associated with water loss, underscore major metabolic implications of excessive eccrine sweating. Aside from potentially critical temperature regulation, the eccrine gland may contribute to general cutaneous homeostasis. For example, patients with congenital

anhidrotic ectodermal dysplasia suffer from heat intolerance that cannot be alleviated by simply adding moisture to the skin surface, suggesting that vasodilation associated with sweating may in some way be linked to eccrine function (198). There is abundant biologically active IL-1 in sweat (199), as well as numerous proteolytic enzymes, raising the possibility that eccrine sweat may possess proinflammatory or protective functions.

The mechanisms and rationale for apocrine-type secretion remain elusive. Schaumburg-Lever and Lever found three types of secretion (193): merocrine, apocrine, and holocrine. In the apocrine type of secretion, three stages were observed: formation of an apical cap, formation of a dividing membrane at the base of the apical cap, and formation of tubules above and parallel to the dividing membrane, supplying a new plasma membrane for both the undersurface of the apical cap and the top of the residual cell, bringing about detachment of the apical cap. Convincing proof of the detachment of entire apical caps in apocrine glands was provided through scanning microscopy by Inoue (200), who observed on each secretory cell a cytoplasmic luminal protuberance about 2 μm in diameter. In the early stage of secretion, the protuberance was hemispheric, but it later increased in height to form a linguiform process.

Why apocrine glands undergo the cellular complexities of decapitation secretion and the functional raison d'être for apocrine secretion in humans remain an enigma, although they may simply be an evolutionary vestige (musk glands of the deer and scent glands of the skunk are modified apocrine-type structures). The characteristic odor in human axillary sweat has recently been shown to reside in volatile C_6-C_{11} acids, with the most abundant being 3-methyl-2-hexenoic acid (201). This initially odorless apocrine secretion is formed at the skin surface from protein precursors via saponification or bacteriolysis. Such chemical interactions are similar to those in lower mammals, in which secreted proteins act as carriers of one or more pheromone signals.

Special Stains

Eccrine and apocrine glands and their products can be identified using special histochemical, enzymatic, and immunohistochemical stains (202,203). With PAS stain the clear secretory cells show a dense, globular PAS-positive material when glycogen is present (there is a depletion of glycogen after sweating). The dark cells show a finely granular, PAS-positive and diastase-resistant cytoplasm that is also seen with acid-fast stains. The ductal cells of eccrine and apocrine glands show a more variable staining with PAS (204). PAS stains the basement membrane of both eccrine and apocrine ducts. PAS stains of the secretory apocrine component vary from negative to focally positive; they can show a markedly positive granularity with iron and acid-fast stains. The mucicarmine stain is usually noncontributory. Enzymatic stains in fresh tissue such as amylophosphorylase and succinic dehydrogenase are very rarely used in routine surgical pathology (204).

Immunohistochemical stains (Figs. 3-35A–F) show that carcinoembryonic antigen is expressed in the luminal border of eccrine and apocrine ducts; it is also expressed in the intercellular canaliculi and cytoplasm of some eccrine secretory cells but is usually negative in secretory apocrine cells (Fig. 3-35D). A characteristic canalicular pattern is observed with epithelial membrane antigen (Fig. 3-37E). Cytokeratins of low molecular weight such as CK7 and CAM 5.2 are expressed only by the secretory portion of both eccrine and apocrine glands (Fig. 3-35A); however, they are not expressed by their excretory ducts. Keratin AE1 stains the secretory and ductal cells of both eccrine and apocrine glands. Keratin 34 β E12 is expressed by ductal cells and basal cells of the secretory portion (Fig. 3-35B). p63 is expressed by basal cells (but not luminal cells) of the ductal portion and only scattered cells of the secretory portion (Fig. 3-35C). The expression of S100 protein is seen in some of the secretory cells of the eccrine glands (Fig. 3-35F) but not in apocrine glands. However, in sections of the axilla, some larger glands do show S100 staining; these may represent apoeccrine glands (204). The myoepithelial cells express smooth muscle actins.

Specialized Keratinization: Nails

The nail unit is a region of specialized keratinization of practical importance because dermatosis, infections, and neoplasms may affect this region, prompting histologic sampling (205). The nail unit has six main components (Figs. 3-38 and 3-39): (a) the nail matrix, which gives rise to the nail plate; (b) the nail plate; (c) the cuticular system, consisting of the dorsal component, or cuticle, and the distal component, or hyponychium; (d) the nail bed, which includes the dermis and underlying bone and soft tissue beneath the nail plate; (e) an anchoring system of ligaments between bone and matrix proximally and between distal grooves distally; and (f) the nail folds proximally, laterally, and distally.

The proximal nail fold is a wedge-shaped fold of the skin on the dorsum of the distal digit underneath where the nail

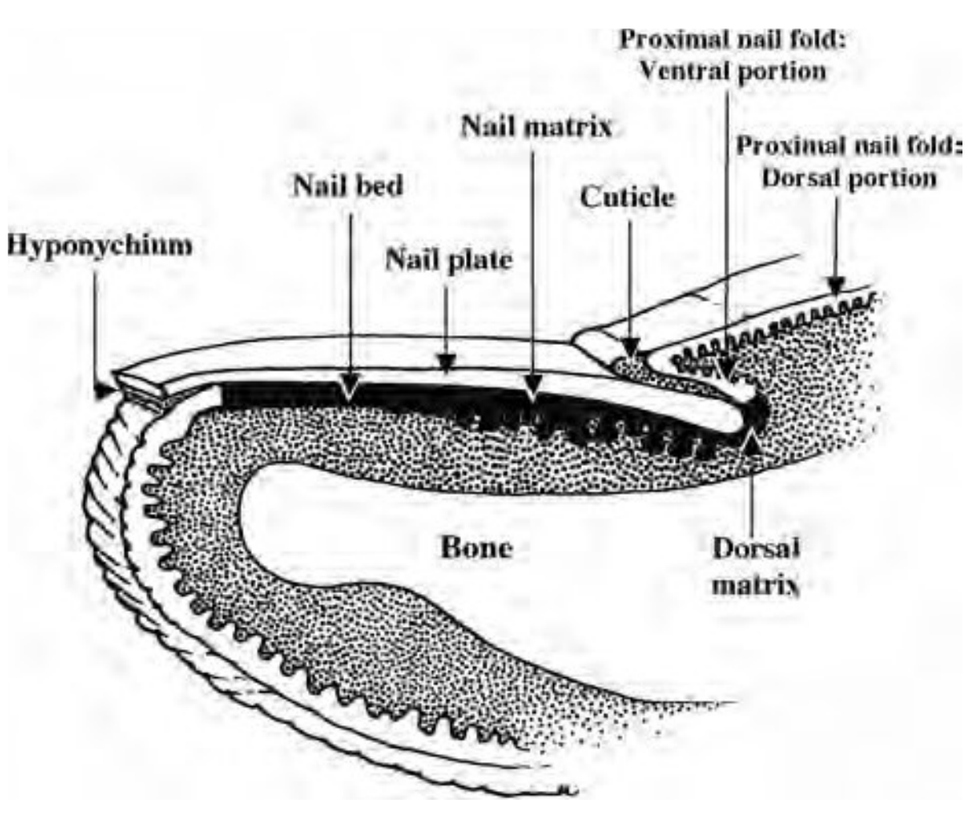
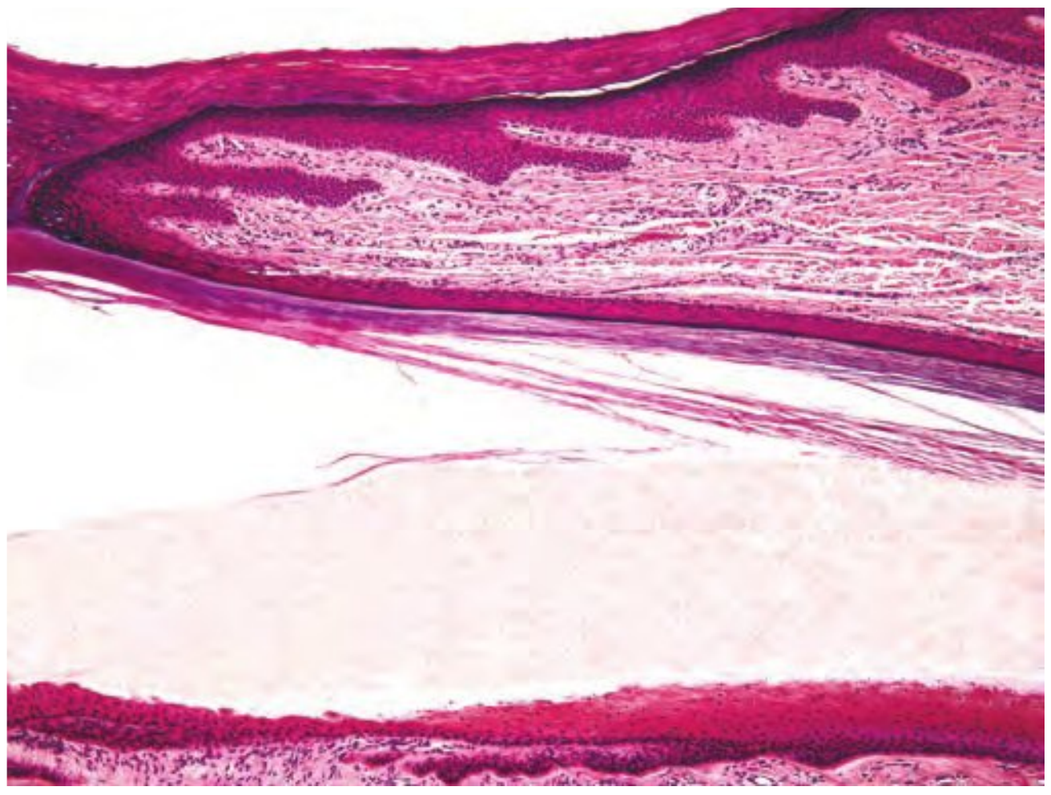


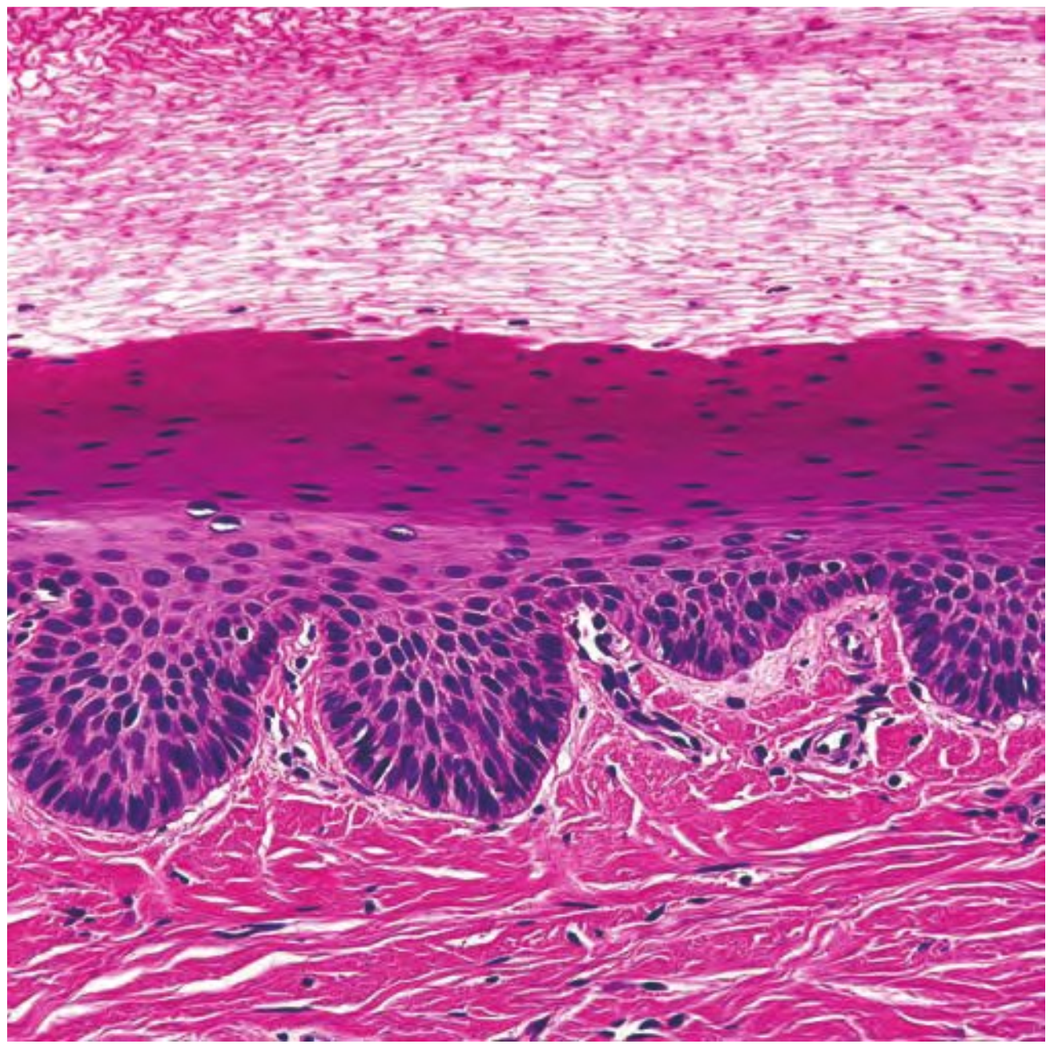
FIGURE 3-38. Diagram of the nail unit.



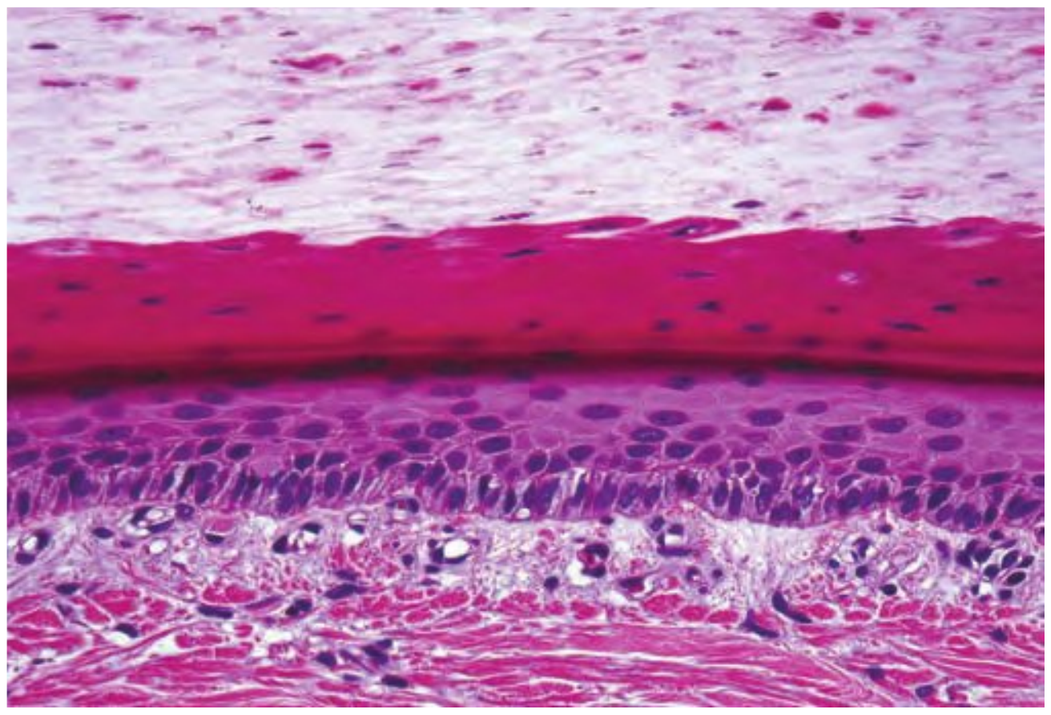
A



B



C



D

FIGURE 3-39. A: Low-power view of a transverse section of the distal portion of a finger including the nail unit. Overlying the nail bed is a thick, acellular nail plate. The lateral folds can be appreciated on both sides. B: Proximal nail fold forming the roof of the nail groove. Note the presence of granular layer on the dorsal and ventral surfaces. The floor of the nail groove corresponds to the nail matrix. Between the two structures lies the nail plate. C: Nail matrix. Note the lack of granular layer and presence of multilayered germinative basal cells. D: Nail bed. Note the lack of granular layer. The epithelium shows a paucity of germinative basal cells.

plate arises. It consists of two layers of epidermis, both of which show a granular layer. The dorsal surface proximal nail fold contains eccrine but not pilosebaceous units and undergoes epidermal-type keratinization with an intervening granular cell layer, resulting in the production of soft keratin. Its ventral surface or eponychium is devoid of rete ridges and appendages. Keratohyalin granules are present in the epidermis of the ventral proximal nail fold, which produces the semihard keratin of the cuticle. The ventral surface of the proximal nail fold forms the roof of the proximal nail groove. The floor of the proximal nail groove is formed by the nail matrix, and the nail plate lies between the two (Figs. 3-38 and 3-39B).

The nail matrix is responsible for the production of the "hard keratin" of the nail plate. This occurs via a process termed onychokeratinization, and, as in trichilemmal keratinization, it occurs by accretion of tonofilaments without the

formation of intervening keratohyalin granules (206,207). This process involves thickening of the cellular envelope of the keratinizing cells to form a marginal band, analogous to similar changes in the surface epidermis (208). The nail matrix may be divided into two regions—one distal, responsible for the formation of the ventral portion of the nail plate and clinically visible (the lunula), and the other proximal and responsible for the formation of the dorsal surface of the nail plate. The nail thickness is determined predominantly by the matrix, although one study suggested that the nail bed may contribute up to 20% as the nail grows (209). The matrix epithelium contains an upper, broad keratogenous zone containing flattened eosinophilic keratinocytes and a basal compartment with active germinative cells (Fig. 3-39C). Compared to the epidermis, this basal compartment is multilayered (210). Melanocytes are present in the distal portion of the nail matrix (211), and Langerhans cells and Merkel cells have also been identified in this region (206).

The nail bed begins at the distal lunula and ends distally at the hyponychium. It also exhibits onycholemmal-type keratinization. The nail bed epidermis is usually thinner than the matrix epidermis, with less prominent basal layer and no melanocytes (Fig. 3-39D). The surface of the bed typically shows parallel longitudinal grooves that correlate with interdigitation of underlying rete ridges and dermal papillae. Clinically, the onychodermal band signifies the separation of the nail plate from the hyponychium, where the normal volar epidermis and epidermal-type keratinization resumes.

The nail plate consists of closely packed, adherent, interdigitating corneocytes lacking nuclei or organelles. Desmosomal junctions are identified.

Recent immunohistochemical studies revealed two types of tissue compartments in the nail unit—compartments that exclusively express epidermal keratins, and others exhibiting a varying, mixed expression of epidermal and hair keratins (210).

DERMIS

The cellular components (resident cells) of the dermis comprise the following:

- Fibroblasts
- Dermal dendritic cells
- Macrophages
- Mast cells

The extracellular components comprise the following:

- Collagen
- Elastic fibers
- Ground substance

The dermis is a dynamic, supportive connective tissue composed of an extracellular matrix that includes collagen, elastic fibers, and ground substance intimately associated with a cellular component that is mainly composed of fibroblasts, myofibroblasts, macrophages, dermal dendritic cells, and mast cells (Figs. 3-40 to 3-55). Within the dermis, there are also epidermal appendages with their connective tissue sheath, arrector pili muscles, blood vessels and nerves, and their end organs. The dermis consists of two layers: the papillary dermis and the reticular dermis. The papillary dermis represents a thin zone beneath the epidermis (and between the rete ridges) (Figs. 3-5 and 3-47). The reticular dermis, which is thicker, lies between papillary dermis and the subcutaneous adipose tissue (Figs. 3-4 and 3-58). The adventitial dermis combines the papillary and periadnexal dermis. The papillary dermis and the epidermis together form a morphologic and functional unit whose interrelatedness is reflected in their alteration jointly in various inflammatory processes, for example, interface dermatitides such as lichen planus and erythema multiforme (Chapters 7 and 9). An analogous relationship exists between adnexal epithelium and periadnexal connective tissue (the "adventitial dermis") (212).

Dermal Fibroblasts

The dermis of a 2-month-old embryo consists of loosely arranged mesenchymal cells that are embedded in ground substance. During the third month, argyrophilic reticulum fibers appear. As these fibers increase in number and in thickness, they arrange themselves in bundles that no longer can be impregnated with silver and, instead, stain with the methods for collagen. Simultaneously, the mesenchymal cells develop into fibroblasts. Electron microscopic examination of the fetal dermis from week 6 to week 14 reveals, apart from Schwann cells identified by their association with neuraxons, three main types of cells: (a) stellate mesenchymal cells with long processes, (b) phagocytic macrophages of probable yolk-sac origin, and (c) cells containing granules, which could be either melanoblasts or mast precursors. From week 14 on, fibroblasts become numerous. In the normal adult dermis, fibroblasts appear as inconspicuous bipolar spindle cells with elongated ovoid nuclei. They cannot reliably be distinguished from other dermal spindle-shaped and dendritic cells. By electron microscopy, fibroblasts that actively synthesize collagen have a prominent rough endoplasmic reticulum composed of many membrane-lined cisternae with large numbers of attached ribosomes (Fig. 3-40B). The dilated cisternae are filled with an amorphous material produced by the ribosomes lining the cisternae (213). This apparently amorphous material consists of triple-helical procollagen molecules, each molecule being composed of three pro–α-polypeptide chains. The procollagen molecules pass from the cisternae of the rough endoplasmic reticulum to the Golgi area, whence they are excreted into the extracellular space by means of secretory vesicles (214,215). Conversion of procollagen molecules into collagen molecules composed of three α chains then occurs outside the cell (216). Immunohistochemically, fibroblasts express vimentin. CD10 immunoreactivity is normally found in periadnexal fibroblasts. Active, regenerative fibroblasts (e.g., in granulation tissue) disclose ultrastructural and immunohistochemical features of myofibroblasts (217). Myofibroblasts may express, in addition

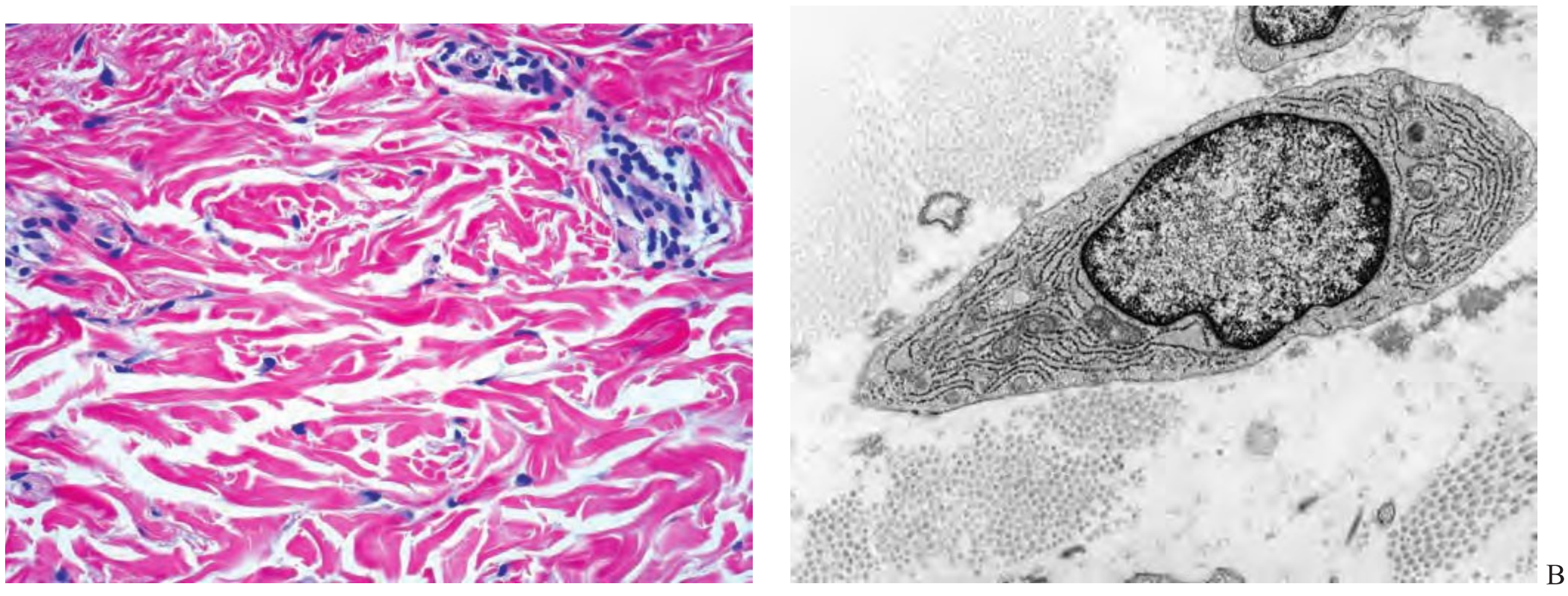


FIGURE 3-40. A: Scattered fibroblasts are present among thick collagen bundles in the reticular dermis. B: Dermal fibroblast viewed by transmission electron microscopy, showing dilated cisternae of rough endoplasmic reticulum and surrounding collagen fibers on cross section.

to vimentin, smooth muscle actin and desmin. Whereas resting fibroblasts may be difficult to differentiate from other dermal spindle cell elements, stimulated fibroblasts may be detected at transcriptional and posttranscriptional levels by probes that identify components involved in active collagen synthesis.

Perivascular and Interstitial Dendritic Cells

In 1986, Headington introduced the term "dermal dendrocyte" to denote newly recognized dendritic cells in the human dermis (218). These cells were primarily but not exclusively perivascular in location and differed from conventional bipolar fibroblasts by their stellate contours. Some of these cells appeared to represent "veil cells," which enshrouded venular walls with thin membrane flaps, as originally described by Braverman et al. (219). Many of these cells were subsequently shown to express the membrane glycoprotein CD1c (220), HLA-DR, and certain macrophage markers as well as the cytoplasmic transglutaminase, factor XIIIa (221) (Fig. 3-41). Heterogeneity of dermal dendrocytes within different dermal strata with regard to their expression of the hematopoietic progenitor antigen, CD34, and FXIIIa has been described (222). Per conventional immunohistochemistry, factor XIIIa–positive cells are predominantly found in perivascular distribution in the papillary dermis and around sweat glands. Although their presence is not specific, factor XIIIa–positive cells have been detected in increased numbers in numerous pathologic conditions, including Kaposi's sarcoma, dermatofibroma, and scar formation. CD34-positive cells are more numerous in the mid and deep dermis and around adnexae (223).

Whereas dermal dendrocytes are dendritic only in cross section, with three-dimensional reconstructions showing elaborate membranous flaps (222), truly dendritic cells also exist in the perivascular space. These cells are Langerhans cell-like, although they generally do not contain Birbeck granules, strongly express HLA-DR, and are believed to be involved in dermal antigen presentation (224). Considerable plasticity among the various subpopulations of dermal perivascular dendritic cells may exist, and alterations in local microenvironment may induce phenotypic transformation from one subtype to another (225).

In general, perivascular dendritic cells are not identifiable as such in routinely prepared and stained sections, although immunohistochemistry for the relevant markers permits the ready identification and classification of these cell types. Dermal dendrocytes may be observed in certain situations in which

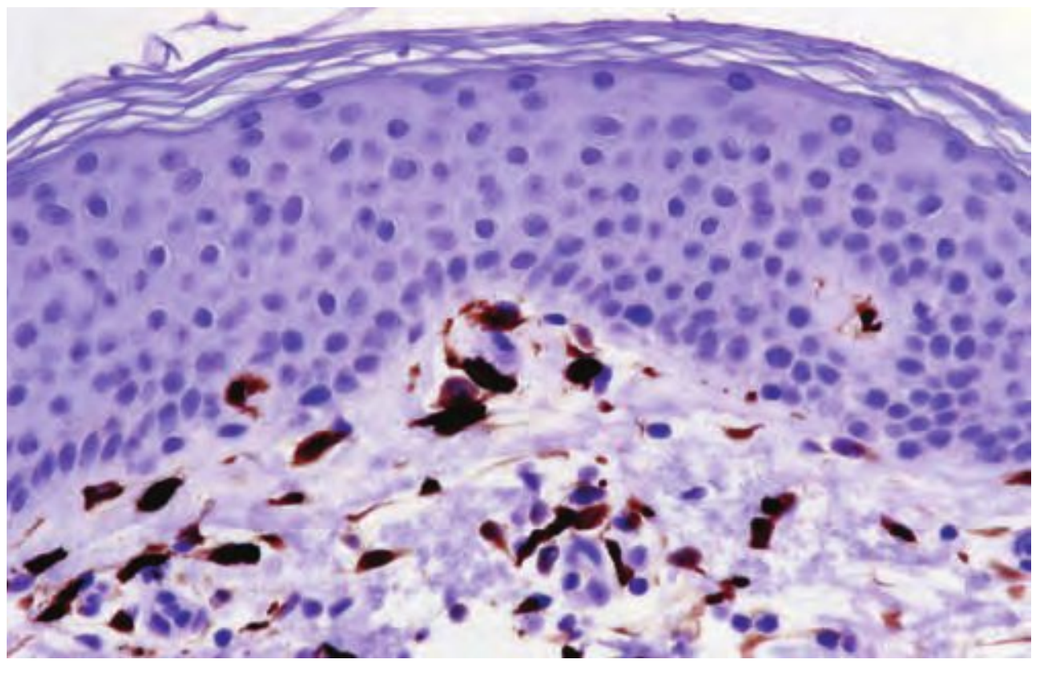


FIGURE 3-41. Factor XIIIa–positive "dermal dendrocytes" concentrated beneath the epidermal layer and about the dermal microvascular unit.

they acquire avid phagocytic potential, taking up hemosiderin, for example. Such phagocytic perivascular dendritic cells have been termed "dendrophages" (226).

Phagocytic Macrophages

Macrophages, also called histiocytes, are of bone marrow origin, circulate in the blood as precursors, and enter the tissue as monocytes (227). On proper stimulation, monocytes can develop into macrophages in the skin, which involves a considerable increase in cell size and changes in cellular composition and architecture, including increases in lysosomal enzymes, such as β-glucuronidase, acid phosphatase, lysozyme, and aryl sulfatase (228). Macrophages may develop further into epithelioid histiocytes and foreign body giant cells. Aggregates of activated macrophages are referred to as granulomas. Macrophages are most often concentrated in the perivascular space of normal skin, although, depending on the nature and location of the stimulus for their activation, may be found anywhere in the dermis (or epidermis).

Macrophages constitute the "mononuclear phagocytic system," a concept that has replaced that of the reticuloendothelial system. The macrophages of the mononuclear phagocytic system, including the alveolar phagocytes in the lungs and the Kupffer cells in the liver, are the "professional" phagocytes, whereas the reticuloendothelial cells, including the dendritic reticulum cells in lymph nodes and the endothelial cells of blood vessels, are merely "facultative" phagocytes and are comparatively inadequate (228). As "professional" phagocytes, macrophages are capable of ingesting large particles and developing a high concentration of lysosomal enzymes, which combine with the particles to form phagolysosomes. In contrast, the facultative phagocytosis carried out by endothelial cells consists merely of pinocytosis of small particles without immune stimulation (228). Macrophages can also be stimulated by immunologic factors having surface receptors for the Fc portion of IgG, for C3, and for immune-associated HLA-DR antigen (human leukocyte antigen-D subregion of the major histocompatibility complex) (229).

Monocytes are indistinguishable by routine histology from lymphocytes because both cells have a small, dark, rounded nucleus and very scanty cytoplasm that cannot be recognized in routine sections. Only slightly larger than lymphocytes, monocytes measure 12 to 15 μm in diameter (229). Monocytes can be differentiated from lymphocytes in histologic sections through staining for lysosomal enzymes, such as acid phosphatase, which are present in monocytes and absent in lymphocytes. In addition, monocytes but not lymphocytes express intracytoplasmic molecules probably associated with lysosomes, such as CD68 and KP1. Such antibodies, however, are generally regarded as organelle rather than cell lineage specific and are not considered exclusive markers of cells of monocyte/macrophage derivation (230). A more recently described monocytic/macrophagic marker is CD163, which is a glycoprotein belonging to the scavenger receptor cysteine-rich superfamily. CD163 is of particular interest because its expression has been shown by *in situ* hybridization, immunofluorescent, and immunohistochemical techniques to be largely restricted to monocytes and tissue macrophages (230). CD68, KP1, and CD163 may be detected immunohistochemically in paraffin sections (231).

Macrophages, because they are activated monocytes, are larger cells than monocytes and measure from 20 to 80 μm in diameter (229). They possess a vesicular, lightly staining, elongated nucleus with a clearly visible nuclear membrane. It is often impossible in routinely stained sections to distinguish macrophages from fibroblasts or from endothelial cells except through their respective locations or phagocytic activities. Macrophages that have ingested melanin are referred to as melanophages and may be observed normally within the papillary dermis of darkly pigmented individuals. Macrophages that have ingested hemosiderin are termed siderophage, and may be suspected due to the characteristic yellow-green color and refractile nature of particulate hemosiderin. Iron stains (e.g., Prussian blue) are confirmatory.

The origin of the tissue monocytes in human skin from blood monocytes has been established in healthy probands through transfusion of tritiated-thymidine–labeled monocytes and their observation 3 hours later in skin window exudates (232). On the other hand, the dermal infiltrate of monocytes and macrophages in patients with chronic dermatitis is largely self-renewing because the monocyte recruitment rate from the blood is low in these patients after the autotransfusion of labeled monocytes (232). Electron microscopic examination reveals in monocytes many primary lysosomes scattered through their cytoplasm as small dense bodies (233). Macrophages, which represent stimulated monocytes, differ from monocytes in that they are larger, show longer processes, and contain a greater number of lysosomes (234) (Fig. 3-42).

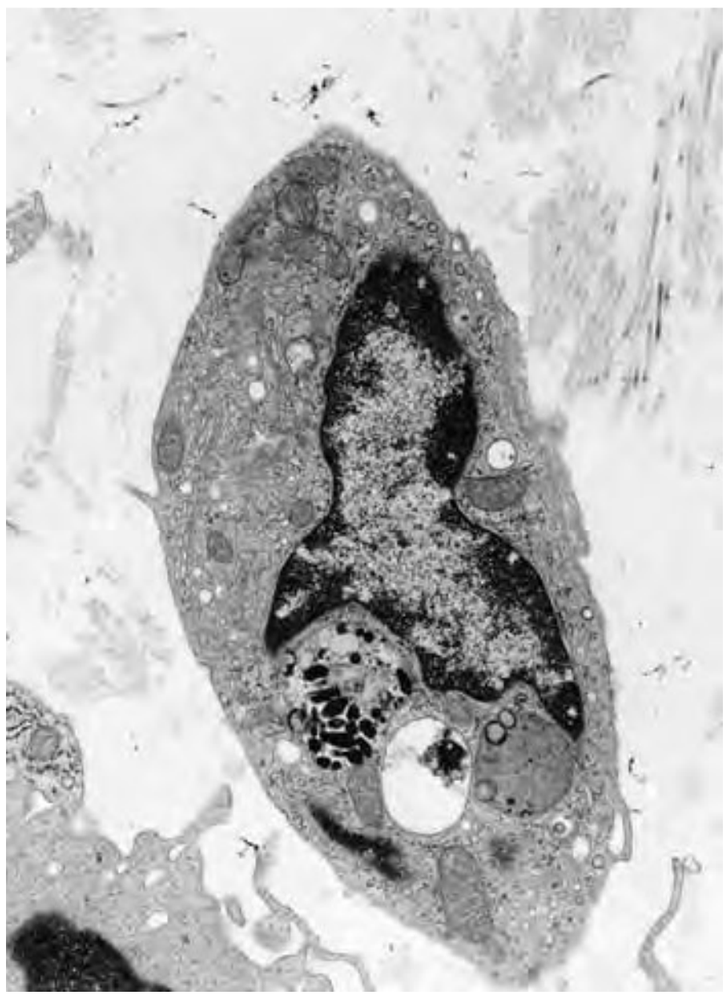


FIGURE 3-42. Ultrastructure of phagocytic macrophage within the dermis. Note the intracytoplasmic lysosomes associated with engulfed cell breakdown products, including a large vacuole containing internalized melanosomes.

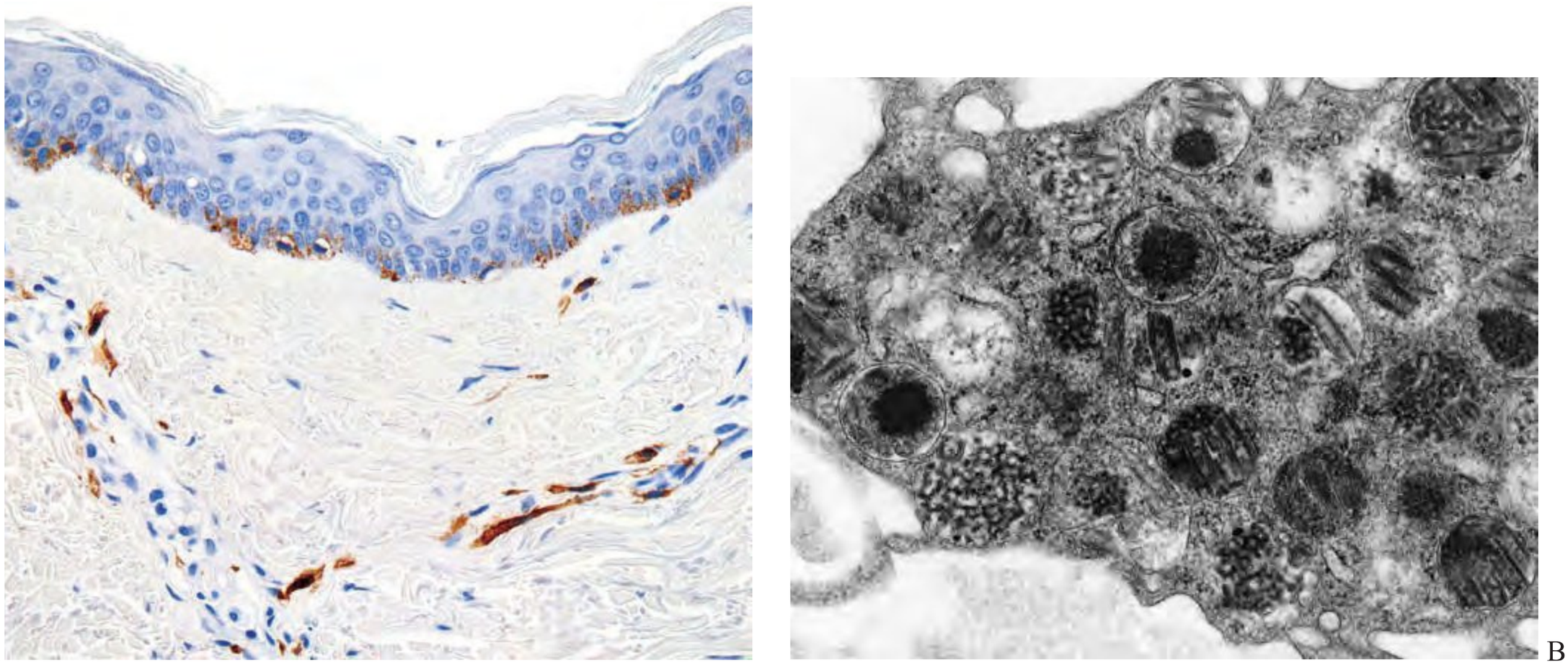


FIGURE 3-43. A: KIT (CD117) highlights dermal mast cells and junctional melanocytes. B: Transmission electron micrograph of a granulated mast cell.

Many macrophages contain phagocytized material within phagosomes, which, through the influx of the contents of primary lysosomes, have become phagolysosomes.

Mast Cells

Mast cells (Fig. 3-43) are bone marrow–derived cells that occur in the normal dermis in small numbers as oval to spindle-shaped cells with a centrally located round to oval nucleus. They are generally concentrated about blood vessels, specifically postcapillary venules (one to three cells per cross-sectional vessel profile). They contain in their cytoplasm numerous granules that do not stain with routine stains like hematoxylin-eosin. Therefore, mast cells in normal skin are not reliably distinguishable from other perivascular cells, although one can occasionally recognize in mast cells a small amount of cytoplasm and the cell membrane. The granules stain with methylene blue, which is present in the Giemsa stain, with toluidine blue, and with alcian blue. They also stain metachromatically with methylene blue and toluidine blue, that is, they stain in a color different from that possessed by the dye and appear purplish red rather than blue.

Electron microscopic examination of mast cells reveals numerous large and long villi at their periphery. The mast cell granules appear as round, oval, or angular-shaped, membrane-bound structures. Mature granules measure up to 0.8 μm in diameter (235) (Fig. 3-43B). They contain two components: lamellae and electron-dense, finely granular material (236). Tangential sectioning of the lamellae reveals paracrystalline lattices as a result of transverse banding. Immunoultrastructural observations indicate that the various granule subcompartments correlate with distribution of serine proteinases tryptase and chymase within granules (237). In addition, mast cells that populate connective tissue environments like dermis tend to contain granules with poorly formed scrolls and express both chymase and tryptase, whereas mast cells found primarily in mucosae and associated lamina propria have granules with well-formed scrolls and express tryptase but not chymase (238,239). Of interest, one of these two granule types may be preferentially expressed in some cases of mastocytosis (240).

Degranulation of mast cells occurs after cross-linking of IgE on the cell surface, exposure to neuropeptides such as substance P, after nonspecific mechanical or thermal stimuli, or after exposure to a variety of exogenous secretagogues (compound 48/80, calcium ionophore, morphine sulfate). Degranulation generally occurs within minutes of exposure of the cell membrane to the secretagogue and usually consists in the extrusion of entire granules, but some granules may undergo intracellular disintegration (235,241,242). Initial stages of degranulation consist in granule swelling with loss of internal substructure and electron density. Extrusion of granules takes place through extensive membrane fusion between the plasma membrane and perigranular membranes and is associated with formation of conduits resulting from fusion of the membranes of multiple granules. This results in extensive labyrinthine channels in the cell through which swollen, less electron-dense granules, all of which have lost their individual surrounding membranes, are released into the extracellular space (236,243). Concomitant with their release into the extracellular space, the granules release their preformed and stored mediators histamine, heparin, serine proteinases, and certain cytokines.

Immediate hypersensitivity reactions can be triggered by mast cells and basophils in "anaphylactically" sensitized persons through the presence on their cell surfaces of specific antibodies of the IgE type. When the specific antigen combines

with these antibodies, an anaphylactic reaction is elicited through the degranulation of mast cells and the release of histamine from the granules (244). Histamine increases the permeability of postcapillary venules and, if released in sufficient amounts, may produce an anaphylactic shock. In delayed hypersensitivity reactions and in experimental allogeneic cytotoxic reactions, mast cells degranulate early, often preceding the initial influx of pioneer lymphocytes (245,246). Part of the reason for this lies in the fact that human mast cells contain TNFα (247), and local release of TNFα as a consequence of mast cell degranulation induces expression of adhesion molecules such as E-selectin in adjacent postcapillary venules (248), with resultant leukocyte binding to the endothelial luminal membrane (249). Cooperation between the mast cell and the endothelial cell is also underscored by the observations that mast cells appear to situate in the laminin-rich perivascular space in association with expression of specific laminin receptors on their membranes (250), and that endothelial cells express mast cell growth factor (also known as c-kit ligand or stem cell factor) (251). CD117 (KIT) is a type III receptor tyrosine kinase operating in cell signal transduction in several cell types. Normally KIT is activated (phosphorylated) by binding of its ligand, the stem cell factor. This leads to a phosphorylation cascade ultimately activating various transcription factors in different cell types. Such activation regulates apoptosis, cell differentiation, proliferation, chemotaxis, and cell adhesion. KIT-dependent cell types in the skin include mast cells, some hematopoietic stem cells, melanocytes, scattered basal keratinocytes, and epithelial cells of skin adnexae (252) (Fig. 3-43A).

Emigrant Inflammatory Cells

Various types of cells, largely derived from the bone marrow, infiltrate the dermis and occasionally also the epidermis in the inflammatory dermatoses. Infiltration is initiated at the level of the dermal microvascular unit, accounting for the observation that on detection, such cells are often partially or exclusively perivascular in location (Figs. 3-44A–D). Such cells may also be present in normal skin in low numbers as part of the skin immune system. It is important for diagnostic purposes to identify the cell types because many diagnostic algorithms for dermatitis classification and identification depend on initial categorization by architecture followed by recognition of inflammatory cell type(s) (see Chapter 5) (253). Three groups of cells are derived from the bone marrow: the granulocytic group; the lymphocytic group, including plasma cells; and the monocytic or macrophagic group (discussed earlier).

Neutrophilic Granulocytes

The neutrophilic granulocyte, also called a neutrophil or polymorphonuclear leukocyte, is 10 to 15 μm in diameter and has a lobated nucleus consisting of several segments that are connected

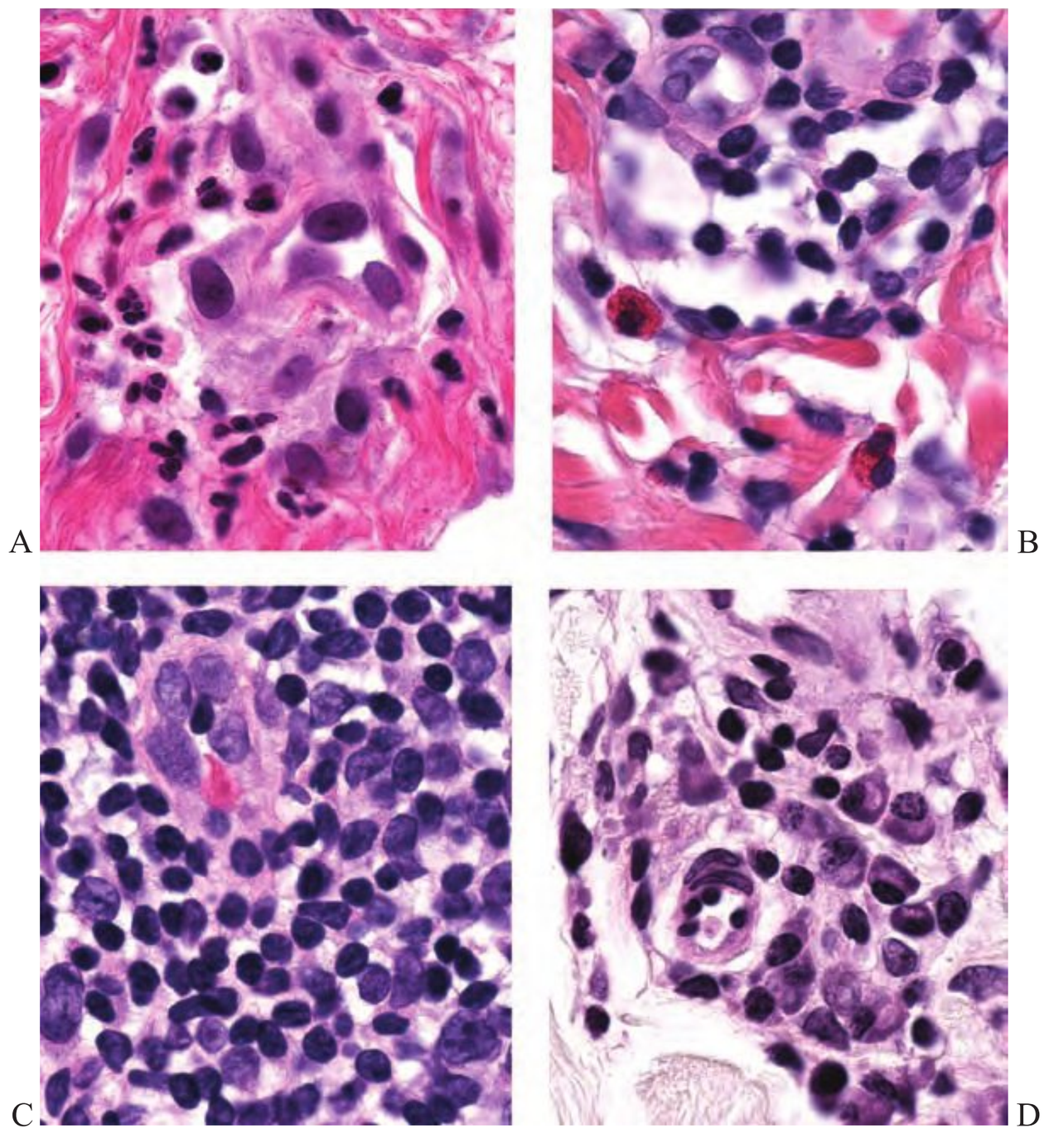


FIGURE 3-44. Emigrant inflammatory cells found in different common dermatitides include neutrophils (A), eosinophils (B), lymphocytes and histiocytes (C), and plasma cells (D).

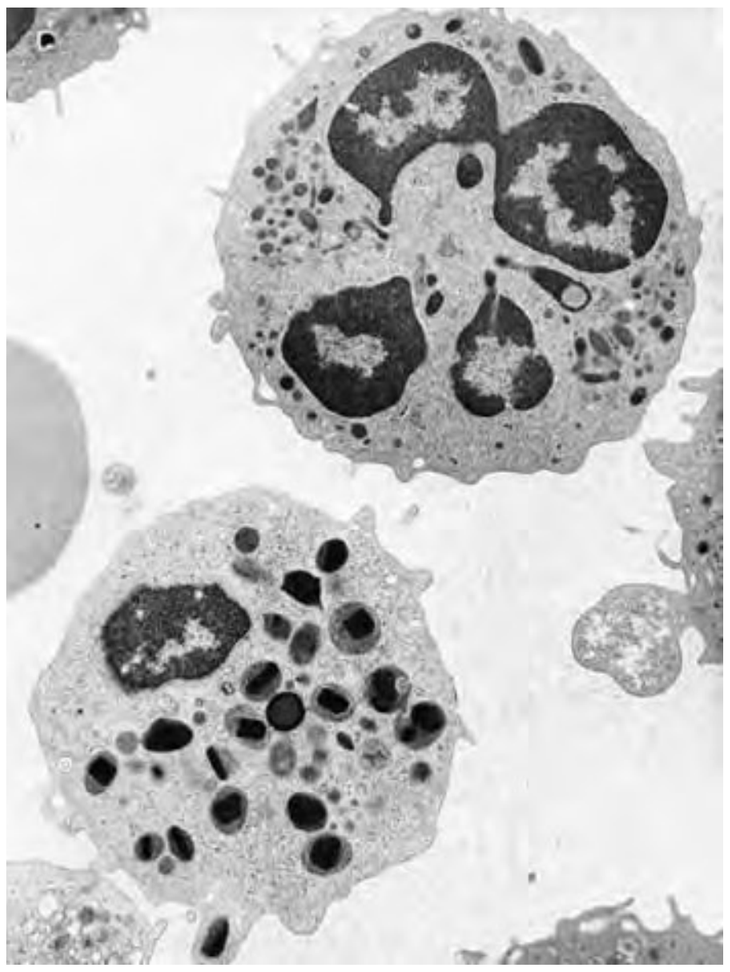


FIGURE 3-45. Ultrastructural comparison between neutrophilic (uppermost cell) and eosinophilic (lowermost cell) granulocytes.

only by narrow bridges of nucleoplasm (Fig. 3-44A). The cytoplasm contains numerous neutrophilic to slightly eosinophilic granules. On histochemical examination, the granules are seen to contain lysosomal enzymes and thus represent primary lysosomes. Two types of membrane-bound cytoplasmic granules or lysosomes are found to be present in neutrophils on electron microscopic examination: azurophilic and specific granules (254) (Fig. 3-45). The azurophilic granules, constituting about 20% of all granules, are relatively dense and large, measuring up to 1 μm in diameter. The more numerous specific granules average 300 nm in diameter. Among other substances, azurophilic granules contain (a) myeloperoxidase, which mediates the formation of hydrogen peroxide, essential for the killing of many microorganisms; (b) acid hydrolases, such as β-glucuronidase and acid phosphatase, capable of degrading dead bacteria and other necrotic material; (c) neutral proteases, such as collagenase and elastase, that may break down collagen and elastin; (d) cationic proteins, which cause an increase in vascular permeability; and (e) lysozyme, an enzyme that degrades and lyses bacterial cell walls. The specific granules also contain lysozyme and, in addition, collagenase, alkaline phosphatase, and lactoferrin, an iron-binding protein with bacteriostatic properties.

Neutrophils are unusual in normal skin but occur typically in a relatively small subset of dermatitides, including various cutaneous infections, urticaria, immune complex–mediated necrotizing vasculitis, and the spectrum of neutrophilic dermatosis (e.g., Sweet's syndrome, pyoderma gangrenosum). Neutrophils may participate, along with other cell types, in other inflammatory processes, such as psoriasis, seborrheic dermatitis, and pityriasis lichenoides et varioliformis acuta. In tissue sections, neutrophils are often recognized by virtue of their "popcorn"-shaped nuclei within pale pink, faintly granular cytoplasm. Nuclear breakdown due to local necrosis or autodigestion results in fragmentation of the multiple nuclear lobes, resulting in the characteristic "nuclear dust" of vasculitis.

Functionally, neutrophilic granulocytes play an important role in (a) certain inflammatory responses (examples were provided earlier), (b) the phagocytosis and killing of microorganisms, and (c) the immobilization and phagocytosis of antigen–antibody complexes in the presence of complement (255). Neutrophils fail to kill bacteria in chronic granulomatous disease, where they are congenitally incapable of oxygen uptake from the surrounding media (256). Phagocytosis of organisms and antigen–antibody complexes by neutrophils is accompanied by their partial or complete degranulation, with associated discharge of lysosomal enzymes (257). Endocytotic uptake of microorganisms by neutrophils results in the formation of intracytoplasmic phagolysosomes, where high enzyme concentrations result in microbial killing. Immune complexes, after activation of complement, may induce the local accumulation of neutrophils via chemotaxis. Phagocytosis of immune complexes by neutrophils and/or neutrophil degranulation may then occur (258). Exocytosis of neutrophil granules containing collagenase and elastase may result in local tissue damage, including necrosis of vessels containing immune complexes in their basement membranes (259).

Eosinophilic Granulocytes

The eosinophil, 12 to 17 μm in diameter, is characterized by strongly eosinophilic granules in the cytoplasm and a characteristically bilobed nucleus (260). Eosinophil granules are larger than the granules of neutrophils. Although visible with routine stains (Fig. 3-44B), these granules stand out more clearly in brilliant red when a Giemsa stain is used. On electron microscopic examination, the granules of eosinophils are seen to be round to oval. They consist of two components—a central, angular-shaped core, often referred to as the crystalloid, and a surrounding matrix. In electron microscopic sections stained with lead compounds, the crystalloid is more darkly stained than the matrix (261) (Fig. 3-45). The granules contain a variety of hydrolytic enzymes, particularly peroxidase and arylsulfatase, and therefore can be classified as lysosomes. The phagocytic potential of eosinophils seems to be limited to immune complexes and mast cell granules. During phagocytosis, which is analogous to that seen in neutrophils, the content of the eosinophilic granules is discharged into phagosomes (262).

Because eosinophils can phagocytize mast cell granules and certain antigen–antibody complexes, tissue eosinophilia in the skin can occur (a) as a result of anaphylactic or atopic hypersensitivity, (b) subsequent to the degranulation of mast cells, and (c) in certain diseases associated with deposits of antigen–antibody complexes in the skin. The tissue eosinophilia appearing in anaphylactic reactions and other forms of "immediate" allergy such as atopy is based on antibodies of the IgE type on the surface of mast cells. The anaphylactic reaction,

classified as type I hypersensitivity reaction (263), occurs after the binding of a specific antigen to a specific antibody on the surface of the mast cells. This leads to degranulation of mast cells and to the release of vasoactive substances, especially histamine. Wherever degranulation of mast cells occurs, eosinophils may appear and phagocytize the released mast cell granules (257). Eosinophils thus may modify an anaphylactic reaction (264). Eosinophils are attracted in an anaphylactic reaction by sensitized mast cells, which release an eosinophil chemotactic factor of anaphylaxis. Eosinophils thus attracted to the site of an anaphylactic reaction accumulate around degranulating mast cells and phagocytize the free mast cell granules (265).

Diseases in which deposition of antigen–antibody complexes is the cause of eosinophilia include pemphigus vulgaris, particularly pemphigus vegetans, pemphigus foliaceus, bullous pemphigoid (see Chapter 9), and granuloma faciale (see Chapter 8). The reasons for the occasional presence of tissue eosinophilia in histiocytosis X (see Chapter 6) and in Hodgkin's disease (see Chapter 31) are not fully apparent. Parasitic infestations often are associated with eosinophilia both in the peripheral blood and in the tissue (see Chapter 24). It is likely that eosinophils function as effector cells in parasite destruction (262). Destruction of parasites, such as those causing schistosomiasis, is accomplished by means of the major basic protein (MBP) of the eosinophils. The MBP is localized in the crystalloid core of the eosinophil granules and accounts for more than 50% of the protein in the granules and for almost 25% of the total protein in the cell. Its toxicity provides a mechanism by which the eosinophil damages parasites. Release of MBP from degranulating eosinophils, however, is not always beneficial to the host. Release of MBP may partly account for the tissue damage seen in chronic hypersensitivity reactions (266).

Basophilic Granulocytes

Although basophils and mast cells have similar or identical functions and supplement each other, they are different cells both in origin and in anatomy (267). Both cells have their origin in the bone marrow, although basophils circulate in the peripheral blood, and mature mast cells are confined to connective tissue and mucosal tissue compartments. Basophils are relatively rare in human dermatitis, although they are active participants in certain forms of dermatitis in rodents (267). The demonstration of basophils in light microscopic sections requires the use of electron microscopic fixation and processing techniques; biopsy specimens must be embedded in plastic resin and sectioned at 1 μm. The sections then are stained with the Giemsa stain. Basophils possess a multilobed nucleus and large, diffusely arranged metachromatic granules, whereas mast cells have a unilobed nucleus and smaller, peripherally located metachromatic granules (268).

Lymphocytes

There are two main types of peripheral lymphocytes—T and B lymphocytes—both of which arise in the bone marrow. One type migrates to the thymus, where it differentiates into a mature lymphocyte and then proceeds to the peripheral lymphoid tissues as a thymus-derived or T lymphocyte. In lymph nodes, T lymphocytes are located predominantly in the interfollicular cortex, also called the paracortical areas. The other type of lymphocyte—the B lymphocyte—matures in the bone marrow (269). The term B lymphocyte, meaning bursa-derived lymphocyte, originally was used because in birds the bursa of Fabricius is held responsible for B-cell maturation (269). In humans, the term B lymphocyte is used to indicate a bone marrow–derived lymphocyte. In lymph nodes, B lymphocytes largely occupy the lymphoid follicles, including their germinal centers. Whereas the T lymphocyte is the effector cell for cellular immunity, the B lymphocyte mediates humoral immunity. T cells can exert important regulating functions on both T cells and B cells in the form of specific functional subsets termed helper T cells and cytotoxic/suppressor T cells (270). The lymph nodes and other lymphoid organs share three principal functions to: (a) concentrate within them antigens from all parts of the body, (b) expose these antigens to naive and antigen-specific lymphocytes that circulate within them, and (c) deliver products of the immune response, namely the antibodies and cells mediating humoral and cellular immunity, respectively, to the blood and peripheral nonlymphoid tissues (269). Tissues that represent significant host–environmental interfaces, like skin and gut, are regular targets for physiologic T-cell trafficking mediated by tissue-specific homing receptors that interact with endothelial adhesion molecules (e.g., T-cell cutaneous lymphocyte-associated antigen and endothelial E-selectin in skin). This intimate homing relationship between central lymphoid organs and tissues like skin, in addition to resident populations of dendritic antigen-presenting cells (Langerhans cells) and effector cells (mast cells, see later discussion) is responsible for the concept of skin-associated lymphoid tissue.

Resting lymphocytes measure on average 8 to 10 μm in diameter and possess a relatively small, round nucleus that appears deeply basophilic because of the presence of numerous chromatin particles (Fig. 3-46). They have only a very narrow rim of cytoplasm that is difficult to delineate by conventional light microscopy. It is also usually not possible by light microscopy to distinguish lymphocytes from monocytes in routinely stained histologic sections. It is therefore preferable to refer to cells with a histologic appearance of lymphocytes as lymphoid cells, and infiltrates likely to contain significant admixtures of both lymphocytes and monocytes are sometimes referred to as involving mononuclear cells. Ultrastructurally, resting lymphocytes contain relatively few organelles within a thin cytoplasmic rim that surrounds a nucleus with coarsely aggregated heterochromatin (Figs. 3-44C and 3-46). Activated lymphocytes, on the other hand, may show enlarged, vesicular nuclei, visible nucleoli, and/or elaborately infolded nuclear contours that may bear some resemblance to Lutzner-Sezary cells.

The patterns of T- and B-cell infiltration in the skin are also of interest. In most inflammatory conditions, T cells are



FIGURE 3-46. Transmission electron micrograph of a mature lymphocyte; note the chromatin-rich nucleus and organelle-poor cytoplasm.

present primarily around blood vessels within the dermis and periadnexal adventitia. Migration into the epidermis (exocytosis) is generally accompanied by related pathologic changes affecting adjacent keratinocytes (e.g., spongiosis, apoptosis). Although interstitial infiltrates of T cells may occur, this pattern is less commonly encountered. B cells, on the other hand, tend not to migrate into the epidermis. When significant dermal B-cell infiltration exists, nodular aggregates replete with actual lymphoid follicles may develop.

Although T and B cells are indistinguishable by light microscopy, they can be differentiated by *in vitro* tests and immunohistochemical studies. Human T lymphocytes have receptors for sheep erythrocytes (E), so that, in the historically important E rosette assay, sheep erythrocytes form rosettes around T lymphocytes (271,272). Antibodies are available for the identification of T cells and B cells in routine paraffin sections [e.g., CD3 for T cells and L26 (CD20) and CD79a for B cells]. Immunohistochemically specific detection of cell surface glycoproteins that correlate with T-cell functional subsets (CD4 for helper/inducer, CD8 for cytotoxic/suppressor) is also possible on paraffin-embedded tissues. The T-cell receptor (TCR) consists of either αβ or γδ heterodimer expressed on the cell surface in association with CD3. The majority of the peripheral T lymphocytes express the αβ TCR and are $CD4^+$ or $CD8^+$. In 1970, Gershon and Kondo (273,274) observed that T cells not only augmented but also dampened immune responses and that this downregulation was mediated by T cells that were different from helper T cells. The phenotype of suppressor T cells corresponded for the most part to $CD8^+$, whereas some of them, in particular those suppressing delayed-type hypersensitivity, were $CD4^+$ cells. More recently, this subset of T lymphocytes has been shown to express CD25 (IL-2 receptor), as well as the Fox P3 marker, in addition to CD4. Such "regulatory" T cells serve to limit/suppress the immune response and may be detected in tissue by conventional immunohistochemical markers (274). It is unclear whether these regulatory T cells ("T regs") represent a subset of the same cells originally described as suppressor T cells (275).

An additional lymphocytic lineage closely related to T cells is composed of the natural killer (NK) cells. These cells represent approximately 10% of the circulating lymphocytes and are reactive to glycolipids presented in the context of the major histocompatibility complex (MHC) class I–like molecule CD1d. NK cells are characterized by the expression of CD56, CD57, and CD16. They lack B-cell markers and surface CD3 but express cytoplasmic CD3ε. They are usually $CD4^-/CD8^-$ but can rarely express CD8. NK cells do not demonstrate rearrangement of immunoglobulin heavy-chain genes or TCR genes (276).

It is important to realize that normal skin will contain small numbers of perivascular T cells with the helper subtype predominating as part of the skin immune system. Recent studies have found that there may be a larger pool of memory T cells in normal skin than originally believed. These T cells can initiate and perpetuate immune reactions in the absence of T-cell recruitment from the blood (277).

T cells play an important role in normal cutaneous immunosurveillance and in delayed hypersensitivity reactions. Initial antigen uptake by Langerhans cells occurs during sensitization. After their migration to draining lymph nodes via dermal lymphatics (see later discussion), Langerhans cells present antigen to naive T cells, which undergo initial clonal expansion to become memory cells. In the challenge reaction, the dermal microvascular unit is activated (possibly in part due to mast cell degranulation stimulated by antigen-specific IgE-like molecules generated during sensitization) (278), resulting in display of leukocyte adhesion molecules on the endothelial luminal surface that facilitate the recruitment of antigen-specific, skin-homing memory T cells. On local antigen presentation at the challenge site, these pioneer memory cells, now capable of antigen recognition, respond by elaboration of a cascade of cytokines that result in recruitment of secondary inflammatory cells.

The B lymphocyte is the effector cell of humoral immunity. On antigenic stimulation, the primary follicles in lymph nodes, composed of small B lymphocytes, develop into secondary follicles, consisting of a germinal center surrounded by a rim of small B lymphocytes (269). In the germinal centers, small B lymphocytes enlarge through an intermediate stage of centrocytes with cleaved nuclei into centroblasts, which are large cells with noncleaved nuclei (279). The centroblasts become immunoblasts as a result of antigenic stimulation and produce a clone of daughter cells that mature into immunoglobulin-secreting plasma cells (280,281). The differentiation of B lymphocytes into plasma cells is facilitated by helper T cells and is suppressed by suppressor T cells (282). The plasma cells collect in the medullary cords of lymph nodes

without entering the bloodstream but secrete immunoglobulins that circulate as "humoral" antibodies. Although these events most commonly occur in lymph nodes, identical alterations may take place in the dermis in response to locally introduced antigen, as is the case in cutaneous lymphoid hyperplasia with prominent germinal center formation (283,284). In clonal neoplasms of B cells, there may be an arrest at any of these differentiation stages, producing a monotonous infiltrate typical of the various categories of lymphoma cutis (see Chapter 31).

Plasma Cells

Plasma cells have an abundant cytoplasm that is deeply basophilic, homogeneous, and sharply defined. The round nucleus is eccentrically placed, and along its membrane it shows coarse, deeply basophilic, regularly distributed chromatin particles, which give the nucleus a cartwheel appearance (Fig. 3-44D). The fact that patients with agammaglobulinemia lack plasma cells was responsible for early recognition of the fact that the plasma cell is the site of formation of all immunoglobulins that circulate as humoral antibodies. The synthesis of immunoglobulins takes place in plasma cells located mainly in the lymph nodes, the spleen, and the bone marrow. Because plasma cells are tissue cells and are not seen in the peripheral circulation, it can be assumed that, if they are present in the dermis, they have developed there from B lymphocytes. Intracytoplasmic immunoglobulins may be demonstrated immunohistochemically in paraffin-embedded tissue. Subclassification of cells according to κ (approximately two thirds of reactive plasma cells) and γ (approximately one third of reactive plasma cells) is also possible and may facilitate in some instances detection of a neoplastic clone where only one of the light chains is produced exclusively. On electron microscopy, plasma cells are characterized by the presence in their cytoplasm of an extensive system of cisternae lined by a ribosome-associated rough endoplasmic reticulum.

Plasma cells are apt to be present in conspicuous numbers in several infectious diseases, such as early syphilis, rhinoscleroma, and granuloma inguinale (see Chapters 21 and 22). In the presence of many plasma cells, but especially in rhinoscleroma, round, hyaline, eosinophilic bodies called Russell bodies may be found inside and outside of plasma cells. They form within plasma cells as the result of a very active synthesis of immunoglobulins and may ultimately completely replace the plasma cells in which they have formed (285). They may possess a size twice that of normal plasma cells, measuring up to 20 μm in diameter. They contain varying amounts of glycoproteins and are as a rule gram positive as well as PAS positive and diastase resistant (286). Russell bodies are initiated by intracisternal secretion, analogous to the secretion of immunoglobulins. When the plasma cell is overloaded with this material, first the nucleus and ultimately the entire cell lyses (285). Immunofluorescence and immunohistochemical stains show the presence of immunoglobulins within the Russell bodies, especially on their surface (287,288).

Dermal Muscle Cells

Smooth Muscle

Smooth or involuntary muscle of the skin occurs as arrectores pilorum, tunica dartos of the external genitals, and in the areola of the nipples. The muscle fibers of the arrectores pilorum arise in the connective tissue of the upper dermis and are attached to the hair follicle below the sebaceous glands (Fig. 3-26). They are situated in the obtuse angle of the hair follicle. Thus, when contracted, they pull the hair follicle into a vertical position and produce the perifollicular elevations of "gooseflesh.""

Smooth muscle is characterized by the absence of striation and by the location of the nucleus in the center of the muscle cell. Typically, the nuclei are cigar shaped with rounded ends, a feature that may be diagnostically helpful in assessing dermal spindle cell proliferations and neoplasms. Argyrophilic reticulum fibers surround each muscle cell. Electron microscopic examination reveals that smooth muscle cells possess a basement membrane peripheral to the plasma membrane. The cytoplasm of the cells is filled with myofilaments 5 nm in diameter that form cytoplasmic and peripheral dense bodies as a result of condensations, just as the myofilaments do in myoepithelial cells, vascular smooth muscle cells, and glomus cells. The rather narrow spaces between the muscle cells are occupied by collagen fibrils and by Schwann cells with associated nonmyelinated axons.

Smooth muscle cells contain vimentin and desmin as intermediate filaments and smooth muscle actin (223).

Striated Muscle

Striated or voluntary muscle is found in the skin of the neck as platysma and in the skin of the face as muscles of expression. The striated muscle bundles take their origin either from a fascia or from the periosteum, or they form a closed ring, as in the musculus sphincter oris. They extend through the subcutaneous tissue into the lower dermis (see Fig. 3-62C). The muscle fibers, like skeletal muscle, show characteristic cytoplasmic cross-striations. Their nuclei are located at the periphery of the fibers immediately beneath the sarcolemma, the limiting membrane of the fibers.

Extracellular Matrix

The extracellular matrix of the dermis consists of collagenous and elastic fibers embedded into ground substance. All three components are formed by fibroblasts.

Collagen Fibers

Collagen represents by far the most abundant constituent of the connective tissue of the dermis. On light microscopy, collagen consists of fibers (Figs. 3-47 to 3-50). The diameter of collagen fibers is quite variable, ranging from 2 to 15 μm. The collagen fibers are present either as a finely woven network or as thick bundles. Collagen as a finely woven meshwork of collagen fibers is found in the papillary layer of the dermis, which includes not only the subepidermal papillae situated between

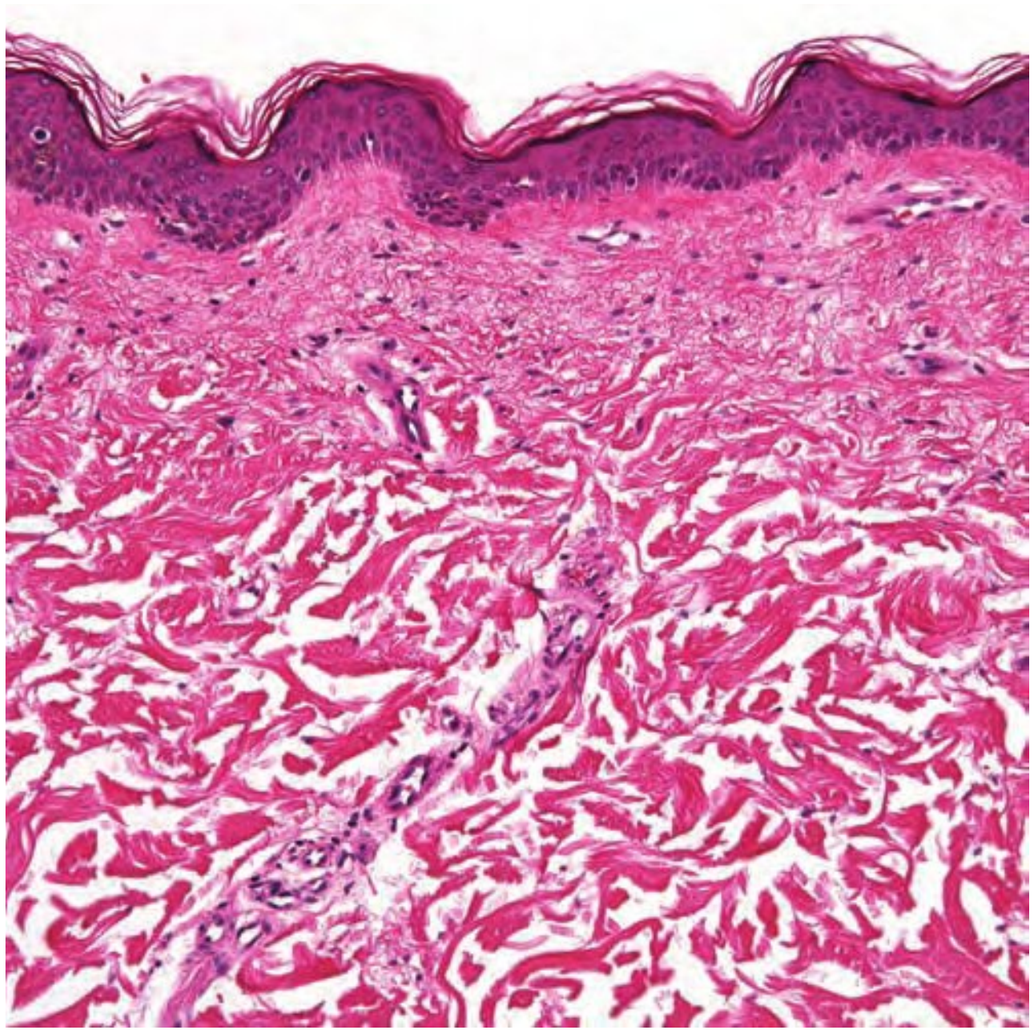


FIGURE 3-47. Conventional histology of the transition between papillary (top) and reticular (bottom) dermis. The dermal collagen in the papillary dermis is more delicate and thin than the thicker collagen bundles in the papillary dermis.

the rete ridges, but also the subpapillary layer forming a narrow ribbon between the rete ridges and the subpapillary blood vessels (Figs. 3-5, 3-47, and 3-50B). This is referred to as the papillary dermis. In addition, the pilosebaceous units and the eccrine and apocrine glands are encircled by a thin meshwork of collagen fibers similar to that present in the papillary dermis. Therefore, the papillary and the periadnexal dermis is regarded as an anatomic unit, the adventitial dermis. The blood vessels of the dermis are also surrounded by a thin layer of fine collagen fibers. Biochemically, the papillary dermis is composed primarily of type III collagen.

The rest of the dermis, constituting by far the largest portion of the dermis and referred to as the reticular dermis, shows the collagen fibers united into thick bundles (Figs. 3-40A and 3-47). These collagen bundles extend in various directions horizontally, and thus some are cut lengthwise and others across in histologic sections. As a rule, collagen bundles that are cut lengthwise appear slightly wavy. Biochemically, reticular dermal collagen is composed primarily of type I collagen.

Reticulum fibers are not recognizable with routine stains, but, being argyrophilic, they can be impregnated with silver nitrate, which, by being subsequently reduced to silver, stains black. Reticulum fibers represent a special type of thin collagen fiber that measures from 0.2 to 1 μm in diameter. The argyrophilia shown by reticulum fibers, in contrast to collagen fibers, probably is related to the fact that reticulum fibers correspond to the distribution of type III collagen rather than type I collagen.

Argyrophilic reticulum fibers are the first-formed fibers during embryonic life and in various pathologic conditions associated with increased fibroblastic activity. In normal skin, even though collagen is being continuously replaced, the formation of new collagen is not preceded by an argyrophilic phase. Instead, all newly formed collagen consists of large fibers. However, there are a few areas in which normally small collagen fibers are present as reticulum fibers without transforming into larger, nonargyrophilic collagen fibers. This occurs above all in the basement membrane zone, the region of the adventitial dermis that lies closest to the epidermis and its appendages. In addition, reticulum fibers are present normally around blood vessels and as a basket-like capsule around each fat cell.

The biosynthesis of collagen begins within the fibroblast by the assembly of three pro–α-polypeptide chains into a triple-helical procollagen molecule (216). After excretion into the extracellular space, the three pro-α chains of each procollagen molecule are shortened by 30% to 40% through removal of the carboxy-terminal and amino-terminal peptide extensions brought about by the action of two enzymes produced by

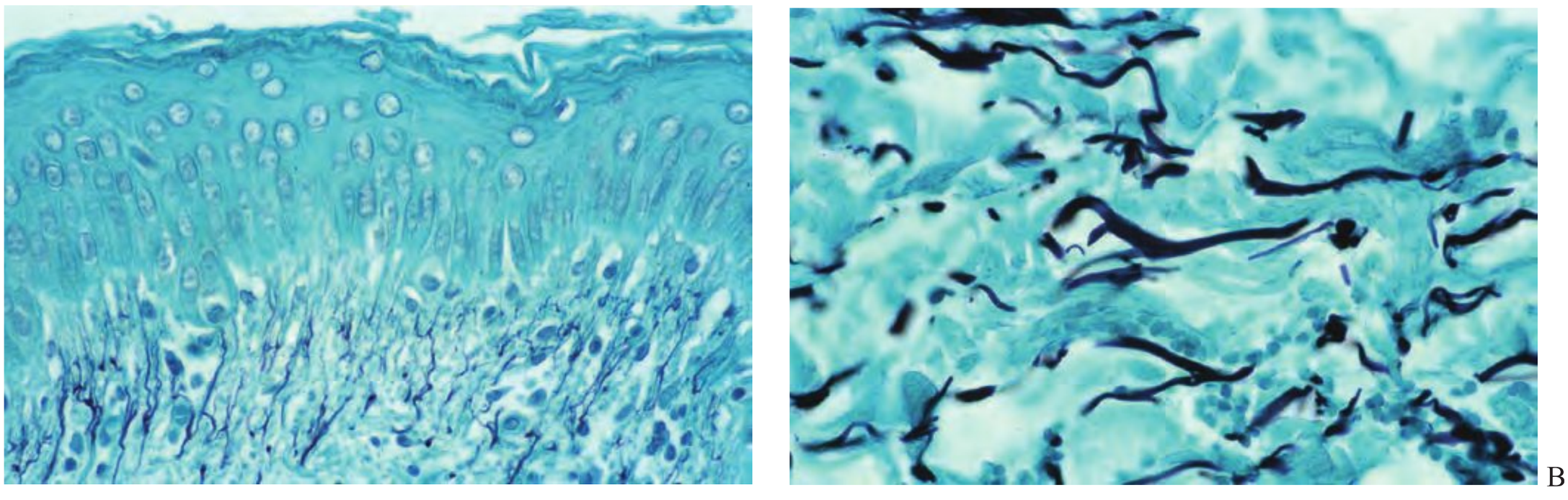


FIGURE 3-48. Histochemical demonstration of elastin fibers within papillary dermis (A) and reticular dermis (B). Silver stain.

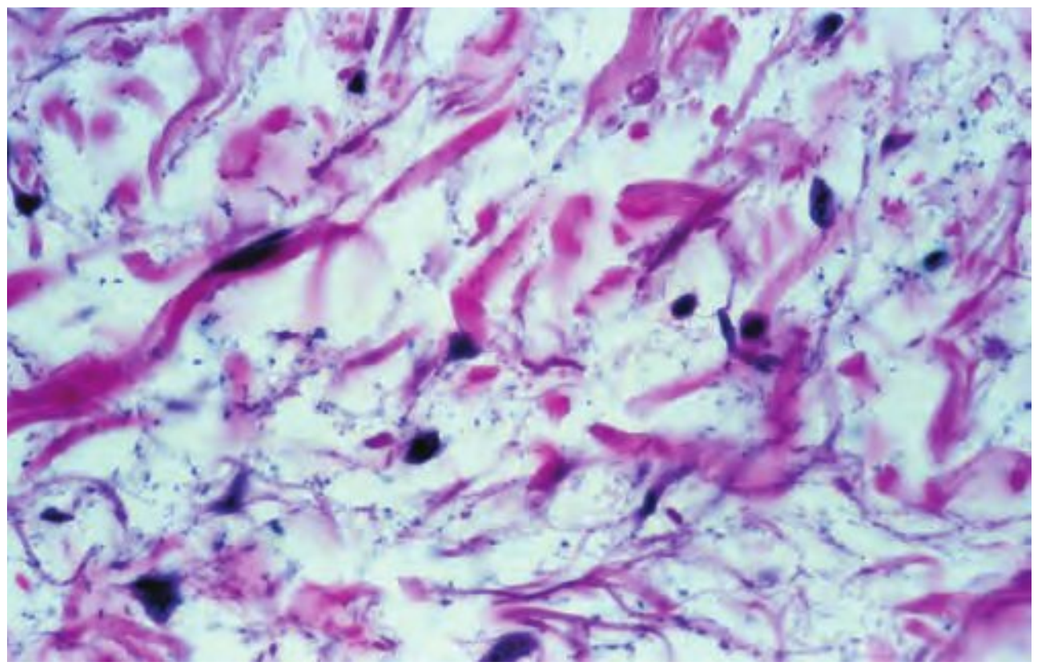
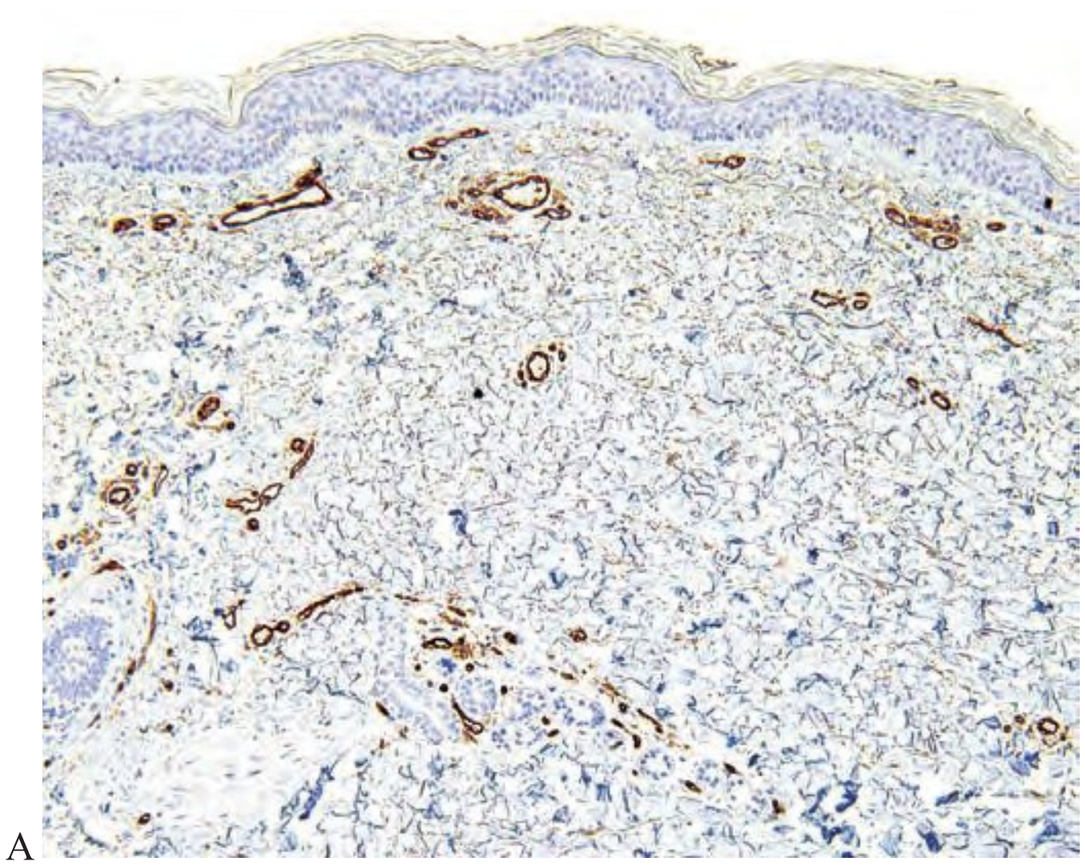


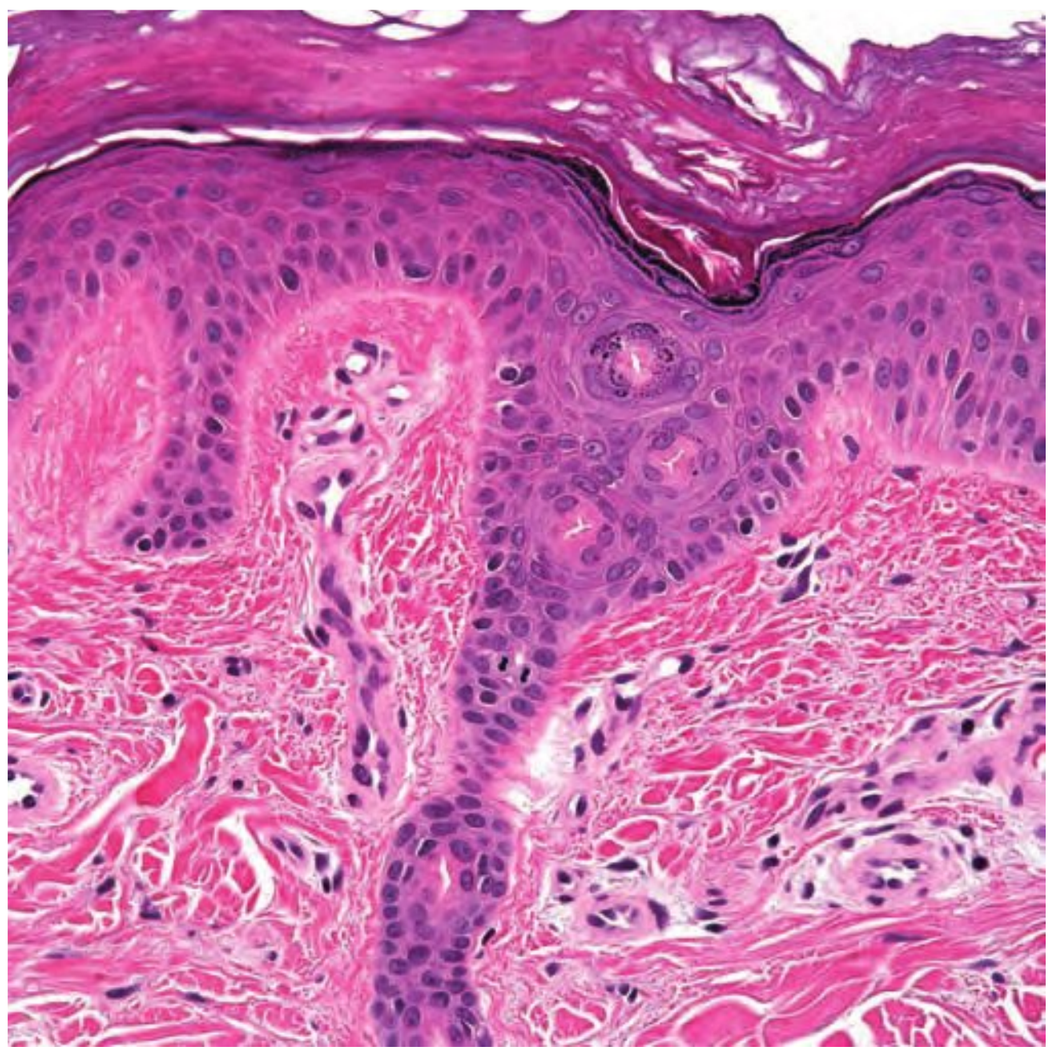
FIGURE 3-49. Ground substance. Although these mucopolysaccharides are normally inconspicuous by conventional light microscopy, in this case they are pathologically increased and thus visible as thin, pale blue-gray strands within widened spaces separating reticular dermal collagen.

the fibroblast: carboxy-terminal peptidase and amino-terminal peptidase (215). This results in conversion of the procollagen molecule into the collagen molecule. Although the additional peptides present in procollagen keep it soluble and prevent its intracellular polymerization, collagen molecules polymerize readily. The collagen molecule is a rigid rod in which each of the three coiled α chains consists of about 1,000 amino acids (216). The collagen molecule is about 300 nm long and 1.5 nm wide (289–291). Collagen fibrils form by both lateral and longitudinal association of collagen molecules. However, the collagen fibrils vary in diameter as a result of varying degrees of polymerization of collagen molecules, with younger collagen fibrils being thinner than older fibrils. In the normal dermis, the thickness of collagen fibrils ranges from 70 to 140 nm; most of the fibrils are approximately 100-nm thick (292).

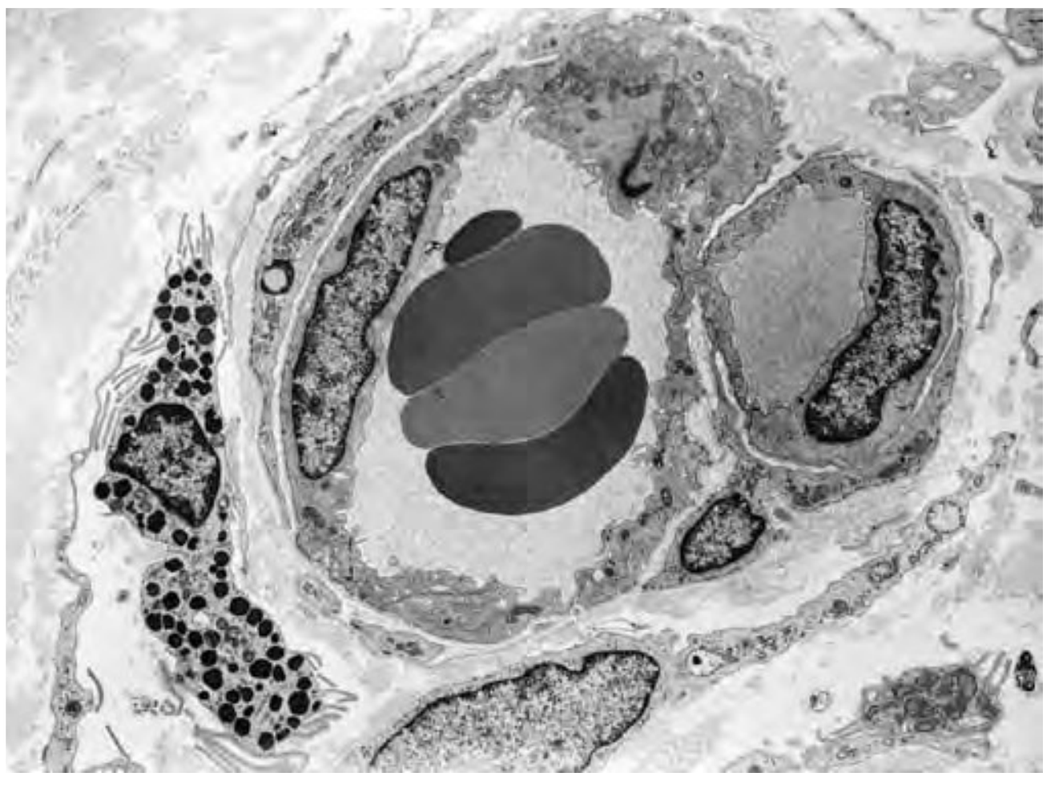
Collagen fibrils possess characteristic cross-striations with a periodicity of 68 nm. The periodicity of the cross-striations in the collagen fibrils can be explained as follows. Each collagen molecule possesses along its length of 300 nm five charged regions 68 nm apart, and although neighboring collagen molecules overlap



A



B



C

FIGURE 3-50. A: Immunohistochemical stain with CD31 highlights the vascular pattern in the dermis. B: Histology of a capillary loop originating from underlying superficial vascular plexus and extending into the dermal papilla. C: Transmission electron micrograph of dermal microvascular unit consisting of a plexus of central vessels and surrounding cells that form the junction between the papillary and reticular dermis. Note the endothelial cells lining the central postcapillary venule surrounded by pericytes and dermal immune cells, including granulated mast cells.

each other, they always have their charged regions lying side by side. This parallel alignment of the charged regions produces the cross-striations (290). Reticulum fibrils possess the same 68-nm periodicity of their cross-striations as collagen fibrils but have a smaller diameter than collagen fibrils, varying between 40 and 65 nm rather than between 70 and 140 nm (293). Furthermore, reticulum and collagen differ in the number of fibrils present in the cross section of each fiber and in the amount of ground substance present within and around each fiber. The amount of ground substance around the fibrils and on the surface of the fiber may explain the presence of argyrophilia in reticulum fibers and its absence in collagen fibers (293).

Seven different types of collagen have been recognized that differ in composition and antigenicity. Type I collagen, the predominant collagen in postfetal skin, is found in the large fiber bundles of the reticular dermis. Reticulum fibers are composed of type III collagen. Although type III collagen is the prevalent type of collagen in early fetal life, in postfetal life it is limited to the subepidermal and periappendageal regions, that is, the basement membrane zones and the perivascular region or the "papillary" and "adventitial" dermis (294). Basement membrane collagen (basal lamina collagen) is type IV, and the collagen of cartilage is type II. Type V collagen has been recognized in fetal membranes and vascular tissue (295). Type VII collagen occurs in different basement membranes, including those of the skin, and forms a major structural component of anchoring fibrils (296). The skin of the human fetus contains a large percentage of type III collagen, in contrast to the skin of the adult, which contains a large proportion of type I collagen (297).

Among the differences in composition are the following. In type I collagen, the three α chains in the collagen molecule consist of two different kinds: two identical α chains designated as α-1(I) and a third chain called α-2. In type II collagen, the collagen molecules are composed of three identical, genetically distinct α chains, α-1(II). Type III collagen is also composed of three identical, distinct α chains (215). Type IV collagen consists of procollagen composed of three identical pro-α chains that have retained their nonhelical extensions. Types V and VI collagen have not yet been adequately characterized. Type VII collagen consists of three α chains, with the terminal regions being noncollagenous (296).

Elastic Fibers

Elastic fibers appear in the dermis at 22 weeks, much later than the collagenous fibers. At this time, acid orcein stains show elastic tissue in the reticular dermis either as granular material interspersed with occasional short fibers or as a delicate network of branching fibers. As gestation progresses, elastic fibers increase in quantity. At 32 weeks, a well-developed network of elastic fibers indistinguishable from that seen in term infants is present in both the papillary and the reticular dermis (298). Young elastic fibers, as seen in a 22-week-old fetal dermis, show masses of peripheral microfibrils surrounding a small, amorphous, electron-lucent core representing elastin, with only a few internal microfibrils. As the embryo matures, the amount of elastin and the number of microfibrils within the elastin increase, whereas the number of peripheral microfibrils decreases (299).

In light microscopic sections that are routinely stained, elastic fibers are inconspicuous. With special elastic tissue stains, such as orcein or resorcin-fuchsin, or in plastic-embedded sections they are found entwined among the collagen bundles (Fig. 3-48). Because elastic fibers are thin in comparison with collagen bundles, measuring from 1 to 3 μm in diameter, and are wavy, only a small portion of any fiber is seen in histologic sections, giving even normal elastic fibers a fragmented appearance. The elastic fibers are thickest in the lower portion of the dermis, where they are arranged, like collagen bundles, chiefly parallel to the surface of the skin. Elastic fibers become thinner as they approach the epidermis. In the papillary dermis, they form an intermediate plexus of thinner elaunin fibers running parallel to the dermal–epidermal junction (Fig. 3-48). From this plexus, thin fibers termed oxytalan fibers run upward in the papillary dermis perpendicular to the dermal–epidermal junction and terminate at the PAS-positive basement membrane zone.

The elastic fibers of the dermis consist of two components: the microfibrils and the matrix elastin. The microfibrils are electron dense and measure 10 to 12 nm in diameter. They are aggregated at the periphery of the elastic fiber, giving the fiber its characteristic frayed appearance by ultrastructure. In addition, microfibrils are present within the elastin as strands 15 to 80 nm in diameter extending in a longitudinal direction (300). The microfibril component amounts to only 15% of the elastic fiber, whereas the amorphous, electron-lucid elastin makes up 85% of the fiber (299). It is the elastin that stains with elastic tissue stains, is removable by elastase, and is markedly extensible, whereas the microfibrils are the elastic resilient component of the elastic fiber (300).

Elastic fibers undergo significant changes during life. One change, representing aging, is best studied in nonexposed skin. The other change, elastotic degeneration, is the result of chronic sun exposure and is described in Chapter 15. In young children up to the age of 10 years, the elastic fibers may not be fully matured, so that microfibrils predominate (301). Physiologic aging is a gradual process and usually becomes quite apparent by age 30 to 50 years. There is a gradual decrease in the number of peripheral microfibrils, so that ultimately there may be none; instead, the surface of the elastic fiber appears irregular and granular (301). The microfibrils within the elastin matrix become thicker and show electron-lucent holes of varying sizes (302). In very old persons, fragmentation and disintegration of some of the elastic fibers may be observed. Oxytalan fibers that consist of microfibrils diminish and ultimately disappear in aging skin.

Ground Substance

The ground substance, an amorphous substance that fills the spaces between collagen fibers and collagen bundles, contains glycosaminoglycans, or acid mucopolysaccharides (Fig. 3-49).

These glycosaminoglycans are covalently linked to peptide chains to form high–molecular-weight complexes called proteoglycans (303). Glycosaminoglycans are present in normal skin in such small amounts that they cannot be demonstrated with either routine or special histologic staining methods except in the hair papilla of anagen hair, which contains both nonsulfated and sulfated acid mucopolysaccharides. However, through the study of tissues with an active growth of fibroblasts, as seen in the papillary dermis in dermatofibroma and in the connective tissue around the tumor islands of basal cell epithelioma, it is known that the dermal ground substance consists largely of nonsulfated acid mucopolysaccharides such as hyaluronic acid (161). In healing wounds, however, in which new collagen is laid down, the ground substance contains sulfated and nonsulfated acid mucopolysaccharides (304).

The nonsulfated acid mucopolysaccharides consist largely of hyaluronic acid, are stainable with alcian blue at pH 3.0 but not at pH 0.5, and show metachromasia with toluidine blue at pH 3.0 but not at pH 1.5. The sulfated acid mucopolysaccharides consist largely of chondroitin sulfate, are stainable with alcian blue at pH 0.5 and at pH 3.0, and show metachromasia with toluidine blue at pH 1.5 and at pH 3.0. Both nonsulfated and sulfated acid mucopolysaccharides stain with colloidal iron. Testicular hyaluronidase hydrolyzes hyaluronic acid but not the sulfated acid mucopolysaccharides (161).

Dermal Microvascular Unit

Not long ago, the dermis was considered to be a leathery cutaneous layer primarily responsible for housing and protection of vessels that served to nourish the keratinizing epidermis. Today we realize that the dermis is a dynamic microenvironment containing a repertoire of cells and matrix molecules arguably more complex and sophisticated than the epidermis and its appendages. The dermal microvascular unit is the heart of this new concept of the dermis, for it represents an intricate assemblage of cells responsible not only for cutaneous nutrition, but also for immune cell trafficking, regulation of vessel tone, and local hemostasis.

Endothelial Cells

General Microanatomy

The dermal microvasculature is divided into two important strata. The first, the superficial vascular plexus, defines the boundary between the papillary and the reticular dermis and extends within an adventitial mantle to envelop adnexal structures (Figs. 3-5 and 3-50A). This plexus forms a layer of anastomosing arterioles and venules in close approximation to the overlying epidermis and is normally surrounded by other cellular components of the dermal microvascular unit (see later discussion). Small capillary loops emanate from the superficial vascular plexus and extend into each dermal papilla (Fig. 3-50B, C). The second plexus—the deep vascular plexus—is connected to the first by vertically oriented reticular dermal vessels and separates the reticular dermis from the subcutaneous fat. Many of these vessels are of larger caliber and communicate with branches that extend within fibrous septae that separate lobules of underlying subcutaneous fat.

The small arteries of the deep vascular plexus and the arterioles of the dermis possess three layers: an intima, composed of endothelial cells and an internal elastic lamina that stains for elastic tissue; a media, which contains two or more layers of muscle cells in the small arteries but only a single layer of muscle cells in the arterioles of the lower dermis and a discontinuous layer of muscle cells in the arterioles of the upper dermis; and an adventitia of connective tissue (305) (Fig. 3-51A). The capillaries that are present throughout the dermis but especially in the papillary dermis are composed of a layer of endothelial cells surrounded by an incomplete layer of pericytes. A basement membrane, which stains positive with PAS, is present peripheral to the endothelial cells and surrounds the pericytes. There is alkaline phosphatase activity in the endothelial cells of all capillaries (306). Staining for alkaline phosphatase thus demonstrates well the capillary loop in each subepidermal dermal papilla, with the ascending, arterial limb of the loop staining more heavily than the descending, venous limb. The abundant capillaries present in the hair papillae of anagen hairs also stain heavily (162,306).

The walls of veins generally are thinner than those of arteries and less clearly divided into the three classic layers (Fig. 3-51B). The postcapillary venules resemble capillaries because they consist of endothelial cells, pericytes, and a basement membrane (Fig. 3-50C). The arteriolar and venous segments can be distinguished from each other on the basis of the basement membrane, which has a homogeneous appearance in the former and is multilaminated in the latter. Furthermore, terminal arterioles have elastin and smooth muscle cells in their walls, whereas postcapillary venules have only pericytes in their walls (307). The capillary loops leading from the subpapillary plexus to the dermal papillae and back can be divided into an intrapapillary portion and an extrapapillary portion. The extrapapillary ascending limb and the intrapapillary portion have the characteristics of an arterial capillary, that is, a homogeneous basement membrane, whereas the extrapapillary descending limb has venous characteristics, that is, a multilayered basement membrane (308). Although some investigators have observed areas of fenestration at the tips of the capillary loops between the endothelial cells (309), others have failed to find them (308). Endothelial cells characteristically show a well-developed endoplasmic reticulum, bundles of fairly thick cytoplasmic filaments with a diameter of 5 to 10 nm, and many pinocytotic vesicles at their luminal surface. Frequently, one can observe in endothelial cells a unique structure, the Weibel-Palade body. It is an electron-dense, rod-shaped cytoplasmic organelle measuring approximately 0.1 μm in diameter and up to 3 μm in length. It is composed of a number of small tubules, approximately 15 nm thick and arranged in the long axis of the rod (309). Peripheral to the endothelium lies a basement membrane. The peripheral row of cells—the pericytes—have long cytoplasmic processes and form a discontinuous

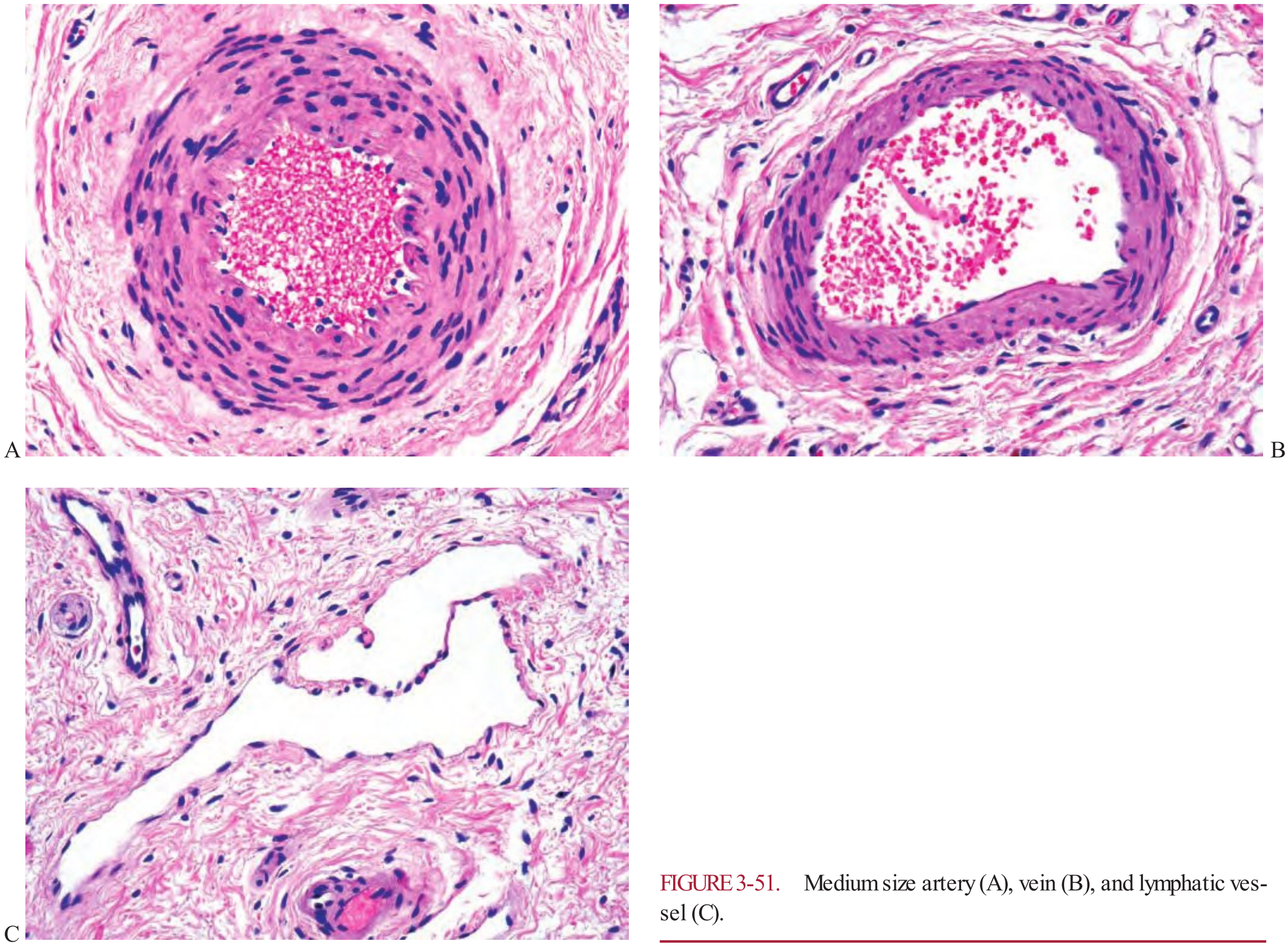


FIGURE 3-51. Medium size artery (A), vein (B), and lymphatic vessel (C).

layer. They are completely surrounded by the capillary basement membrane. In larger capillaries, more than one layer of pericytes may be present, and transitional forms between pericytes and smooth muscle cells may be seen (310).

Endothelial cells of blood capillaries contain α-L-fucose, which can be demonstrated with *Ulex europaeus* (311), and they contain factor VIII–related antigen. *U. europaeus* and an antibody against factor VIII–related antigen are used as endothelial markers for the identification of neoplastic endothelial cells. Endothelial cells also express CD31 (312,313), a marker that may be the most sensitive for normal and neoplastic endothelial cells. In addition, endothelial cells of blood capillaries contain class I antigens (HLA-A, B, C) and class II antigen (HLA-DR) (314). HLA-DR is considered to play a role in antigen presentation and elicitation of an immune response (315), and endothelial cells and perivascular dermal dendritic cells are capable of dermal antigen presentation (see later discussion). Laminin and type IV collagen are present within the vascular basement membranes. Blood capillaries contain vimentin intermediate filaments.

Specialized Structure and Function

Recent evidence indicates that endothelial cells are active participants in transmural shuttling of macromolecules, as well as facilitators of normal and pathologic trafficking of immune cells. The luminal surface of the endothelial cell that lines the superficial postcapillary venule is the primary site of adhesive interactions that initiate subsequent diapedesis of leukocytes. The outer membrane of the Weibel-Palade body contains a glycoprotein termed CD62, which is rapidly transported to the luminal endothelial membrane on exposure to histamine or thrombin (316,317). This molecule mediates the initial loose rolling adhesion between circulating leukocytes and the endothelial surface. Subsequently, other cytokine-inducible glycoproteins are expressed in a cascade (E-selectin, vascular cell adhesion molecule-1, intercellular adhesion molecule-1) on the endothelial surface, resulting in orchestrated and progressively stable leukocyte-endothelial adhesion (318–322). Some luminal molecules that are constitutively and diffusely expressed (e.g., CD31) redistribute to cell–cell junctions on endothelial stimulation, thus creating a situation potentially conducive to

concentrating adherent leukocytes at sites where transmural diapedesis may occur (322). Provocative signals for such events may come from inflammatory cells themselves or from native cells in the perivascular space (see mast cells, earlier discussion).

Glomus Cells

A special vascular structure, the glomus, is located within the reticular dermis in certain areas. Glomus formations occur most abundantly in the pads and nailbeds of the fingers and toes but also elsewhere on the volar aspect of the hands and feet, in the skin of the ears, and in the center of the face (Fig. 3-52A). The glomus is concerned with temperature regulation and represents a special arteriovenous shunt that, without the interposition of capillaries, connects an arteriole with a venule. When open, these shunts cause a great increase in blood flow in the area. Each glomus consists of an arterial and a venous segment. The arterial segment, called the Suquet-Hoyer canal, branches from an arteriole and has a narrow lumen and a thick wall measuring 20 to 40 μm in diameter. The wall shows a single layer of endothelium, surrounded by a PAS-positive, diastase-resistant basement membrane zone, and a media that is densely packed with four to six layers of glomus cells (Fig. 3-52B). These are large cells with a clear cytoplasm resembling epithelioid cells. Although myofibrils cannot be recognized within glomus cells with light microscopic staining methods, these cells have generally been regarded as smooth muscle cells (323). Peripheral to the glomus cells is a zone of loose connective tissue. Staining with silver salts shows many nerve fibers extending to the glomus cells within this zone. The venous segment of the glomus is thin walled and has a wide lumen. This wide collecting venule functions as a reservoir and drains into a dermal venule. As many as four Suquet-Hoyer canals may be found in a single glomus body, which is encapsulated (324).

Electron microscopic study of the Suquet-Hoyer canal reveals the glomus cells to be vascular smooth muscle cells. As such, each glomus cell is surrounded by a basement membrane.

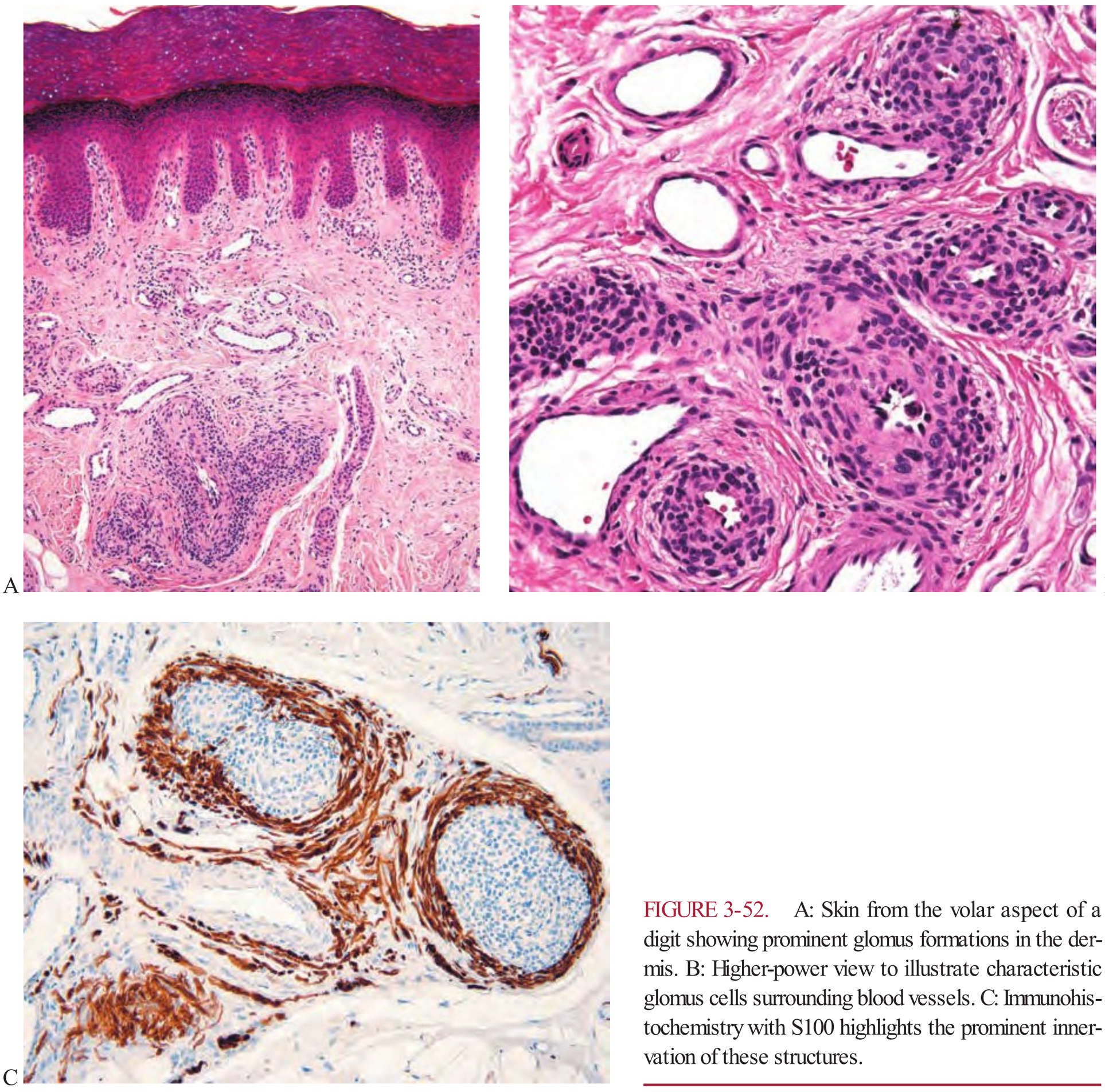


FIGURE 3-52. A: Skin from the volar aspect of a digit showing prominent glomus formations in the dermis. B: Higher-power view to illustrate characteristic glomus cells surrounding blood vessels. C: Immunohistochemistry with S100 highlights the prominent innervation of these structures.

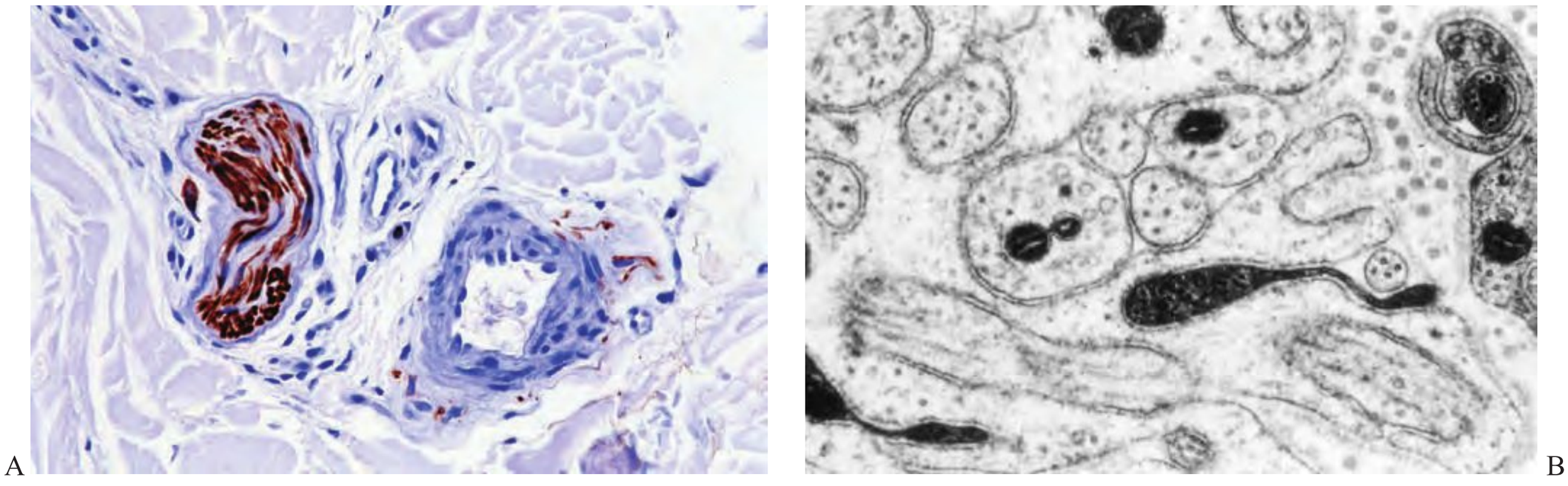


FIGURE 3-53. Dermal nerve fibers demonstrated by S100 immunohistochemical staining (A) and by transmission electron microscopy as individual axons enveloped by Schwann cells (B).

The cytoplasm of the glomus cells is filled with filaments with a diameter of about 5 nm. Cytoplasmic and peripheral dense bodies, 300 to 400 nm in diameter, are present in the glomus cells as a result of condensations of the myofilaments. Numerous nonmyelinated nerves ensheathed by Schwann cells are present peripheral to the glomus cells (325) (Fig. 3-52C).

Dermal Lymphatics

Dermal lymphatics are often inconspicuous in normal skin because they do not have a well-developed wall, as is the case with blood vessels. They are easily detected, however, when they become slightly ectatic as a result of increased lymphatic drainage, as in urticaria. Lymph vessels typically are not rounded in contour, but instead show angulations dictated by the fact that their lining lymphatics are buttressed by adjacent collagen bundles (Fig. 3-51C). In normal skin, the perilymphatic space is relatively devoid of other cells, and the lumen is lined by relatively flattened endothelial cells. Occasional valves may be observed emanating from the endothelial lining. By electron microscopy, the thin layer of endothelium does not contain Weibel-Palade bodies and is devoid of a basement membrane or surrounding pericytes. Lymphatic vessels show a negative or weakly positive reaction when incubated with *U. europaeus* and no reaction with an antibody against factor VIII–related antigen in most instances. They do not contain class I (HLA-A, B, C) or class II (HLA-DR) antigens (314). Endothelial cells of lymphatic vessels contain cytoplasmic filaments (326), which probably represent vimentin filaments. Lymphatic vessels contain podoplanin and can be specifically labeled using an antibody such as D2-40 or LYVE-1 (326).

Neural Network

In sections stained with routine methods, one can recognize only the larger myelinated nerve bundles and the Meissner and Vater-Pacini end organs. The finer nerves require special staining, and accordingly the enormous importance of these structures to cutaneous homeostasis and pathology has been overlooked. Among the staining methods used are impregnation with silver salts (327), vital staining with methylene blue (328), and *in vitro* staining of thick sections with methylene blue (329). More recently nerves have been identified by the S100 technique (Fig. 3-53A) and by using antibodies to specific neurofilaments, neuropeptides, and adhesion molecules (neural cell adhesion molecule-1). Nerves are composed of neuraxons, a cytoplasmic process that conducts neural impulses from cell bodies in the central nervous system, and Schwann cells (sheath cells or neurilemmal cells) enveloping the neuraxons (Figs. 3-53A, B). This primary functioning unit may or may not be myelinated and is surrounded by an endoneurium—a mucinous or fibrous matrix containing fibroblasts—which supports the primary functioning unit. A perineurium composed of elongated, flattened cells surrounds several primary functioning units and their endoneurial matrix (330).

The skin is supplied with sensory nerves and autonomic nerves, which permeate the entire dermis with nerve fibers and show frequent branching. Sensory and autonomic nerves differ in that sensory nerves possess a myelin sheath up to their terminal ramifications, but autonomic nerves do not. The autonomic nerves, derived from the sympathetic nervous system, supply the blood vessels, the arrectores pilorum, and the eccrine and apocrine glands. The sebaceous glands possess no autonomic innervation, and their functioning depends on endocrine stimuli. All autonomic nerves end in fine arborizations. So do the sensory nerves, except in a few areas in which there are, in addition to fine arborizations, special nerve end-organs. Hair follicles, especially large hair follicles, are also surrounded below the entry of the sebaceous duct by a network of sensory nerves that lose their myelin sheaths a short distance from the outer root sheath and end in numerous arborizations of fine nonmyelinated fibers.

The papillary dermis is richly invested in unmyelinated nerve fibers, particularly about the dermal microvascular unit, where axons often terminate in close proximity to mast cells (331). This relationship is of interest inasmuch as small neurosecretory granules within axons contain a variety of mediators,

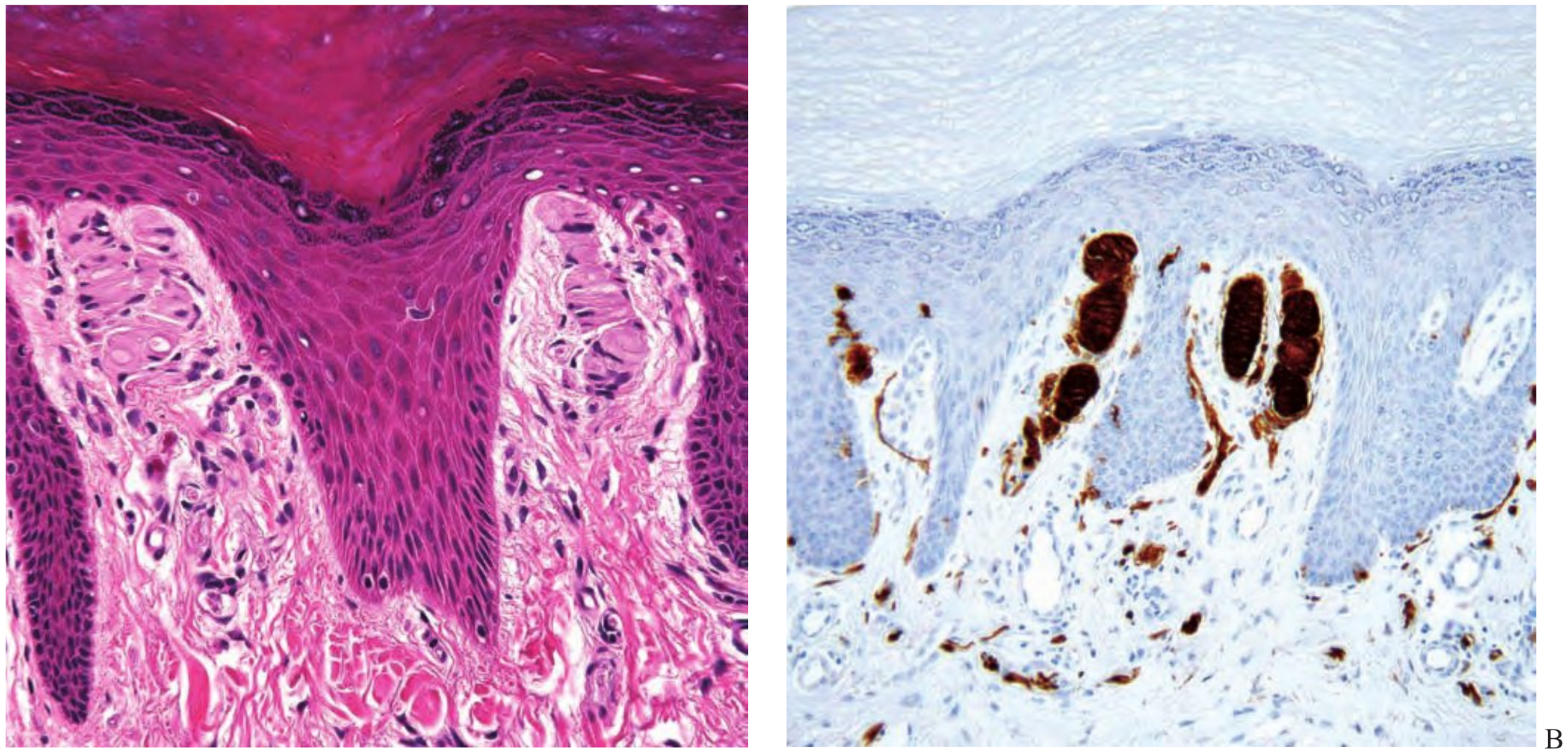


FIGURE 3-54. A: Meissner corpuscle within dermal papillae of human palm skin. B: Meissner corpuscles are strongly positive with S100 immunostain.

including neuropeptides that may serve as mast cell secretagogues, such as substance P. The development of confocal scanning laser microscopy has permitted assessment of complicated spatial relationships between axons and skin cells. Recently, superficial dermal axons containing another neuropeptide, calcitonin gene–related peptide (CGRP), were documented to enter the epidermis and to associate selectively with the cell bodies of Langerhans cells (332). Substance P–induced mast cell degranulation may elicit expression of endothelial-leukocyte adhesion molecules and thus be proinflammatory (333), and CGRP has been shown to diminish antigen presentation by Langerhans cells (334). Thus, the superficial dermal plexus of unmyelinated axons may represent a heretofore-unappreciated influence of normal and perturbed cutaneous immunity.

Special Nerve End-Organs

In the areas of hairless skin on the palms and the soles and in the areas of modified hairless skin at the mucocutaneous junctions, some of the sensory nerves end in special nerve end-organs. They are of three types: mucocutaneous end-organs, Meissner corpuscles (Figs. 3-54A, B), and Vater-Pacini corpuscles (Fig. 3-55). Although it is customary to speak of them as end organs, they actually represent starting organs in a functional sense because nerve impulses start there and are transmitted to the sensory cells of the spinal cord (335).

The mucocutaneous end organs, on the average 50 μm in diameter, are found in the modified hairless skin at the mucocutaneous junctions, namely, the glans, the prepuce, the clitoris, the labia minora, the perianal region, and the vermilion border of the lip. They are in the papillary dermis. They cannot be recognized in routinely stained sections, in contrast to the Meissner corpuscles in the dermal papillae. Impregnation with silver nitrate reveals that from two to six myelinated nerve fibers enter each mucocutaneous end organ and, after losing their myelin sheaths, form many loops of nerve fibers resembling

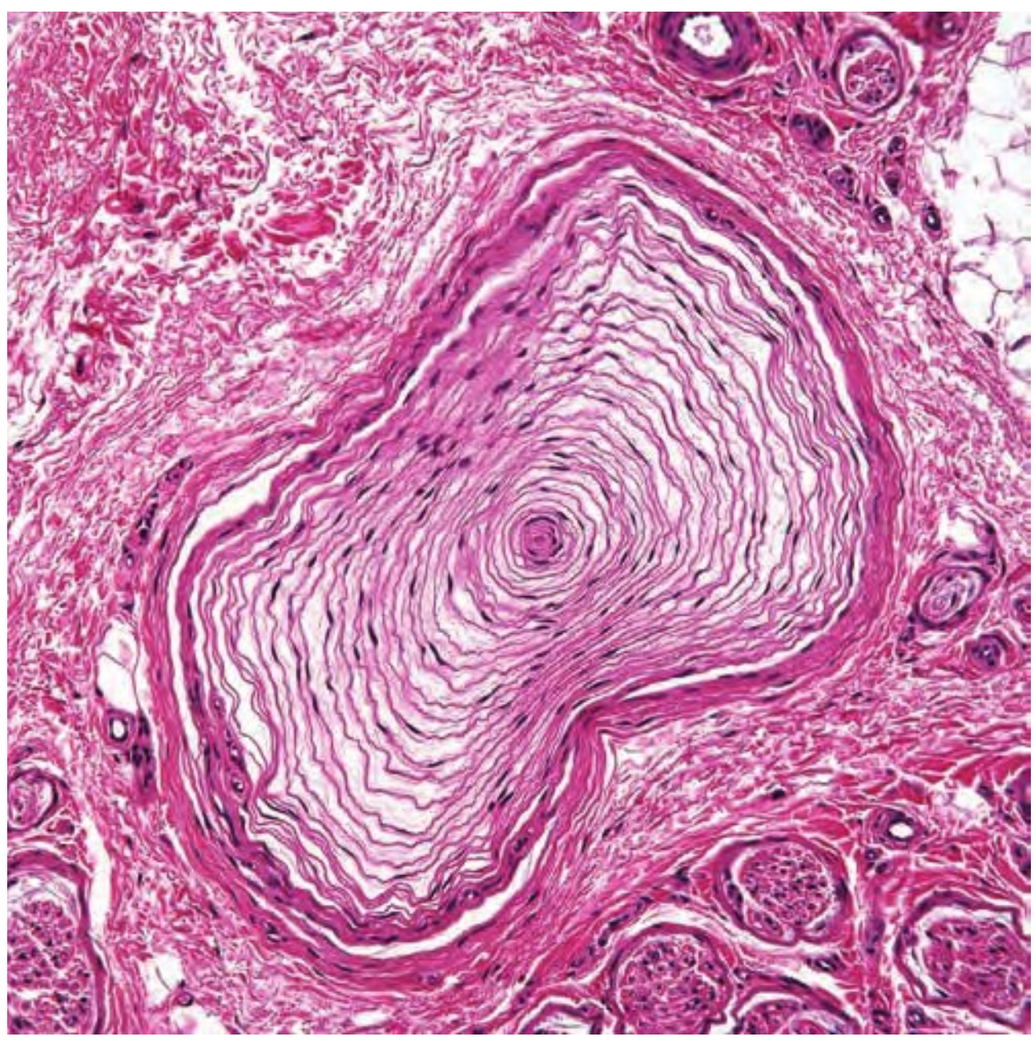


FIGURE 3-55. Vater-Pacini structure with characteristic concentric pattern.

an irregularly wound ball of yarn. The electron microscopic features of mucocutaneous end organs are similar to those of Meissner corpuscles (336), despite minor differences in their light microscopic appearance. They show a subdivision into lobules, each containing a complex arrangement of axon terminals. These axon terminals are surrounded by concentric lamellar processes derived from so-called laminar cells, the nuclei of which are situated toward the periphery of the lobules. It is assumed that the laminar cells represent modified Schwann cells. The mucocutaneous end organs are always separated from the basal layer of the epidermis by a band of papillary dermal collagen.

Meissner corpuscles are located in dermal papillae (Fig. 3-54A, B) and mediate a sense of touch. They occur exclusively on the ventral aspects of the hands and feet, their number increasing distally. There are more Meissner corpuscles on the hands than on the feet. At the site of their greatest concentration, the fingertips, approximately every fourth papilla contains a Meissner corpuscle. The size of the Meissner corpuscles averages 30 by 80 μm in diameter. Owing to their size and their elongated shape, resembling that of a pine cone, they occupy the greater part of the papilla in which they are located. They possess a capsule composed of several layers of flattened Schwann cells that are arranged transverse to the long axis of the corpuscle. Impregnation with silver salts reveals that several myelinated nerves, as they approach the base or the side of the corpuscle, lose their myelin sheaths and then enter it. Within the corpuscle, the nerves take a meandering course upward. Electron microscopic studies reveal that the principal part of the Meissner corpuscle is made up of irregular layers of flattened, greatly elongated laminar cells. The nuclei of the laminar cells are located largely at the periphery of the corpuscle. The axons terminating within the Meissner corpuscle are surrounded by slender processes of the laminar cells. This enveloping of axons by laminar cells or their lamellar processes is analogous to the enveloping of axons by infolding of the plasma membrane of Schwann cells and indicates that the laminar cells are modified Schwann cells (337). The axon terminals and laminar cells are in direct contact with the epidermal basal cells at the upper end of the Meissner corpuscle without interposition of a basement membrane (338).

Vater-Pacini corpuscles are large nerve end organs that are located in the subcutis and mediate a sense of pressure. They measure up to 1 mm in diameter and thus are detected easily by light microscopy (Fig. 3-55). They are found most commonly below the skin of the volar aspects of the palms and soles, showing their greatest concentration at the tips of the fingers and toes. In addition, a few Vater-Pacini corpuscles occur in the subcutis of the nipple and of the anogenital region (336). Vater-Pacini corpuscles vary in shape. Some are ovoid, others have the appearance of a flattened sphere, and still others have an irregular shape. They consist of a stalk and of the body proper, the latter having a small core and a thick capsule. In the stalk, the single thick nerve supplying the Vater-Pacini corpuscle makes several turns and, just after entering the stalk, loses its myelin sheath. The core shows a granular substance surrounding the ascending meandering nerve. The thick capsule consists of 30 or more concentric, loosely arranged lamellae. On electron microscopic examination, the single nerve fiber present in the inner portion of the core retains its Schwann cell cytoplasmic covering for a short distance. The outer portion of the core shows closely packed, greatly elongated laminar cells. The thick capsule consists of at least 30 layers of flattened laminar cells separated from one another by fluid-filled spaces (339). The laminar cells of the Vater-Pacini corpuscle, analogous to those of the Meissner corpuscle, are modified Schwann cells.

SUBCUTANEOUS FAT

Fat cells begin to develop in the subcutaneous tissue toward the end of the fifth month. Histologic examination at that time shows (a) spindle-shaped, lipid-free mesenchymal cells as precursor cells, (b) young-type fat cells containing two or more small lipid droplets, and (c) mature fat cells possessing one large central lipid droplet and a peripherally located nucleus, so-called signet-ring cells. Although some of the cells containing multiple small lipid droplets resemble the multivacuolated mulberry cells present in brown fat and in hibernoma, only few such cells occur in embryonic white fat. Brown and white fat are two separate entities incapable of interconversion (340).

Mature subcutaneous fat consists of lobules composed of adipocytes with cytoplasm markedly expanded by nonvacuolated or membrane-bound lipid that displaces the cell nucleus eccentrically to produce a thin, fusiform contour compressed along the inner plasma membrane. The lipid dissolves in routinely processed specimens, although it is visible in glutaraldehyde-fixed, plastic-embedded specimens. It may be stained histochemically in frozen section obtained from fresh or "wet" tissue retrieved while still in formalin. The lobules that form the subcutis are separated by thin fibrous septae through which small vessels course (Fig. 3-56). The septae provide structural

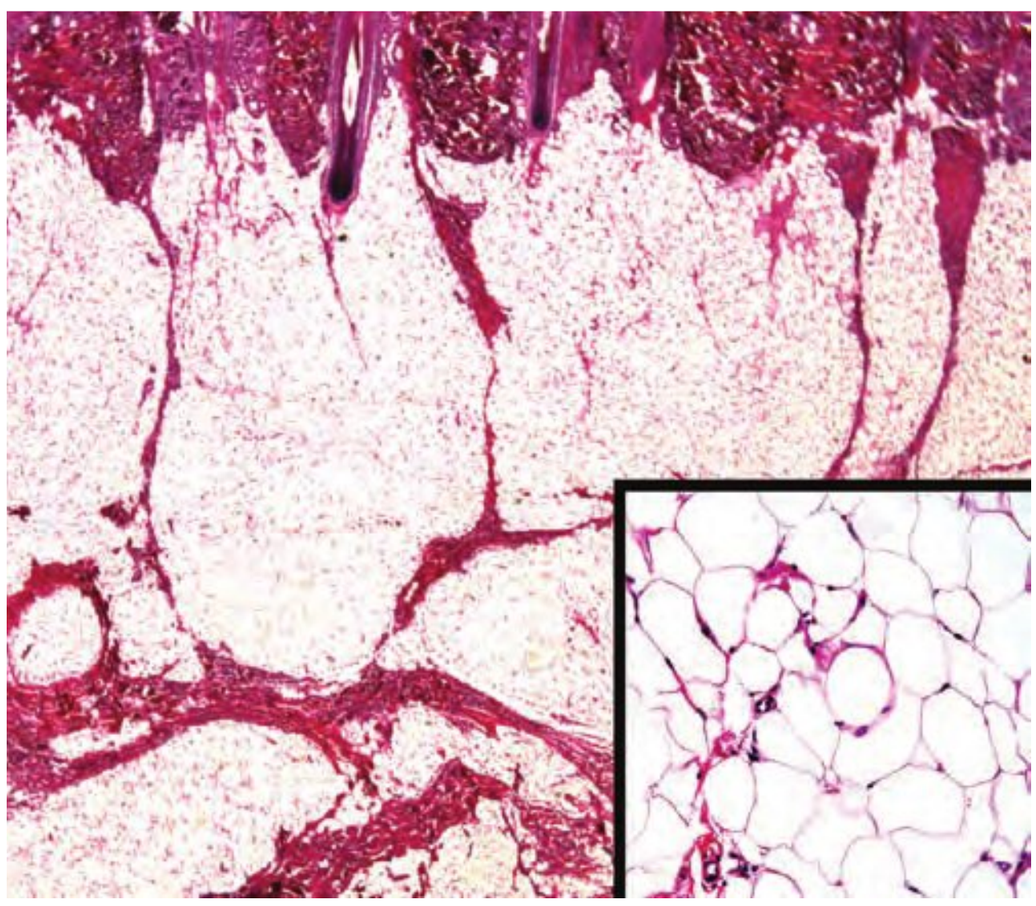


FIGURE 3-56. Low-power view of the subcutaneous tissue. Lobules of adipose tissue are separated by fibrous septa. Inset: A higher-power view of a subcutaneous lobule.

stability to the subcutaneous layer by compartmentalizing it and by connecting the lowermost reticular dermis to the fascial planes that underlie the subcutis.

AGE- AND ENVIRONMENTAL-RELATED VARIATIONS

Structural and functional alterations caused by intrinsic aging and independent of environmental insults are now recognized in the skin of elderly individuals and must be considered a fundamental component of "normal" histology (341). Changes associated with skin aging include a thinner epidermis with flattened dermal–epidermal junction (341–343). The keratinocytes become less adherent to one another and tend to be arranged haphazardly because of the aberrant proliferation of basal cells. The melanocyte density declines slowly, and a reduction in the number of melanosomes leads to reduced pigmentation (343). Although it is conceptually important to distinguish between the effects of true biological aging and environmental factors such as sun exposure, in general the observed changes are a practical consequence of the combined effect of both. Despite the decreased melanocyte density, photoaged skin has irregular or heterogeneous pigmentation. Heterogeneity in skin color in exposed areas of skin is due to uneven distribution of pigment cells. Associated with a local loss of melanocytes are noncontiguous areas where melanocytes are increased in number and size (Figs. 3-17A,B) (344,345). Langerhans cells decrease in number and function with age and chronic sun damage, which partially contributes to age-associated deterioration of the immune system. In general the dermis becomes atrophic, and it is relatively acellular and avascular. Dermal changes involve alteration and reduction of collagen, elastin, and ground substance. There is attenuation in the number and diameter of elastic fibers in the papillary dermis, an increase in number and thickness of the same fibers in the reticular dermis, and a coarsening of collagen fibers, which become thicker and stiffer (342). Fibroblasts, dendritic cells, and mast cells are reduced in number. In chronically sun-damaged skin, however, the dermis may be rich in cells showing some enlarged, angulated fibroblast/myofibroblast (343). The hallmark of sun-damaged skin is the presence of solar elastosis characterized by a fibrillary basophilic material present in the upper dermis (Fig. 3-57). The elastotic material is composed of elastin, fibronectin, fibrillin (microfibrillary proteins), and glycosaminoglycans. The pathogenesis of solar elastosis is complex and not fully understood, but it appears to include both *de novo* synthesis of elastotic material and degradation of previously synthesized dermal matrix proteins (346).

A consistent finding in aged skin everywhere is the dilation of lymphatic channels, and this is especially evident in areas where elastosis has taken place (343) (Fig. 3-57). Eccrine and apocrine glands are reduced in number and function. Sebaceous glands may remain unchanged or may increase in size; they are, however, less active (341). There is a progressive reduction in the density of hair follicles per unit area on the face and scalp and a decline in the rate of growth. The hair

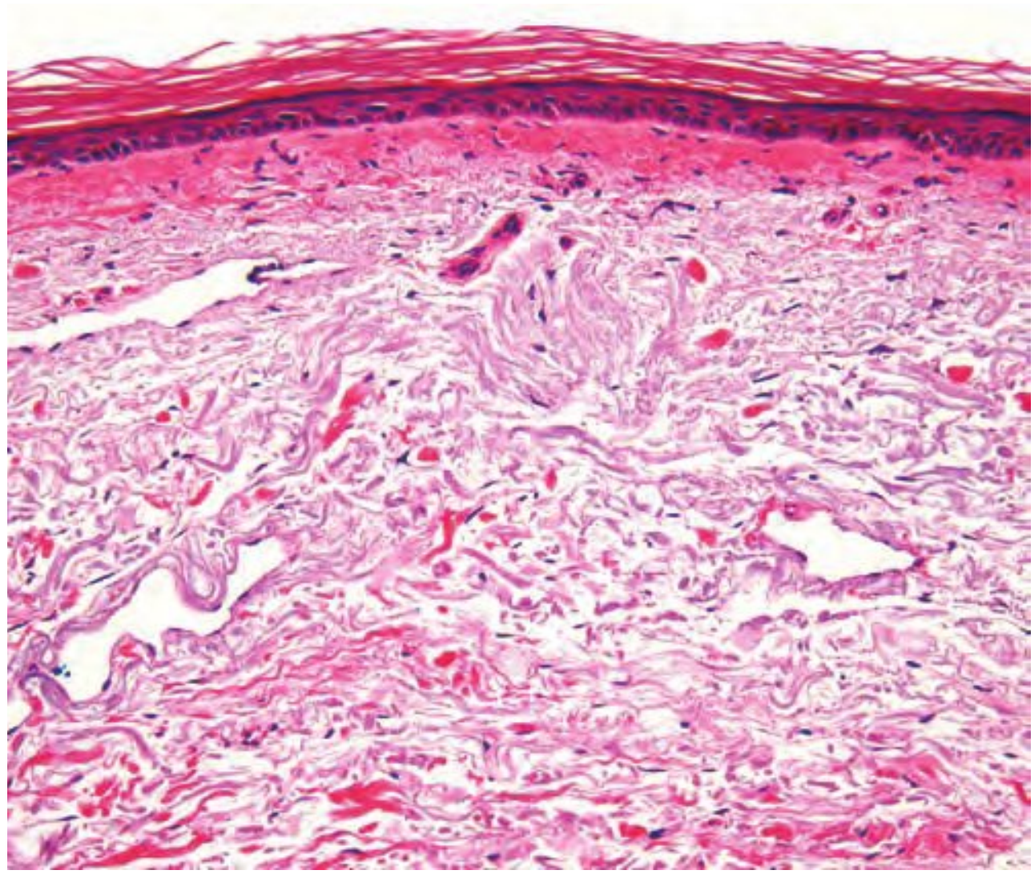


FIGURE 3-57. Changes associated with skin aging include a thinner epidermis with flattened dermal–epidermal junction and telangiectatic dermal vessels associated with marked solar elastosis in the form of bluish-gray fibers, the latter related to chronic sun damage.

shaft diameter is generally reduced, but in some areas, especially the ears, nose, and eyebrows of men and the upper lip and chin in women, it is increased as vellus hairs convert to cosmetically compromising terminal hairs (341).

The subcutaneous tissue is diminished in some areas, especially the face, shins, hands, and feet, whereas in others, particularly the abdomen in men and the thighs in women, it is increased (341).

The nail plate is generally thinned, the surface ridged and lusterless, and the lunula decreased in size; these structural changes are associated with a slowing of the rate of nail growth (341).

REGIONAL VARIATION OF THE SKIN

As a final consideration in the context of the many different components of the skin discussed to this point, it is important to emphasize that although the skin has basically the same components at different anatomic sites, the distribution of these components is variable, so that the skin has different morphology at different sites. The skin of the trunk and especially the back has a significantly thicker reticular dermis compared to other regions (Fig. 3-58), and the skin of the umbilical area also shows a thick and fibrotic dermis. Acral skin from palms and soles has a typical thickened and compact stratum corneum containing a stratum lucidum, numerous eccrine glands, and no pilosebaceous units (Figs. 3-7 and 3-52A). Glomus structures and nerve end organs are seen in the dermis (Figs. 3-52B and 3-54A, B). The scalp is characterized by numerous terminal hair follicles, with most of their bulbs in the subcutaneous tissue (Fig. 3-59). The skin from the face has prominent sebaceous glands in vellus hairs and especially on the nose (Fig. 3-60). Anywhere in hairy skin, but especially in the

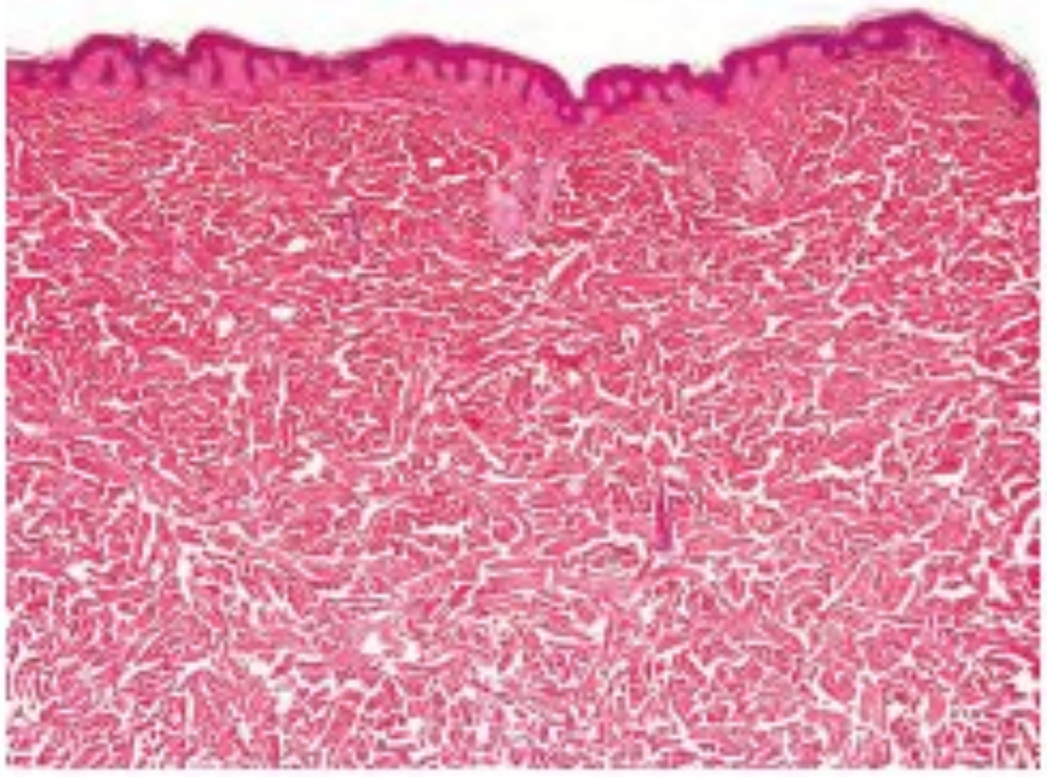


FIGURE 3-58. Skin from the back, showing a significantly thicker reticular dermis compared to most other regions.

beard area, it is possible to find pili multigemini characterized by more than one hair shaft emerging from a single infundibulum. Although classically considered a rare developmental defect of hair, recent studies suggest that they are commonly present in variable numbers in otherwise normal skin (347) (Fig. 3-61). Skeletal muscle is more superficial on the face, including lips and periorbital areas; skeletal muscle fibers may be seen in the dermis in these areas (Fig. 3-62D). Numerous vellous hairs are seen in the ear. The eyelid epidermis is thin (two to three layers thick) with basaloid buds (Fig. 3-62A, B). The basal layer tends to show increased pigmentation and more melanocytes compared with specimens from other anatomic locations from the same person. Modified apocrine glands (Moll's glands) and vellus hairs are seen in the dermis (Fig. 3-62D). The mucosal portion of the eyelid is lined by a nonkeratinizing stratified epithelium with scattered goblet cells (Fig. 3-62C). Smooth muscle fibers are numerous in the

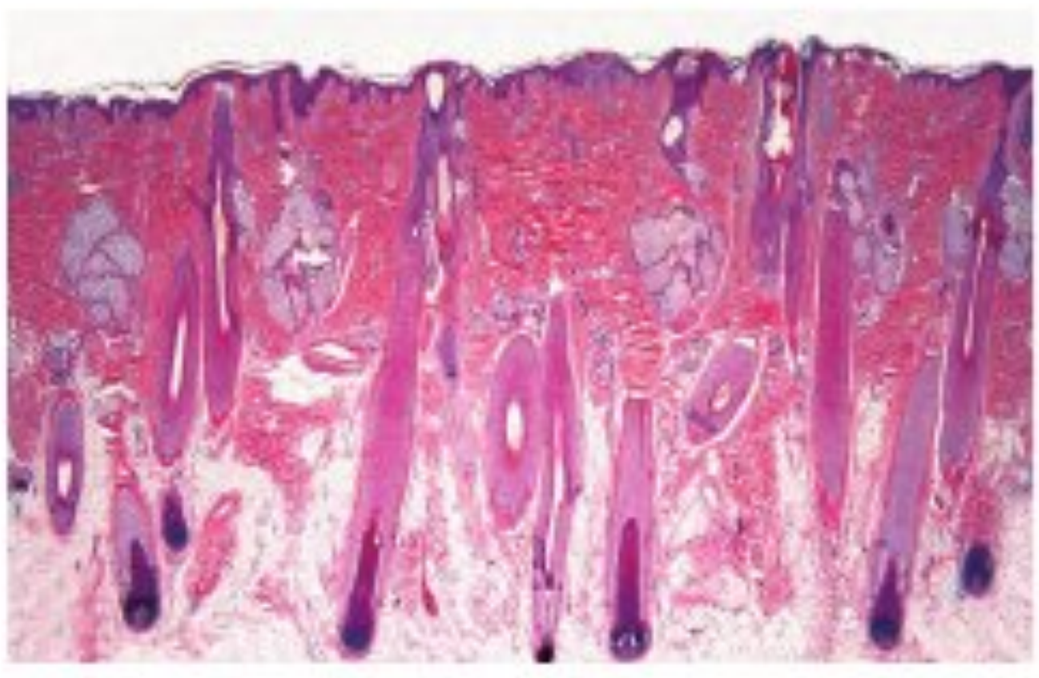


FIGURE 3-59. The scalp is characterized by numerous terminal hair follicles with most of their bulbs in the subcutaneous tissue, as also illustrated on Fig. 3-27.

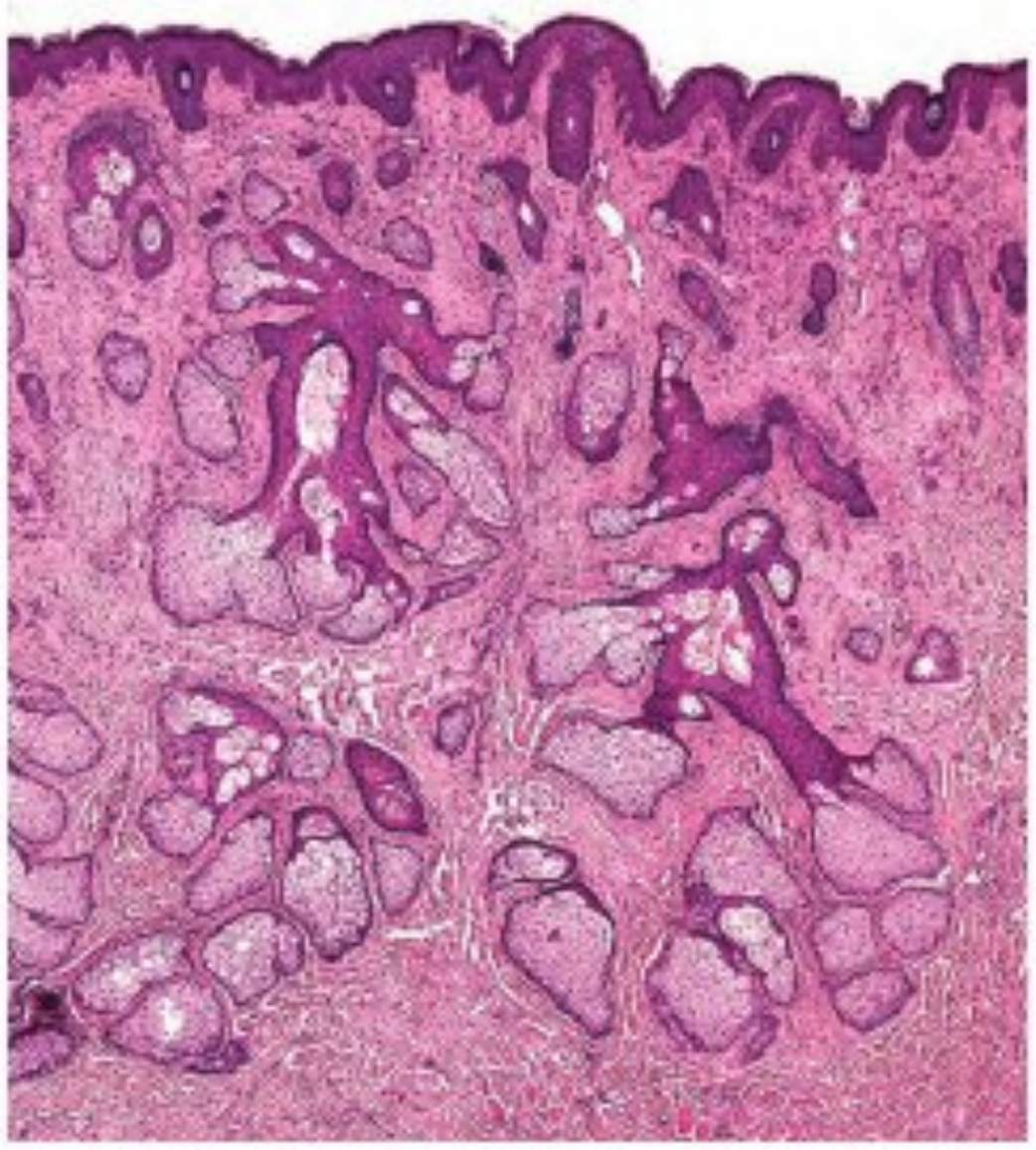


FIGURE 3-60. Skin from the nose, showing vellus hairs and prominent sebaceous glands.

dermis of the areola and nipple and are also seen in the dartos layer (underneath the dermis) in foreskin and scrotum (Fig. 3-63). Skin biopsies from the legs, especially in adults, may show prominent thick-walled blood vessels due to gravity and stasis (Fig. 3-64).

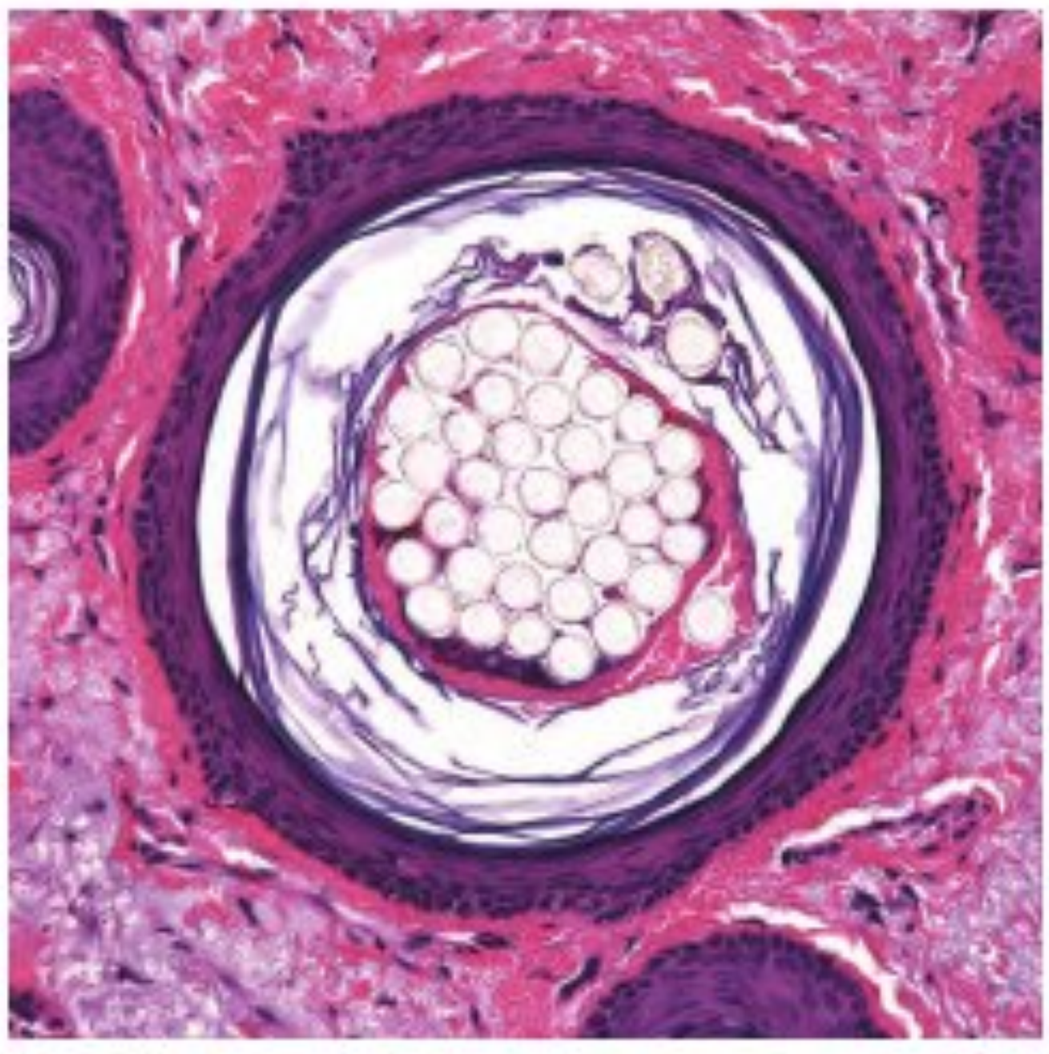
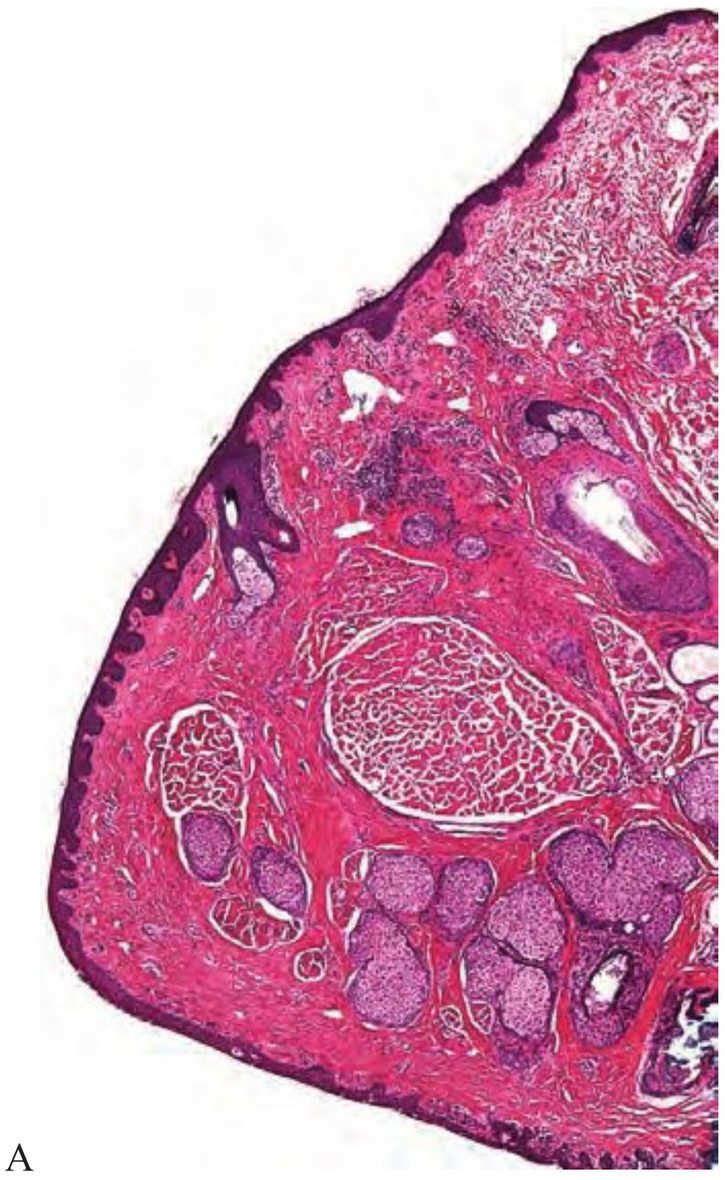
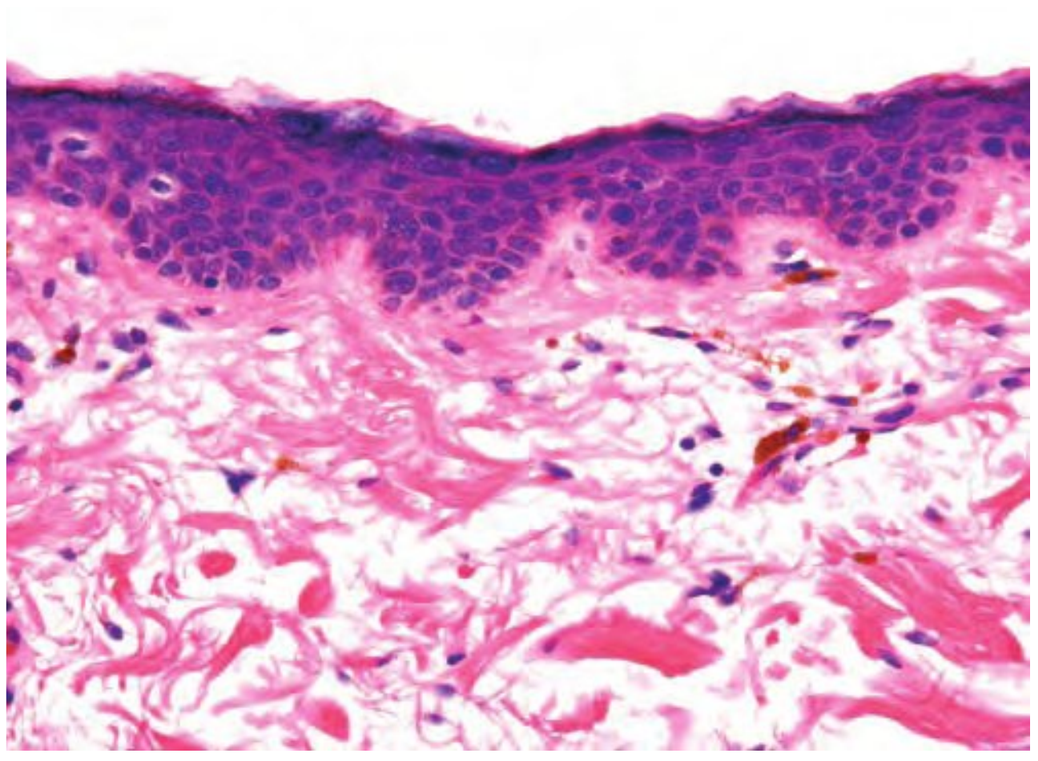


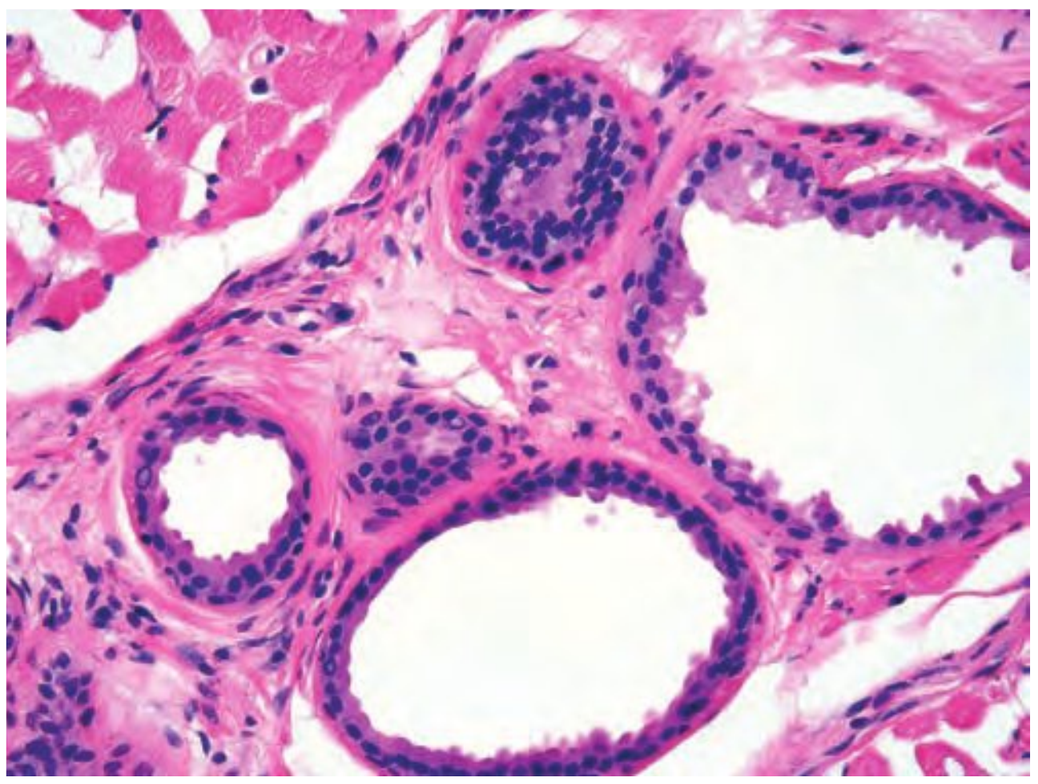
FIGURE 3-61. Pili multigemini, showing clusters of shafts emerging from a single follicular canal. They typically are found in the beard area of males.



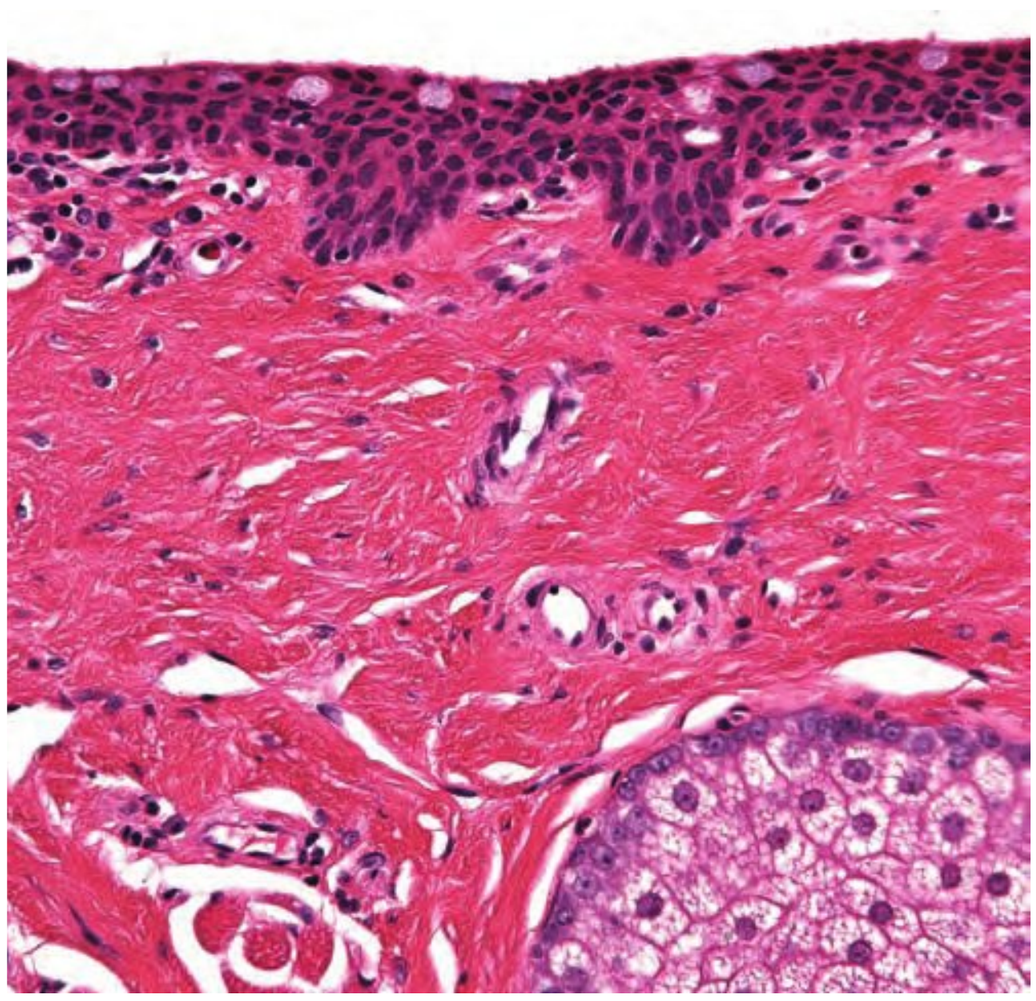
A



B



D



C

FIGURE 3-62. A: Lower-power view of the eyelid, showing the transition from eyelid skin (top) to eyelid mucosa (left bottom). Note the prominent meibomian sebaceous glands. B: The eyelid epidermis is thin (two to three layers thick) with basaloid buds. The basal layer tends to show increased pigmentation and more melanocytes compared with specimens from other regions. C: The mucosal (conjunctival) epithelium shows scattered goblet cells. D: Note the modified apocrine glands (glands of Moll) and the presence of superficial skeletal muscle fibers in the dermis.

INCIDENTAL FINDINGS IN SKIN SPECIMEN

"Normal" skin is seldom perfect and pristine. As discussed earlier, it must be viewed in the context of alterations implicit to normal aging, unavoidable environmental agents, and anatomic site. In this section, some of the "incidental findings" in normal skin that may be at times confused with pathologic and clinically significant changes are briefly discussed.

Focal Epidermolytic Hyperkeratosis

Incidental (focal) epidermolytic hyperkeratosis is a common, nonspecific finding that may be seen in normal and especially sun-damaged skin (348). It has been also described adjacent or within different unrelated lesions such as seborrheic keratosis, scars, fibrous histiocytomas, actinic keratosis, carcinomas, and melanocytic lesions. Incidental epidermolytic hyperkeratosis is characterized by a focal area showing hyperkeratosis, acanthosis, thickened and abnormal granular layer containing irregular, enlarged, and deeply eosinophilic intracytoplasmic inclusions resembling trichohyaline granules, and suprabasal keratinocytes showing marked intracellular edema (cytolysis). There is no clinical correlate, and the pathogenesis is unclear. Incidental epidermolytic hyperkeratosis should be distinguished from congenital bullous ichthyosiform erythroderma,

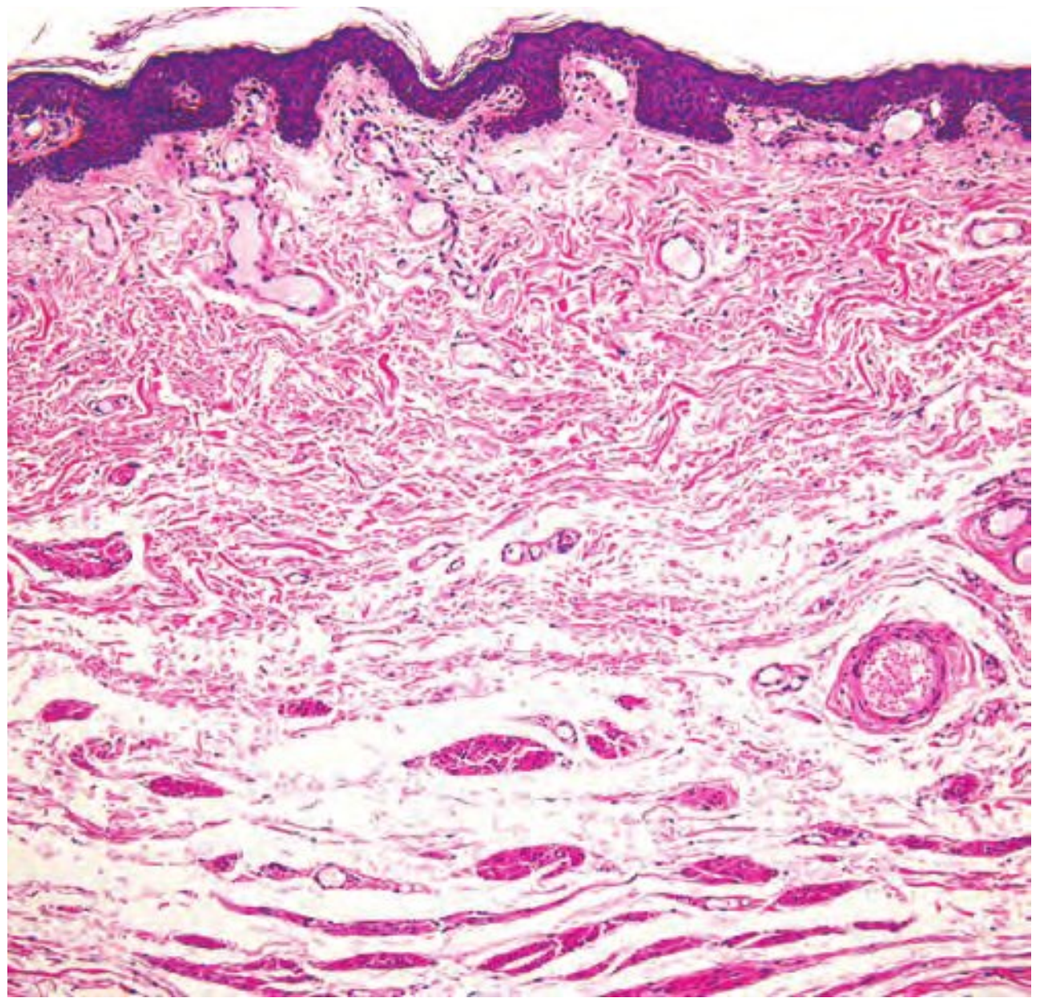


FIGURE 3-63. Smooth muscle fibers are numerous in the dartos layer (underneath the dermis) in foreskin.

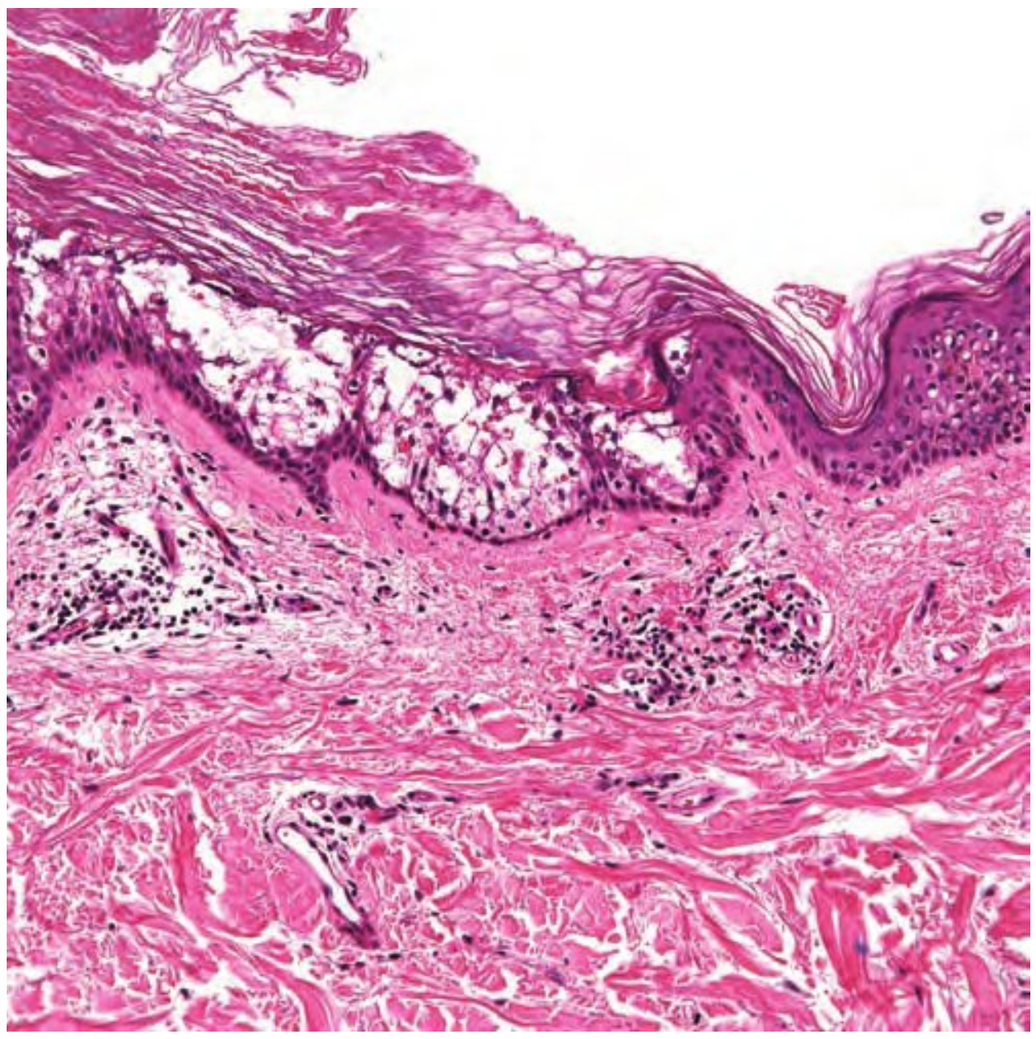


FIGURE 3-65. Incidental (focal) epidermolytic hyperkeratosis is a common, nonspecific finding that may be seen in normal and especially sun-damaged skin.

linear verrucous epidermal nevus, epidermolytic keratoderma, and epidermolytic acanthoma (see Chapter 6). The changes in the incidental form are less extensive and limited to the epidermis (Fig. 3-65).

Focal Acantholytic Dyskeratosis

Another incidental finding that can be seen in normal skin is focal acantholytic dyskeratosis. Like incidental epidermolytic hyperkeratosis, focal acantholytic dyskeratosis is a subclinical condition of unknown pathogenesis frequently identified in normal skin or adjacent to unrelated pathologic conditions including dermatitis, benign tumors, carcinomas, and melanomas (349,350). Histologically, there is a focal area of hyperkeratosis, parakeratosis, and suprabasal cleft formation

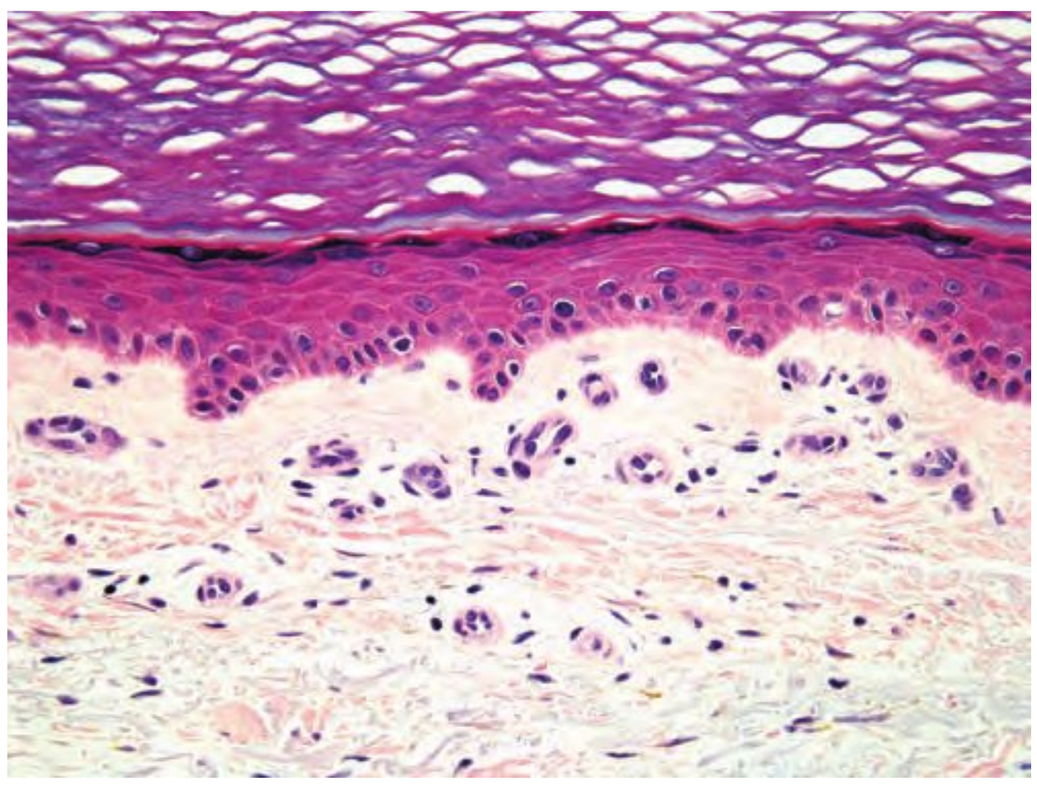


FIGURE 3-64. Skin biopsies from the legs, especially in adults, may show prominent thick-walled blood vessels due to gravity and stasis.

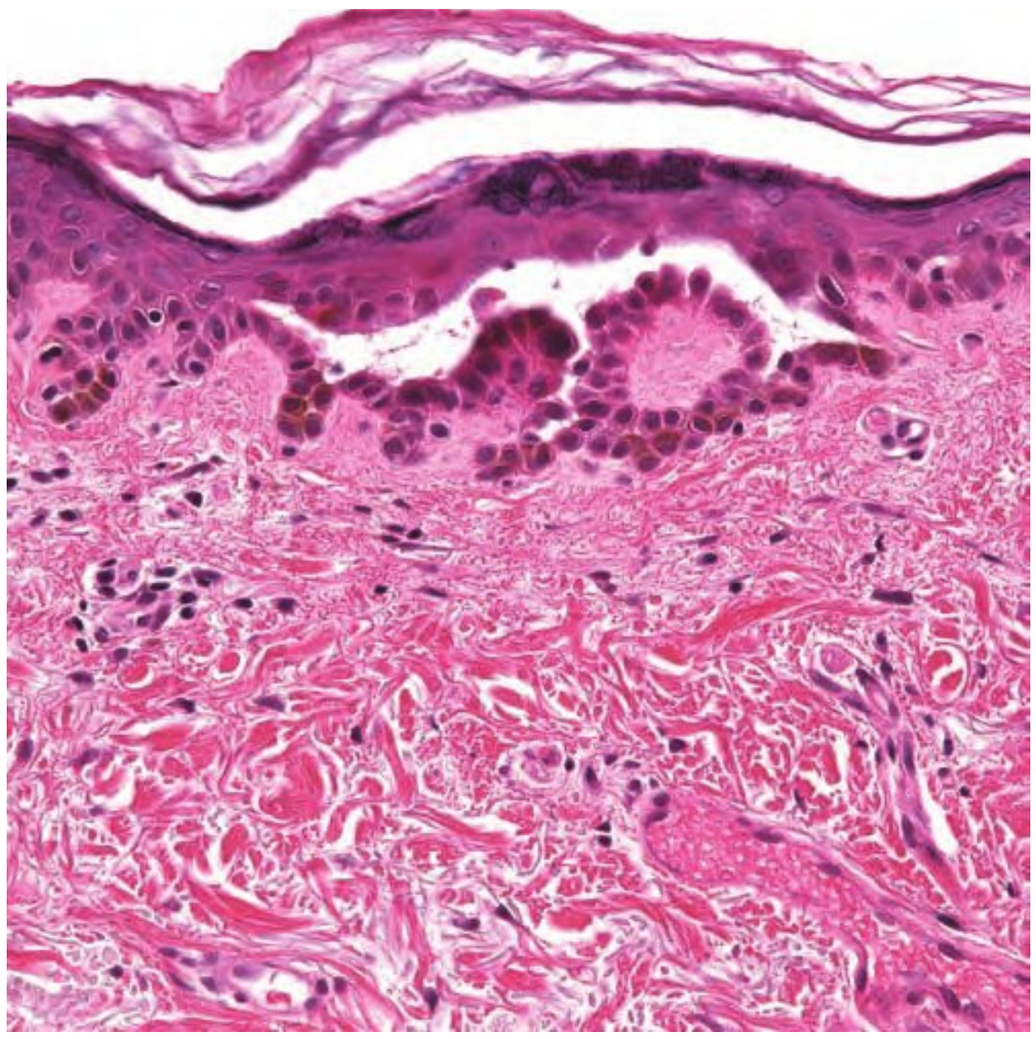


FIGURE 3-66. Focal acantholytic dyskeratosis represents another incidental finding that can be seen in normal skin.

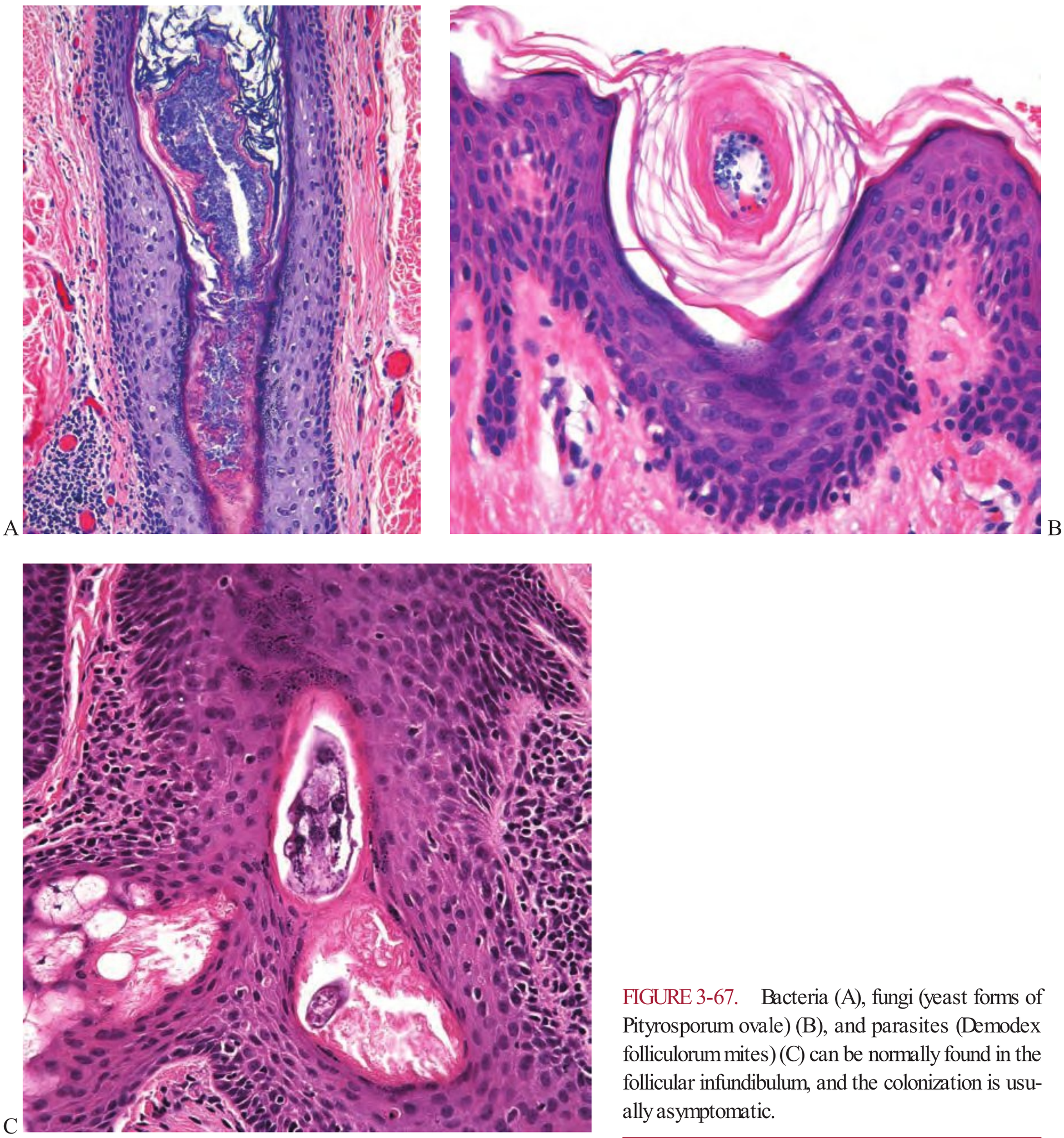


FIGURE 3-67. Bacteria (A), fungi (yeast forms of Pityrosporum ovale) (B), and parasites (Demodex folliculorum mites) (C) can be normally found in the follicular infundibulum, and the colonization is usually asymptomatic.

with dyskeratosis and acantholysis (349) (Fig. 3-66). The differential diagnosis includes Darier's disease, Grover's disease, warty dyskeratoma, acantholytic acanthoma, epidermal nevus, and others.

MICROORGANISMS PRESENT IN NORMAL SKIN

Microorganisms such as *Staphylococcus epidermidis*, yeast forms of *Malassezia furfur* (*Pityrosporum ovale*) (351), and *Demodex folliculorum* mites can be normally found in the follicular infundibulum, and the colonization is usually asymptomatic (Fig. 3-67A–C). The role of *D. folliculorum* in rosacea and other skin disorders is controversial. *Malassezia* yeasts are residents of normal human skin with a fine balance between commensalism and pathogenicity. They may play a role in seborrheic dermatitis and atopic eczema, and a form of *Pityrosporum* folliculitis has been described. They are the cause of tinea versicolor (in this last condition, however, hyphae are found admixed with yeasts in the cornified layer).

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CHAPTER 4

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Laboratory Methods

There are a number of important steps in preparing histologic sections prior to their interpretation by the dermatopathologist. Failure to handle the tissue properly may make it difficult to provide an accurate diagnosis or appropriate margins.

PREPARATION OF SPECIMENS

Fixation

It is important properly to fix a skin biopsy to stabilize proteins and prevent tissue decay. The specimen should be placed in fixative immediately after it is removed from the patient; artifacts may result if it is allowed to dry. The fixative of choice is a 10% neutral-buffered formalin solution. The volume of formalin should be 10 to 20 times the volume of the specimen. During winter, either 95% ethyl alcohol, 10% by volume, should be added to the formalin solution or the specimen should be allowed to stand in the formalin solution at room temperature for at least 6 hours before mailing.

Adequate time should be allowed for fixation. Fixation time is 1 to 2 hours per millimeter thickness. Large specimens, such as excised tumors, should be cut in the laboratory into slices 4 to 5 mm thick for further fixation, generally overnight. These specimens also require greater volumes of formalin.

Grossing

After fixation, ink should be applied to the deep and lateral margins of an excisional specimen for which examination of margins has been requested. The specimen should be appropriately cut for the examination of margins. Some examples are demonstrated in Fig. 4-1. It is important to remember that these cuts are only representative of the margins because it is almost impossible to evaluate every marginal cell. If a localizing suture has been placed by the surgeon, ink of a different color should be applied to that margin, or some other method of labeling should be used to identify the margins. Both 4- and 6-mm punch biopsies are generally bisected, and specimens less than 3 mm in size should be submitted in toto. If a laboratory does not handle many skin specimens, discussion with the embedding technician may be appropriate to facilitate optimal orientation of the blocks.

Demonstration of Enzyme Activities

With few exceptions, specimens should not be placed in formalin for the demonstration of enzyme activities. Instead, they should be delivered to the laboratory wrapped in water-moistened gauze and placed in a clean container because frozen sections cut on a cryostat are usually used for enzyme staining. Staining for enzyme activities is not routinely done and therefore should not be requested without first checking with the laboratory.

Although immunohistochemistry has largely replaced histochemistry for routine diagnostic use, demonstration of dopa-oxidase activity in melanocytes could potentially aid in distinguishing a malignant melanoma from tumors not composed of melanocytes. In addition, certain enzymes, such as succinic dehydrogenase and phosphorylase (eccrine), and acid phosphatase and β-glucuronidase (apocrine) can be detected in glandular tumors. However, these differentials are not usually significant clinically.

Several enzyme reactions can be carried out on formalin-fixed, paraffin-embedded tissue: (a) demonstration of naphthol AS-D chloroacetate esterase activity, with naphthol AS-D chloroacetate as substrate [present in mature and immature granulocytes, except in myeloblasts (1) and mast cells], and (b) demonstration of lysozyme with the antilysozyme immunohistochemical technique (lysozyme being present in mature and immature granulocytes, even in myeloblasts, and in histiocytes) (see Chapter 31).

In two diseases—scleredema of Buschke and amyloidosis—unfixed frozen sections may show a more conclusive reaction to specific staining methods than is obtainable with formalin-fixed material. It is therefore recommended that in these two diseases only part of the tissue be fixed in formalin and the remainder be used for frozen sections. In scleredema, demonstration of hyaluronic acid with toluidine blue at pH 7.0 may be more intense in unfixed, frozen sections than in formalin-fixed sections; in amyloidosis, the reactions of the amyloid with crystal violet or Congo red may be conclusive only in unfixed, frozen sections (see Chapter 17).

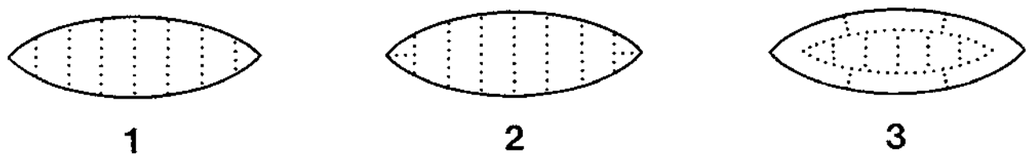


FIGURE 4-1. Preparation of blocks from a skin ellipse. After the margins have been painted with ink, the specimen is sectioned for processing and later embedding. In example 1 the tissue is cut as if one is slicing a loaf of bread; this is one of the most common methods used in dermatopathology laboratories. Example 2 allows for better evaluation of the "tips" of the ellipse; however, embedding of these small pieces is more difficult. Often only the center section of the "tips" is embedded, or the tips may be cut in half and embedded flat, especially for smaller specimens. In example 3, the entire margin is theoretically visualized; however, this method requires the technician meticulously to embed and orient small pieces of tissue and is not recommended for most specimens in most routine laboratories (65).

Processing

The purpose of processing is to remove the extractable water from the skin and to provide a supporting matrix (paraffin) so that the tissue can be cut with minimal distortion. After fixation, routine specimens are processed in an automatic processor. An exception is made for specimens that are to be stained for lipids. Because lipids are extracted by the xylene used for the processing of specimens, frozen sections are cut and postfixed in 10% neutral buffered formalin for lipid staining.

In the automated histology processor, the specimens pass first through increasing concentrations of ethanol for dehydration, then through xylene for lipid extraction and clearing of alcohol. Finally, the tissues are infiltrated with several changes of hot, melted paraffin (or Paraplast) to provide a matrix so that the tissue can be stabilized and cut easily. This processing takes between 4 and 12 hours; in most laboratories, processing is run overnight. Newer methodology includes microwave-assisted tissue processing, an application of microwave irradiation that accelerates tissue fixation and processing, allowing processing times of only 1 to 2 hours (1). This rapid tissue processing, when perfected, has yielded histologic material and immunohistochemical staining comparable in quality to conventional overnight tissue processing (2).

The next morning, the specimens are embedded with the cut surface face down into the cassette base mold, in the liquid paraffin, which is allowed to harden. To prevent tangentially oriented sections, it is important that this cut surface be firmly embedded in the base of this mold. The specimens are then cut on a rotary microtome into sections 5 to 7 μm thick.

Staining

Routine sections are usually stained with hematoxylin-eosin, the most widely used routine stain. With this staining method, nuclei stain blue or "basophilic," and collagen, muscles, and nerves stain red or "eosinophilic." Special stains are employed when particular structures need to be demonstrated (for details, see later discussion and ref. 3).

HISTOCHEMICAL STAINING

Histochemistry, especially immunohistochemistry, at both the light microscopic and electron microscopic level has gained increasing importance in recent years and has been largely responsible for the expansion of histopathology from a purely descriptive science to one that is dynamic and functional. Many enzyme histochemical methods are used only for research and have the limitation of usually requiring fresh tissue in the place of formalin-fixed tissue.

Most histochemical "special" stains can be carried out on formalin-fixed, paraffin-embedded material. Their primary uses in dermatopathology are listed in Table 4-1.

The *periodic acid-Schiff* (*PAS*) *stain* demonstrates the presence of certain polysaccharides, particularly glycogen and mucoproteins containing neutral mucopolysaccharides, by staining them red. The PAS reaction consists in the oxidation of adjacent hydroxyl groups in 1,2-glycols to aldehydes and the staining of the aldehydes with fuchsin-sulfuric acid. The PAS reaction is of value also in the study of basement membrane thickening, such as in lupus erythematosus or porphyria cutanea tarda. Furthermore, because the cell walls of fungi are composed of a mixture of cellulose and chitin and thus contain polysaccharides, fungi stain bright pink-red with the PAS reaction.

For the distinction of neutral mucopolysaccharides and fungi from glycogen deposits, it is necessary to compare two serial sections, one exposed to diastase before staining and the other not. Because glycogen is digested by the diastase and thus is no longer colored red by the PAS reaction, it can be easily distinguished from neutral mucopolysaccharides and fungi that are diastase resistant. Because glycogen is present in outer root sheath cells and eccrine gland cells, demonstration of glycogen may be of diagnostic value in adnexal tumors with outer root sheath or eccrine differentiation. Demonstration of neutral mucopolysaccharides is of value in Paget's disease of the breast and in extramammary Paget's disease.

The *alcian blue reaction* demonstrates the presence of acid mucopolysaccharides by staining them blue. Acid mucopolysaccharides are present in the dermal ground substance but in amounts too small to be demonstrable in normal skin. However, in the dermal mucinoses, there is a great increase in nonsulfated acid mucopolysaccharides, mainly hyaluronic acid, so that the mucin stains with alcian blue (see Chapter 17). In extramammary Paget's disease of the anus with rectal carcinoma (see Chapter 29) and in cutaneous metastases of carcinoma of the gastrointestinal tract containing goblet cells (see Chapter 36), tumor cells in the skin, like their parent cells, secrete sialomucin. Sialomucin contains nonsulfated acid mucopolysaccharides staining with alcian blue, as well as PAS-positive neutral mucopolysaccharides. Whereas nonsulfated acid mucopolysaccharides stain with alcian blue at

TABLE 4-1 Histochemical Stains Used in Dermatopathology

Stain	Purpose of stain	Results
Hematoxylin-eosin	Routine	Nuclei: blue Collagen, muscles, nerves: red
Masson trichrome	Collagen	Collagen: blue or green Nuclei, muscles, nerves: dark red
Verhoeff-van Gieson	Elastic fibers	Elastic fibers: black Collagen: red Nuclei, muscles, nerves: yellow
Pinkus acid orcein	Elastic fibers	Elastic fibers: dark brown
Silver nitrate	Melanin, reticulum fibers (argyrophilic)	Melanin, reticulum fibers: black
Fontana-Masson	Melanin (argentaffin)	Melanin: black
Methenamine silver	Fungi, Donovan bodies, Frisch bacilli (rhinoscleroma), basement membranes	Black
Grocott	Fungi	Fungus cell walls: black
Periodic acid-Schiff/diastase (PAS)	Glycogen, neutral MPS, fungi	Glycogen: red; diastase labile Neutral MPS, fungi: red; diastase resistant
Alcian blue, pH 2.5	Acid MPS	Blue
Alcian blue, pH 0.5	Sulfated MPS	Blue
Toluidine blue	Acid MPS	Blue
Colloidal iron	Acid MPS	Blue
Hyaluronidase	Hyaluronic acid	Hyaluronidase labile
Mucicarmine	"Epithelial" mucin	Red
Giemsa	Mast cell granules, acid MPS, myeloid granules, Leishmania	MCG, acid MPS: metachromatically purple Myeloid granules, Leishmania: red
Fite	Acid-fast bacilli	Red
Perl's potassium ferrocyanide	Hemosiderin (iron)	Blue
Alkaline Congo red	Amyloid	Pink-red, green birefringence in polarized light
Von Kossa	Calcium	Black
Scarlet red	Lipids	Red
Oil red O	Lipids	Red
Dopa (in unfixed tissue)	Tyrosinase in melanocytes	Black dopa-melanin
Naphthol-AS-D-chloroacetate esterase	Mast cells, neutrophils, myelocytes	Granules stain red
Warthin-Starry	Spirochetes	Black
Dieterle and Steiner	Spirochetes, bacillary angiomatosis	Black
Ziehl Neilson	Acid-fast bacilli	Red

MCG, mast cell granules; MPS, mucopolysaccharides.
Note: All stains, except those for lipids, can be carried out on formalin-fixed, paraffin-embedded specimens. The stains for lipids require formalin-fixed frozen sections.

pH 2.5 but not at pH 0.5, strongly acidic sulfated acid mucopolysaccharides, such as heparin in mast cell granules and chondroitin sulfate in cartilage, stain with alcian blue both at pH 2.5 and at pH 0.5.

Several special stains for elastic tissue are available. The most commonly used stains are the Verhoeff-van Gieson stain (Fig. 4-2) or Weigert's resorcin-fuchsin. Additional techniques, such as the Luna stain and the Miller stain, may allow better visualization of elastic fibers than traditional methods (4). These stains are beneficial in the diagnosis of anetoderma, connective tissue nevi, mid-dermal elastolysis, and other alterations of elastic tissue.

The Giemsa stain is frequently used to highlight mast cells. Giemsa contains methylene blue, a metachromatic stain. The granules of a mast cell stain metachromatically purple (Fig. 4-3).

POLARISCOPIC EXAMINATION

Polariscopic examination is the examination of histologic sections under the microscope with polarized light, that is, light from which all waves except those vibrating in one plane are excluded.

For polariscopic examination, two disks made of polarizing plastics are placed on the microscope. One disk is placed below the condenser of the microscope and acts as the polarizer. The second disk is placed in the eyepiece of the

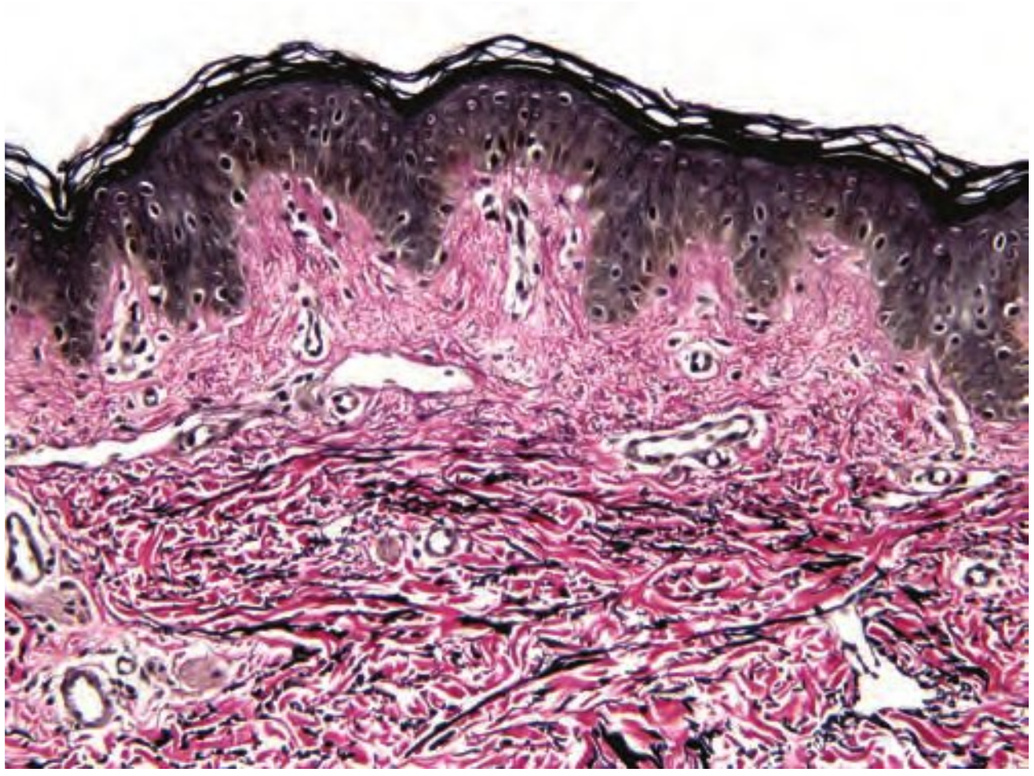


FIGURE 4-2. Elastic fibers. This Verhoeff-van Gieson stain demonstrates the darkly staining normal elastic fibers of the skin.

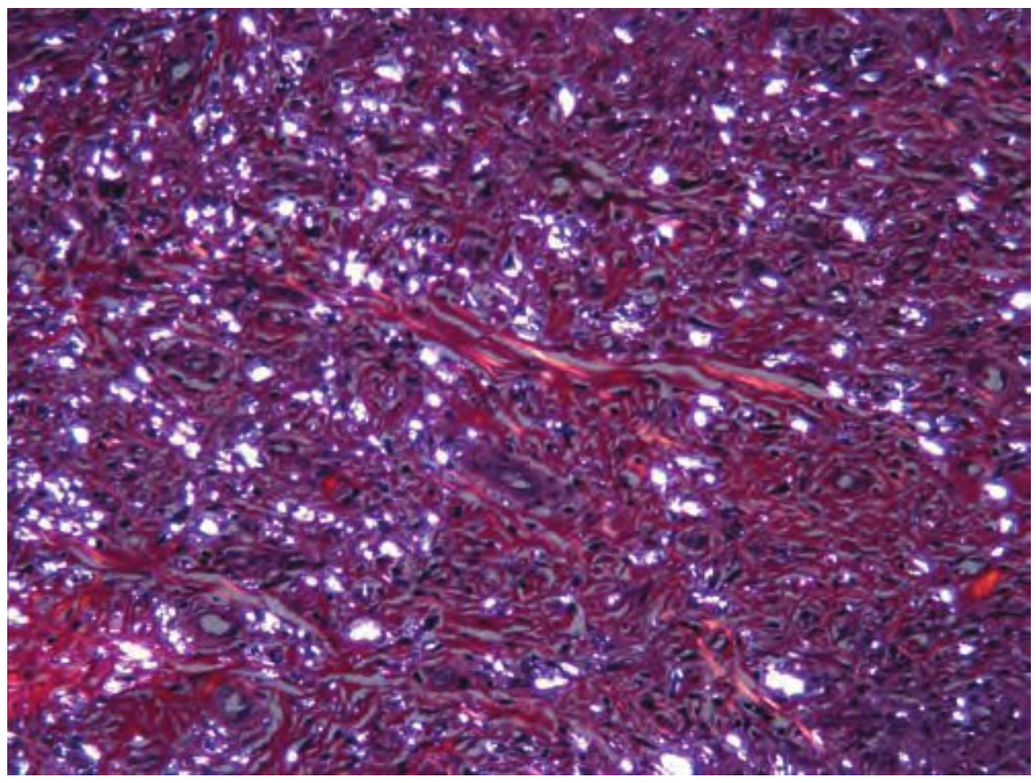


FIGURE 4-4. Polariscopic examination. In this talc granuloma, polariscopy reveals hundreds of refractile foreign bodies within the dermis.

microscope or on top of the glass slide and acts as the analyzer. When one of the two disks is rotated so that the path of the light through the two disks is broken at a right angle, the field is dark. However, when doubly refractile substances are introduced between the two disks, they break the polarization and are visible as bright white bodies in the dark field.

Polariscopic examination is useful in evaluating lipid deposits, certain foreign bodies, gout, and amyloid.

With regard to lipids, it is not fully known why certain lipids are doubly refractile and others are not. In general, cholesterol esters are doubly refractile, but free cholesterol, phospholipids, and neutral fat are not. Only formalin-fixed, frozen sections can be used for a polariscopic examination for lipids.

Doubly refractile lipids are regularly present in the tuberous and plane xanthomas and xanthelasmata (but not always in the eruptive xanthomas) of hyperlipoproteinemia, in the cutaneous lesions of diffuse normolipemic plane xanthoma, and in the vascular walls of angiokeratoma corporis diffusum (Fabry disease) (see Chapter 33). Doubly refractile lipids are present, as long as the cutaneous lesions contain a sufficient amount of lipid, in histiocytosis X (Hand-Schüller-Christian type) (see Chapter 26), in juvenile xanthogranuloma (see Chapter 26), in erythema elevatum diutinum (extracellular cholesterosis) (see Chapter 8), and in dermatofibroma (lipidized "histiocytoma") (see Chapter 32).

Doubly refractile lipids are absent in lipid-containing lesions, as a rule, in necrobiosis lipoidica (see Chapter 14), in hyalinosis cutis et mucosae or lipoid proteinosis (see Chapter 17), and in multicentric reticulohistiocytosis and solitary reticulohistiocytic granuloma (see Chapter 26).

Among foreign bodies, silica causes granulomas showing doubly refractile spicules. These granulomas are caused either by particles of soil or glass (silicon dioxide) or by talcum powder (magnesium silicate) (see Chapter 14). Wooden splinters, suture material, and starch granules are also doubly refractile. An example of polariscopic examination is seen in Fig. 4-4.

Gout tophi show double refraction of the urate crystals if the crystals are sufficiently preserved. They are preserved by the use of alcohol rather than formalin for fixation (see Chapter 17).

Amyloid shows a characteristic green birefringence in polarized light after staining with alkaline Congo red (see Chapter 17).

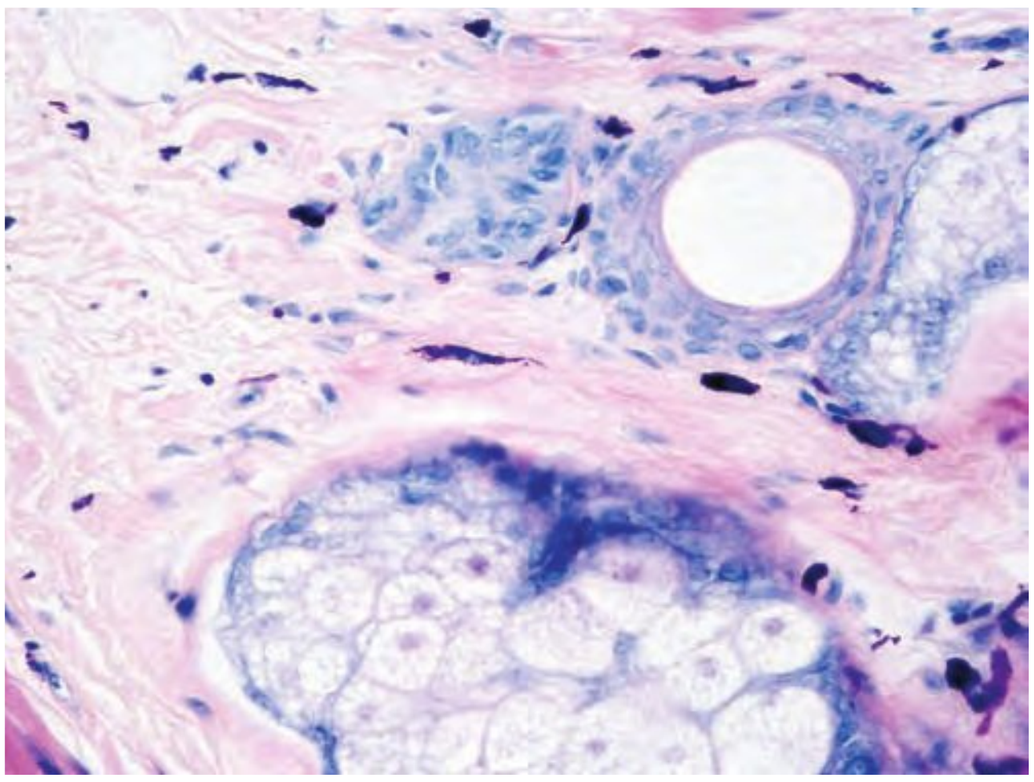


FIGURE 4-3. Giemsa stain. Mast cell cytoplasmic granules are purple.

IMMUNOFLUORESCENCE TESTING

Two immunofluorescence methods are commonly used in dermatology: direct immunofluorescence testing, which probes for immunoreactants localized in patients' skin or mucous membranes, and indirect immunofluorescence testing, which

is used to identify and titer circulating autoantibodies in the patient's serum. A modified indirect immunofluorescence technique using the patient's skin as a substrate, known as immunomapping, is used to determine the site of cleavage or abnormalities in the distribution of mutated proteins in various forms of hereditary epidermolysis bullosa.

DIRECT IMMUNOFLUORESCENCE

Direct immunofluorescence testing has a valuable diagnostic role in several autoimmune and inflammatory mucocutaneous diseases, including autoimmune-mediated blistering diseases, dermatitis herpetiformis, Henoch-Schoenlein purpura [immunoglobulin (Ig) A vasculitis], and cutaneous lupus erythematosus. The role of direct immunofluorescence as a diagnostic procedure is important but not critical in other dermatoses, such as dermatomyositis, cutaneous porphyrias, pseudoporphyria, lichen planus, and vasculitides other than Henoch-Schoenlein purpura (5). Table 4-2 illustrates a stepwise schematic for evaluation of immunofluorescence sections prior to making an immunopathologic diagnosis.

Biopsy Techniques

A 3- to 4-mm punch biopsy is generally adequate. In the group of autoimmune blistering diseases an inflamed but unblistered perilesional area is the ideal specimen. Blistered-lesional sampling is the most common cause of false-negative results. On the other hand, sampling too distant from the blistering also can cause false-negative results. In a few cases of pemphigus, pemphigoid, and epidermolysis bullosa acquisita, false-positive results can occur in blistered lesions. Of note, due to the often focal and skipping nature of the immunoreactants in dermatitis herpetiformis, a shave biopsy often provides a broader surface with which to evaluate dermal papillae than a punch biopsy.

The performance of an adequate perilesional biopsy in mucosal lesions is often not feasible, and thus a high incidence of false negatives and even false positives may occur in these specimens. In patients with desquamative gingivitis secondary to mucous membrane pemphigoid an easy way to obtain sampling is by the so-called "peeling technique," in which rubbing the perilesional affected gingivae with a cotton swab induces a "fresh peeling of the mucosa." In most cases of mucous membrane pemphigoid, the 180- and 230-kD hemidesmosomal antigens are the autoantigens; therefore, the hemidesmosomes will be available for interpretation in the peeled gingivae specimens, and a linear immunostaining with "capping" phenomenon is observed (6).

It has been reported that there is a theoretical higher incidence of false-negative results in bullous pemphigoid lesions from lower extremities; however, this finding has not been confirmed by others.

In asymptomatic dermatitis herpetiformis patients who have strictly adhered to a gluten-free diet for less than 6 months, or even patients that have not done so but remain lesion-free due to dapsone therapy, wide-shaved specimens from the elbows or any other classically affected area will still show the typical IgA deposits at the tips of dermal papillae (7).

In autoimmune and inflammatory disorders other than autoimmune blistering diseases in which direct immunofluorescence plays an important role, the specimens should be taken from lesional areas, including cutaneous lupus erythematosus, dermatomyositis, vasculitides, lichen planus, cutaneous porphyria, and pseudoporphyria.

Transport and Processing of Biopsy Specimens

Tissue for immunofluorescence studies should be obtained fresh and kept moist until it is quickly frozen. Skin specimens can be kept on saline-moistened gauze in a small Petri dish for 24 hours but not longer before processing. For longer delay times the specimens should be put into Michel's transport medium. This medium is composed of 5% ammonium sulfate, the potassium inhibitor *N*-ethylmaleimide, and magnesium sulfate in citrate buffer (pH 7.25). This solution is stable at room temperature but must be kept in a tightly capped container to prevent absorption of CO_2 and acidification. Specimens stored in Michel's medium are stable for at least 2 weeks at room temperature. Specimens stored in Michel's medium and kept in the refrigerator can be preserved for several weeks or even months. This method of transportation has made the direct immunofluorescence technique much more readily applicable. When the specimen is received in a laboratory the ammonium sulfate is washed out and the specimen is oriented and embedded in O.C.T. (Optimal Cutting Temperature) compound and then the specimen is snap frozen. The tissue is then sectioned at 6 μm. The frozen sections are incubated with antihuman antibodies to IgG, IgA, IgM, C3, C5b-9, and fibrinogen. These antibodies are linked to a fluorescent label such

TABLE 4-2 Multistep Scheme for the Interpretation of Cutaneous Direct Immunofluorescence (IF)

Real vs. artifact
Relevant vs. irrelevant
Specific vs. nonspecific
T
Location of IF
(Epithelial, basement membrane zone, vascular)
T
Dominant immunoreactant
(immunoglobulin [Ig] G? IgA? IgM? C3? Fibrin?)
T
Characteristics
(granular? Linear)
T
Diagnostic algorithm based on IF patterns

as fluorescein isothiocyanate to allow visualization using a fluorescence microscope (5).

Direct Immunofluorescence Interpretation

Autoimmune Blistering Diseases

Sensitivity of direct immunofluorescence with active autoimmune blistering disease should be close to 100%. If it is not, it is likely due to technical reasons (8). In pemphigus vulgaris and pemphigus foliaceus the IgG immunostaining on the epithelial cell surfaces can be granular and/or linear, giving a characteristic "chicken wire" pattern. Nonspecific patchy granular staining along the basement membrane is not uncommon, especially in mucosal lesions. In paraneoplastic pemphigus the IgG "chicken wire" immunostaining tends to be linear, thick, and homogeneous throughout the epidermis and mucosal specimens, including those from bronchi with or without a concomitant linear basement membrane (9). Lichenoid mucosal and even cutaneous lesions in paraneoplastic pemphigus tend to show focal granular IgG and other immunoreactants along the basement membrane without the typical "chicken wire" pattern. The presence of low titers of circulating autoantibodies may preclude differentiation among the subepithelial autoimmune blistering disorders using indirect immunofluorescence or any other serologic test. In these cases a technique called salt-split direct immunofluorescence often circumvents this problem. This technique consists of thawing the frozen specimen formerly used for routine direct immunofluorescence and incubating it in 1 M NaCl for 48 to 72 hours, allowing for separation of the epidermis from the dermis. This salt cleaves the basement membrane zone through the lamina lucida, leaving the hemidesmosomes on the epidermal side and deeper-seated proteins such as type VII collagen and epiligrin on the dermal side of an artificially induced blister. Therefore, in virtually all cases of bullous pemphigoid the linear IgG immunostaining will be localized on the epidermal side (occasionally epidermal and dermal) and in epidermolysis bullosa acquisita on the dermal side.

Cutaneous Lupus Erythematosus

Direct immunofluorescence has a significant value in the evaluation of patients with active cutaneous connective tissue disease. The intensity of the deposits of immunoreactants along the basement membrane in these patients correlates with the degree of interface/lichenoid dermatitis/mucositis.

In discoid lupus erythematosus the most common immunoreactant visualized with direct immunofluorescence is IgM; in systemic lupus erythematosus and in subacute cutaneous lupus erythematosus it is IgG. Of note, most patients with anti-Ro–positive subacute cutaneous lupus erythematosus may have a characteristic granular IgG speckling pattern along the basement membrane and throughout the epidermis. The lupus band test, described as positive when granular IgG is present along the basement membrane zone in specimens from sun-protected nonlesional areas, is rapidly being abandoned due to its unreliability and the availability of more reliable methods for the early diagnosis and prediction of systemic disease in lupus erythematosus (10,11).

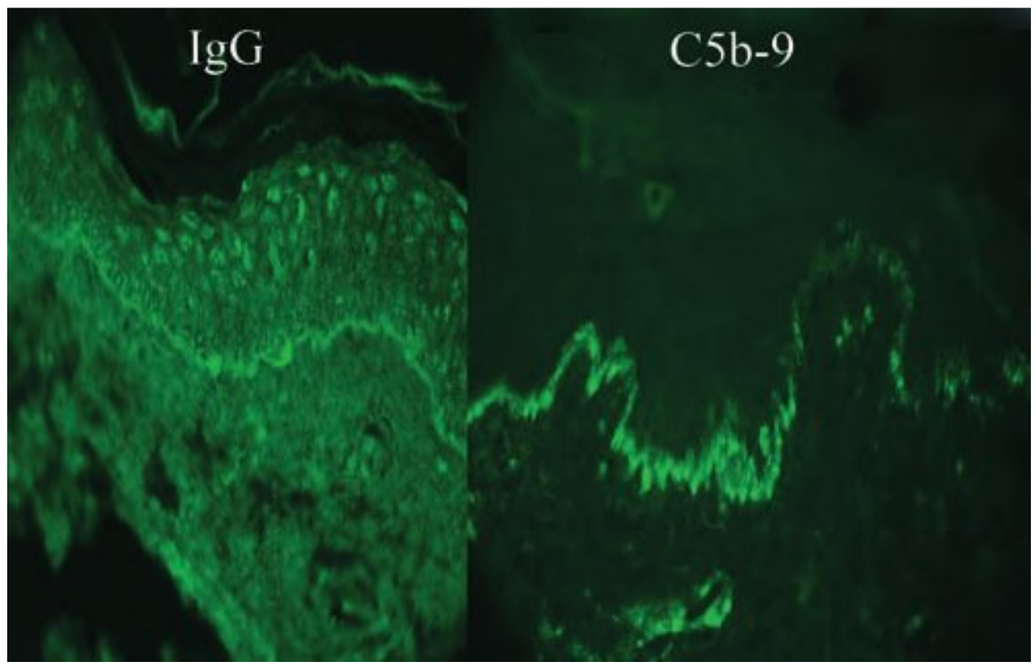


FIGURE 4-5. Cutaneous Ro-positive cutaneous lupus erythematosus (idiopathic or drug induced) and dermatomyositis direct immunofluorescence patterns. Left: Ro-positive cutaneous lupus erythematosus (idiopathic or drug induced). Granular immunoglobulin G speckling "dusting" pattern throughout the epidermis (keratinocyte cytoplasmic) with mild deposits at the basement membrane zone and an often in vivo antinuclear antibody pattern highlighting keratinocyte nuclei. Right: Dermatomyositis. Dense granular C5b-9 (membrane attack complex) deposits along the basement membrane zone and upper dermal vessels.

In cutaneous lesions of dermatomyositis, dense, granular C5b-9 (membrane attack complex) deposition at the basement membrane zone and upper dermal vessels along with that of weaker C3, IgG, and IgM deposits is a quite characteristic immunofluorescence pattern that often helps to distinguish dermatomyositis from lupus erythematosus spectrum, namely in acute phases of these diseases (Fig. 4-5) (12,13).

Cutaneous Vasculitides

Direct immunofluorescence evaluation is a very important diagnostic tool in the workup of cutaneous small vessel vasculitis, especially Henoch-Schoenlein purpura. The best immunofluorescence diagnostic yield in Henoch-Schoenlein purpura is obtained from 1- to 2-day-old lesions. As lesions get older, the IgA deposits get degraded and cleared. Because most patients have older lesions at the time of the evaluation, a high index of suspicion is required and exhaustive search for scant granular IgA deposits in very superficial papillary dermis is mandatory before ruling out Henoch-Schoenlein purpura.

Hypocomplementemic urticarial vasculitis is another small-vessel vasculitis in which direct immunofluorescence plays a critical diagnostic role. In this type of cutaneous vasculitis, granular IgG and C3 deposits are seen in and around small dermal vessels and along the basement membrane zone. The presence of basement membrane granular immunostaining among other clinical and serologic findings in patients with hypocomplementemic urticarial vasculitis have led some

authors to believe that this vasculitis is no more than a subset of systemic lupus erythematosus (14).

Other Autoimmune and Inflammatory Skin Diseases

Lichen planus lesions, mainly the mucosal variant, are characterized by typical yet not pathognomonic, linear and shaggy fibrin deposits and patchy granular IgM and C3 along the basement membrane.

The direct immunofluorescence findings in cutaneous porphyrias are indistinguishable from those seen in pseudoporphyria. These findings are characterized by thick and glassy linear IgG and IgA deposits in superficial dermal vessels in a "doughnut pattern" and along the basement membrane. It is believed that immunoglobulins become trapped and bound to glycoproteins in a thickened basement membrane zone and degenerated blood vessels in this disorder.

INDIRECT IMMUNOFLUORESCENCE

Indirect immunofluorescence is a semiquantitative procedure in which a double immunolabeling is carried out to evaluate the presence and titer of circulating antibodies or specifically to localize antigen in the skin.

Indirect Immunofluorescence in the Evaluation of Circulating Antiepithelial Antibodies

Blood is drawn into a tube without anticoagulant, and the serum is serially diluted. Substrates most commonly used are 6-μm frozen sections of monkey esophagus, human salt-split skin, and murine bladder. The substrate is incubated with serum dilutions for 30 minutes at room temperature and then washed; antibodies bound to the substrates are detected by incubation with fluorescein isothiocyanate–labeled goat anti-human IgG and/or IgA.

Monkey esophagus is probably the best substrate for the evaluation of antiepithelial surface antibodies specifically for pemphigus vulgaris and paraneoplastic pemphigus. Pemphigus foliaceus has a high incidence of false-negative results with this substrate. Low titers of antiepithelial surface antibodies up to 1:80 or even higher can also be seen in control sera (15). In pemphigus vulgaris and foliaceus, antidesmoglein antibodies give a "chicken wire" staining that is more predominant on superficial epithelial cells, whereas in paraneoplastic pemphigus the antiplakin antibodies give a pattern that is consistently homogeneous throughout the epithelium and sometimes is even associated with immunostaining along the basement membrane zone.

Transitional epithelium is a plakin-rich substrate, and thus murine bladder is a common substrate for the screening of circulating antiplakin antibodies in paraneoplastic pemphigus (16). Exceptional cases of pemphigus vulgaris and foliaceus and pemphigoid can have concomitant low-titer antidesmoplakin antibodies (Fig. 4-6).

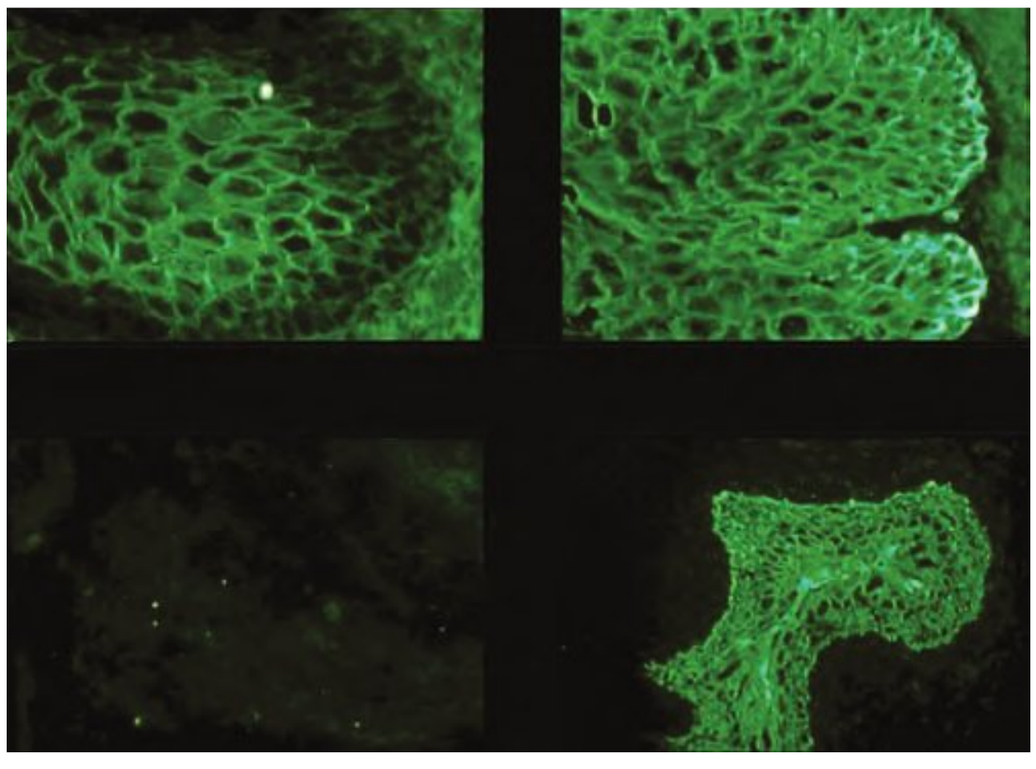


FIGURE 4-6. Differentiation between pemphigus vulgaris and paraneoplastic pemphigus, using indirect immunofluorescence. Left upper quadrant shows pemphigus vulgaris. Indirect immunofluorescence showing immunoglobulin G (IgG) bound to the epithelial cell surface of the stratified squamous epithelium of monkey esophagus. Of note, the "chicken wire" pattern is more prominent in the most superficial aspects of the epithelium. Left lower quadrant shows pemphigus vulgaris. Indirect immunofluorescence showing no IgG bound to the epithelial cell surface of transitional epithelium of murine bladder. Transitional epithelium does not have desmogleins, the autoantigens of pemphigus vulgaris and foliaceus. Right upper quadrant shows paraneoplastic pemphigus. Indirect immunofluorescence showing IgG bound to the epithelial cell surface of the stratified squamous epithelium of monkey esophagus. Of note, the "chicken wire" pattern is consistent throughout the epithelium and also along the basement membrane zone. Plakins, the autoantigens in paraneoplastic pemphigus, are ubiquitous desmosomal and hemidesmosomal proteins present in squamous and nonsquamous epithelia. Right lower quadrant shows paraneoplastic pemphigus. Indirect immunofluorescence showing IgG bound to the epithelial cell surface of transitional epithelium of the bladder. Transitional epithelium is rich in plakins.

Monkey esophagus is also a useful substrate in the indirect immunofluorescence screening for subepidermal autoimmune blistering disease. However, human salt-split skin renders better definition of the subtypes of subepidermal blistering disorders. Disorders characterized by antibodies to hemidesmosomal proteins BP180 and BP230, including those seen in bullous and gestational pemphigoid, some cases of mucous membrane pemphigoid, and linear IgA bullous disease, are associated with a linear immunostaining on the epidermal side (roof) of the salt-split human skin.

On the other hand, patients with circulating antibodies reacting against type VII collagen and antiepiligrin (laminin 5), as is seen in epidermolysis bullosa acquisita and antiepiligrin mucous membrane pemphigoid, respectively, have circulating IgG autoantibodies that bind the dermal side of the salt-split human skin.

More sensitive and specific assays for the evaluation of circulating autoantibodies, including enzyme-linked immunosorbent assay for antidesmoglein and anti-BP180 antibodies, immunoblotting and immunoprecipitation for pemphigoid, epidermolysis bullosa acquisita, and antiepiligrin, and immunoprecipitation for paraneoplastic pemphigus, have been recently incorporated into the diagnostic armamentarium of autoimmune blistering diseases.

Indirect Immunofluorescence for the Evaluation of Site of Cleavage in Hereditary Epidermolysis Bullosa

This technique offers a practical yet useful diagnostic tool in hereditary epidermolysis bullosa by revealing the site of the defect in these mechanobullous disorders. Thus, this technique classifies these disorders into epidermolytic, functional, and dermolytic categories (Table 4-3).

In brief, this technique is performed as follows: A freshly induced blister is obtained by twisting a rubber-ended pencil, and then this artificially induced blister skin specimen is incubated with anti–type IV collagen and anti-BP180 antigen. Then, according to localization of the immunolabeling of these antibodies, the site of cleavage can be deduced.

In some cases of generalized atrophic benign epidermolysis bullosa where the mutated protein is the BP180 antigen the immunostaining in the floor of the induced blister given by the anti-BP180 may be focal or absent. Specific antibodies to the mutated protein are also used for complementary diagnostic purposes. These antibodies include antiplectin antibodies for epidermolysis bullosa simplex with muscular dystrophy, anti-$\alpha 6\beta 4$ for junctional epidermolysis bullosa with pyloric atresia, anti–laminin 5 antibodies for most cases of junctional epidermolysis bullosa, and anti–type VII collagen for most cases of the dystrophic form of hereditary epidermolysis bullosa. These specific antibodies are intended to identify a disrupted linear staining due to an even distribution of the probed mutated protein (17,18). The definite diagnosis of hereditary epidermolysis bullosa is made with electron microcopy and genetic analysis.

TABLE 4-3 Indirect Immunofluorescence for the Evaluation of site of Cleavage in Hereditary Epidermolysis Bullosa (HEB)

Type of HEB	Anti-BP180 immunostaining	Anti–type IV collagen immunostaining
Epidermolytic (simplex)	Floor	Floor
Junctional	Roof	Floor
Dermolytic	Roof	Roof

IMMUNOHISTOCHEMISTRY

Introduction, Techniques

Immunohistochemistry techniques have been available since the early 1970s, but they have been used widely for diagnostic pathology only since the early 1980s. They are mainly used to diagnose poorly differentiated malignant tumors and lymphoma. They can also be beneficial in the diagnosis of bullous diseases (14). With the refinement of techniques, immunohistochemistry methods have achieved the same sensitivity for many antigens in paraffin-embedded tissues as the direct immunofluorescence method in frozen sections. The paraffin-embedded tissues offer the advantage over frozen sections of better preservation of cellular details and permanency of the reaction, so that the specimens can be preserved and stored. Most monoclonal antibodies, especially those necessary for the diagnosis of lymphoma, when first introduced required frozen section studies, but monoclonal and polyclonal antibodies are now available that can be applied to formalin-fixed, paraffin-embedded tissue, such as antibodies for the identification of B cells, T cells, and macrophages and many other cell types.

Sections that will be incubated with polyclonal or monoclonal antibodies should be mounted on glass slides specially coated or charged to ensure better adherence (19).

Certain antibodies, including antibodies against keratins, lysozyme, or chymotrypsin, require protease digestion if formalin-fixed, paraffin-embedded sections are used. Other "antigen retrieval" methods include the use of heat, either by microwaving or steaming the sections, and pretreatment of the sections with acid (HCl).

Immunohistologic Techniques

In most laboratories, immunopathology techniques are well established. Historically, several techniques have been used; the peroxidase–antiperoxidase technique has been replaced by more sensitive techniques, namely, techniques using avidin-biotin-peroxidase complex, alkaline phosphatase/anti–alkaline phosphatase, and streptavidin peroxidase or alkaline phosphatase. In all of these methods, the antibody is used to localize an enzyme (peroxidase or phosphatase) to sites of antigen expression in tissue sections. An appropriate "chromogen" is then added—a reagent that has the property of developing a color that can be visualized at sites of localization of the enzyme-antibody-antigen complex.

The Alkaline Phosphatase/Anti–Alkaline Phosphatase Technique

This is an unlabeled antibody bridge technique that uses three antibodies; the first and third antibodies are from the same species and are monoclonal. The second antibody is polyclonal, from the rabbit, and forms a bridge between the first and third antibodies (20). The third antibody is linked to the enzyme alkaline phosphatase. After applying these antibodies with the linked enzyme, an alkaline phosphatase

substrate is added containing a compatible indole chromogen such as 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-phenyltetrazolium chloride (INT)/5-bromo-4-chloro-3′-indolyl phosphate *p*-toluidine salt (BCIP) (which yields a red color after the phosphatase-catalyzed reaction), naphthol fast red (red color), or nitro-blue tetrazolium chloride (NBT)/BCIP (blue). This method may be useful for pigmented tumors because the blue or red reagents can be distinguished easily from melanin (19).

The Avidin-Biotin-Peroxidase Complex and Streptavidin Peroxidase or Alkaline Phosphatase Techniques

The avidin-biotin technique takes advantage of the strong interaction of avidin with biotin (21,22). Avidin is a glycoprotein found in egg white that has a strong affinity to biotin, a vitamin of low molecular weight. The streptavidin technique is exactly analogous, but achieves sensitivity one to two orders of magnitude greater by using streptavidin in place of avidin. This method is becoming standard. In these techniques, the primary antibody (which may be monoclonal or polyclonal) binds directly with the specific antigen, in or on the cells, to form a stable antigen–antibody complex within the tissue section. A secondary antibody that has been labeled with biotin (biotinylated) and is directed against the same species and immunoglobulin type binds to the primary antibody, leaving the biotinylated end available. A peroxidase or an alkaline phosphatase detection system can be used. In a peroxidase method, the biotinylated complex is detected by avidin or streptavidin that has been conjugated to the peroxidase enzyme. A peroxidase-oriented chromogen is then added, such as diaminobenzidine (yielding a brown color) or aminoethylcarbazole (red color, and therefore useful for pigmented lesions). The alkaline phosphatase-streptavidin method is analogous to the streptavidin peroxidase method, but in this case the biotinylated complex is detected with an alkaline phosphatase–linked streptavidin and requires a compatible chromogen such as the indole reagents INT/BCIP (red color), naphthol fast red (red), or NBT/BCIP (blue). This technique in the authors' experience achieves the greatest sensitivity of all immunohistochemical methods.

The origin of an undifferentiated cell can usually be determined with the application of monoclonal or polyclonal antibodies. A "panel approach" using multiple markers is the best method for evaluating problem neoplasms. Positive and negative controls should be used. If tumor cells unexpectedly do not show a positive reaction with a certain antibody, several possibilities exist, including technical difficulties with the assay. One may encounter nonspecific staining as well as aberrant immunoreactivity (observed staining with a particular antibody where it is theoretically unexpected). Caution should be taken not to make a diagnosis based on immunohistochemistry alone. Unfortunately, there is no antibody that reliably distinguishes between benign and malignant cells.

APPLICATIONS OF IMMUNOHISTOPATHOLOGY

Diagnosis of Tumors (Excluding Lymphomas)

The most important antibodies for routine dermatopathology and their occurrence in certain cells and tissues are listed in Table 4-4. The most frequently used antibodies in dermatopathology are discussed below. The list of available antibodies is extensive; detailed information is available in literature and text reviews (23–27).

Antibodies Against Cytoskeletal Antigens

The cytoskeleton of a cell consists of intermediate filaments measuring 7 to 11 nm in diameter, actin-containing microfilaments, and tubulin-containing microtubules (28–30). Intermediate filaments are smaller than microtubules (25 nm) but larger than microfilaments (6 nm), hence the designation intermediate.

Antibodies against intermediate filaments (IFs) help to identify the origin of an anaplastic cell. Malignant tumors usually retain the intermediate filament type characteristic of the tissue of origin, and metastases generally continue to express these intermediate filaments (31). There are six groups of intermediate filaments. Type 1 and 2 IFs include cytokeratins, which are present in epithelia. Type 3 IFs include vimentin, found in mesenchymal cells and melanocytes; desmin, found in most muscle cells; and glial fibrillary acidic protein, found in glial cells and astrocytes. Type 4 IFs include neurofilaments, which are components of neurons. Nuclear lamins constitute type 5 IFs, and nestin comprises type 6 and is found in some stem cells. In dermatopathology, keratin antibodies are used to differentiate epithelial from nonepithelial (melanocytic, hematopoietic, and mesenchymal) tumors. A mixture of antibodies against low and intermediate keratins such as AE1 and AE3 (AE1/3) is commonly used (32). An additional antibody to low–molecular weight keratins such as CAM 5.2 may be beneficial in poorly differentiated carcinomas (33). The keratin marker CK20 has useful specificity for Merkel cell carcinoma (34).

Atypical spindle cell tumors, for example, are often difficult to diagnose with routine stains. The differential diagnosis for such lesions includes spindle cell squamous cell carcinoma, atypical fibroxanthoma, leiomyosarcoma, and spindle cell malignant melanoma. Table 4-5 lists the most important antibodies to use (35).

Vimentin

Vimentin is an intermediate filament originally isolated from chick embryo fibroblasts. It is found in fibroblasts, endothelial cells, macrophages, melanocytes, lymphocytes, and smooth muscle cells. Antibodies to vimentin are found in both benign and malignant counterparts of these cells (36). There have also been reports of positivity in epithelial tumors (37); however, normal epidermis is negative with this antibody. Because of the nonspecific nature of the antibody, it is useful only as a panel approach to support mesenchymal or melanocytic differentiation.

TABLE 4-4 Common Antigens That Can Be Detected in Formalin-Fixed, Paraffin-Embedded Sections

Antigen	Location
Cytokeratins, including AE1, AE3, CAM 5.2, CK20	Epidermis and its appendages and their tumors
Vimentin	Mesenchymal cells, melanocytes, lymphomas, sarcomas, melanomas
Desmin	Smooth and skeletal muscle, muscle tumors
Leukocyte common antigen (LCA)	Benign leukocytes, lymphoma, leukemia
CD45-RO (UCHL-1)	T lymphocytes
CD20 (L-26)	B lymphocytes
Epithelial membrane antigen (EMA)	Sweat and sebaceous glands, carcinoma, epithelioid sarcoma
Carcinoembryonic antigen (CEA)	Eccrine and apocrine glands and their tumors, Paget cells
S100 protein	Melanocytes, Langerhans cells, eccrine and apocrine glands and their tumors, Schwann cells, nerves, interdigitating reticulum cells, chondrocytes, melanomas, adipose tissue, liposarcomas, Langerhans cell histiocytosis
HMB-45	Melanoma cells, some nevus cells
Chromogranin	Neuroendocrine cells, Merkel cell carcinoma, eccrine gland cells
Synaptophysin	Neuroendocrine cells, Merkel cell carcinoma
Lysozyme	Macrophages, granulocytes, myeloid cells
α1-Antitrypsin, α1-antichymotrypsin	Macrophages, "fibrohistiocytic" neoplasms including malignant fibrous histiocytoma, but nonspecific in most routine practice
Factor VIII–related antigen	Endothelial cells, angiosarcomas, Kaposi's sarcoma
Ulex europaeus agglutinin I	Endothelial cells, keratinocytes, angiosarcomas, Kaposi's sarcoma
CD31	Endothelial cells
CD34	Endothelial cells, bone marrow progenitor cells, cells of dermatofibrosarcoma protuberans
Smooth muscle actin	Smooth muscle cells and tumors, myofibroblastic cells
MART-1/Melan-A	Melanocytes, nevi, melanoma
Factor XIIIa	Dermatofibromas, certain fibrohistiocytic cells (see text)
CD1a	Langerhans cells

Note: Few if any of these reagents are perfectly specific for their target antigens. Every test must be interpreted in the context of all of the available histologic and clinical information.

Carcinoembryonic Antigen and Epithelial Membrane Antigen

Carcinoembryonic antigen (CEA) has been found in normal eccrine and apocrine cells, in benign sweat gland tumors, and in mammary and extramammary Paget's disease of the skin. Incubation with anti-CEA can be helpful in distinguishing Paget cells from atypical melanocytes in melanoma *in situ*. However, reactivity of melanomas with CEA has been reported (see Chapter 28) (38). Carcinoembryonic antigen typically stains adenocarcinomas from most organ systems. Most epithelial tumors react with antibodies against epithelial membrane antigen (EMA), including squamous cell carcinoma, breast carcinoma, and large cell lung carcinoma. EMA will also stain normal sweat and sebaceous glands, although epidermis

TABLE 4-5 Differential Diagnosis of Malignant Spindle Cell Tumors

Diagnosis	Keratin	Vimentin	Desmin	S100	HMB-45	Factor VIII/CD31
Squamous cell carcinoma	+	−	−	−	−	−
Atypical fibroxanthoma	−	+	−	−	−	−
Melanoma	−	+	−	+	+	−
Leiomyosarcoma	−	+	+	−	−	−
Angiosarcoma	−	+/−	−	−	−	+

Note: Few if any of these reagents are perfectly specific for their target antigens. Every test must be interpreted in the context of all of the available histologic and clinical information.

is nonreactive with this antibody. Epithelioid sarcoma is also stained by EMA (see Chapter 32).

Neuron-Specific Enolase

Neuron-specific enolase (NSE) is an acidic enzyme found in neuroendocrine cells, neurons, and tumors derived from them. Merkel cell carcinoma contains NSE; however, NSE can be detected in a variety of other tumors, including malignant melanoma, and therefore has low specificity. The keratin marker CK20 has better specificity for Merkel cell tumor than for melanoma and other neuroendocrine tumors (39).

Chromogranin

The soluble proteins of chromaffin granules are called *chromogranin* (40). Chromogranins consist of three families of acidic proteins: chromogranin A, B, and C. They are normally found in most endocrine cells (e.g., thyroid, parathyroid, anterior pituitary). In the skin, chromogranin A has been found in Merkel cell carcinoma (41). In contrast, nevi and melanoma do not contain chromogranin.

Synaptophysin

Synaptophysin is a 38-kD glycoprotein that participates in calcium-dependent release of neurotransmitters (42). It is a neuroendocrine antigen with a distribution similar to chromogranin. Positive staining with antibodies to synaptophysin is useful in the diagnosis of neuroendocrine tumors such as Merkel cell carcinoma. Of interest, normal Merkel cells are negative with this antibody. Similar to chromogranin, melanocytic tumors do not stain with synaptophysin.

S100 Protein

S100 protein is an acidic protein that binds Ca^{2+} and Zn^{2+}. It was called S100 because of its solubility in 100% ammonium sulfate at neutral pH. It is found in the cytoplasm and in the nucleus. S100 protein can be detected in a large variety of cells: melanocytes, Langerhans cells, eccrine and apocrine gland cells, nerves, muscles, Schwann cells, myoepithelial cells, chondrocytes, adipocytes, and their malignant counterparts. Histiocytes may also stain positively with S100 protein. The polyclonal antibody against S100 works well on paraffin sections. Its high sensitivity contrasts with a low specificity, a feature that supports the concept of a panel approach to immunohistochemistry.

Useful applications of the antibody against S100 protein include (a) diagnosing spindle cell melanoma and desmoplastic melanoma, (b) distinguishing between melanocytes and lymphocytes in halo nevi, (c) differentiating between pigmented actinic keratoses and lentigo maligna, and (d) diagnosing poorly differentiated cutaneous metastases.

HMB-45

HMB-45 is a monoclonal antibody that was initially generated from an extract of metastatic melanoma. Both primary and metastatic melanomas reveal cytoplasmic staining with HMB-45; spindle cell melanomas and desmoplastic melanomas are frequently negative. This antibody reacts with a melanosomal protein, GP-100, which tends to be expressed in immature or proliferating cells. Unfortunately, HMB-45 may react with melanocytes in nevi, including dysplastic nevi and Spitz nevi (39). Therefore, it should not be used for the differential diagnosis between a malignant melanoma and a benign nevus. Most desmosplastic melanomas, as well as some metastatic melanomas, may show negative staining with HMB-45 (43).

MART-1/Melan-A

Melanoma antigen recognized by T cells (MART-1) is a relatively new melanocytic differentiation marker. The antigen is expressed in normal melanocytes, common nevi, Spitz nevi, and malignant melanoma (Fig. 4-7). Monoclonal antibodies to MART-1/Melan-A are commercially available and are suitable for both frozen tissue and formalin-fixed paraffin-embedded tissue. Negative staining is frequently seen in neurotized nevi and desmoplastic melanomas (44). In the skin, Melan-A mRNA has only been found in melanocytic lesions and angiomyolipomas (45). Immunoreactivity can also be seen in the adrenal cortex, Leydig cell of the testes, granulosa cells of the ovary, and tumors derived from these cells. This antibody is a useful addition when evaluating intraepidermal melanocytes (vitiligo, early melanoma *in situ*), as well as amelanotic melanomas.

CD34

CD34 is a heavy glycosylated molecule that is expressed on virtually all human hematopoietic progenitor cells. Expression is normally lost during maturation in the skin. Both benign and malignant vascular tumors express this antigen. In dermatopathology, CD34 positivity in dermatofibrosarcoma protuberans is useful in differentiating these lesions from dermatofibromas, which are CD34 negative and factor XIIIa positive (46). Other cutaneous neoplasms that express CD34

FIGURE 4-7. MART-1/Melan-A immunoperoxidase staining highlights normal melanocytes in the basal layer of the epidermis.

include solitary fibrous tumor, giant cell fibroblastoma, neurofibroma, epithelioid sarcoma, spindle cell lipoma, sclerotic fibroma, and fibrous papule of the nose.

Factor VIII–Related Antigen and Ulex europaeus Agglutinin I

Factor VIII–related antigen (von Willebrand factor) is a large glycoprotein produced by endothelial cells and therefore useful in benign and malignant vascular neoplasms. However, some studies have demonstrated factor VIII positivity in only 50% of hemangiomas and 5% to 25% of malignant endothelial tumors (47,48).

Ulex europaeus agglutinin I (UEA) is a lectin that reacts specifically with α-L-fucose present in endothelial cells, keratinocytes, and most eccrine glands. UEA is a reliable marker for endothelial cells of blood vessels and lymphatics, although it is less specific than factor VIII–related antigen (49).

CD31

CD31 is a marker of endothelial differentiation that is normally expressed in endothelial cells and selected hematopoietic elements (Fig. 4-8) (50). This 130-kD glycoprotein, whose major function is to mediate platelet adhesion in vascular endothelial cells, is also known as platelet endothelial cell adhesion molecule. CD31 is a sensitive marker for vascular tumors, except Kaposi's sarcoma (51). It is a more sensitive marker for cutaneous angiosarcoma than factor VIII–related antigen.

Factor XIIIa

Factor XIIIa, a blood coagulation factor, is responsible for stabilizing newly formed clots by cross-linking fibrin. It is present in fibroblast-like mesenchymal cells, dermal dendrocytes, platelets, megakaryocytes, peritoneal and alveolar macrophages, normal adipose tissue, monocytes, and placenta, uterine, and prostate tissue. As noted earlier, using factor XIIIa in combination with CD34 can be helpful in differentiating dermatofibroma from dermatofibrosarcoma protuberans. Factor XIIIa has also been reported to be positive in a multitude of other lesions, including fibrous papule, atypical fibroxanthoma, xanthogranuloma, multinucleate cell angiohistiocytoma, epithelioid cell histiocytoma, and atypical cells in radiation dermatitis (52–54).

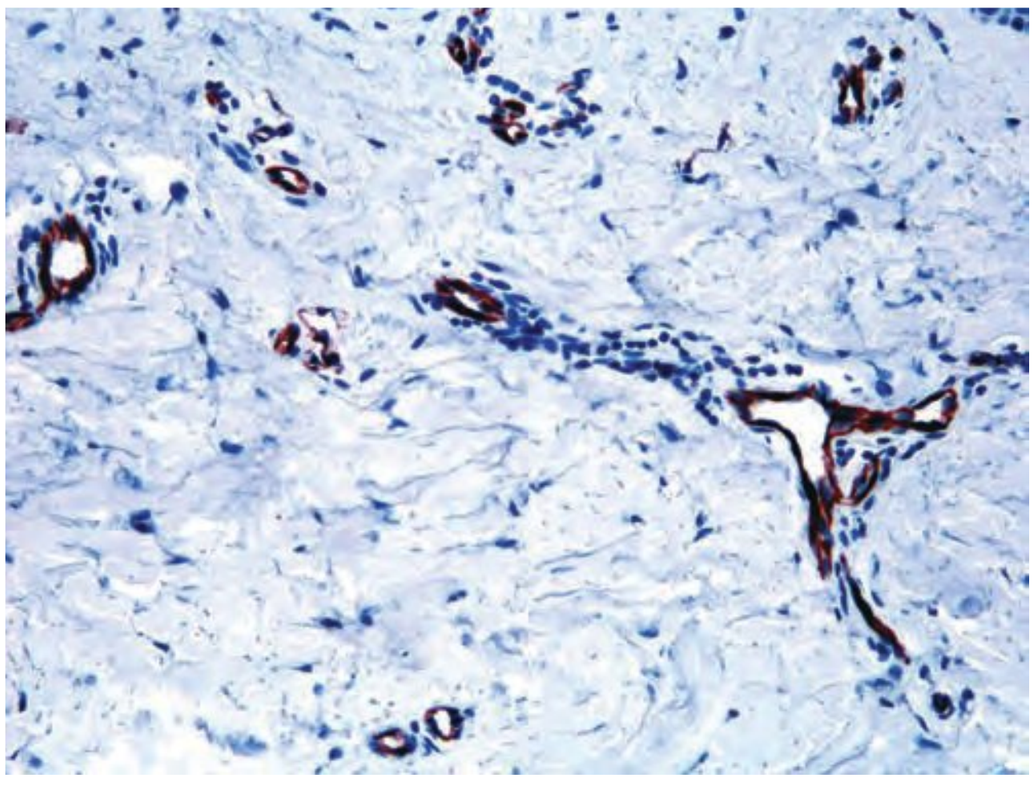


FIGURE 4-8. CD31 staining of vascular endothelium.

Antibodies Against Lysozyme, α_1-Antitrypsin, α_1-Antichymotrypsins

These antibodies have been regarded as markers of mononuclear phagocytic cells. Although once felt to be markers for "fibrohistiocytic" neoplasms, they have also been identified in carcinomas and melanomas, making them less specific.

c-kit (CD117)

The human proto-oncogene c-kit is a member of the type III receptor tyrosine kinase family that includes macrophage growth factor, platelet-derived growth factor, and flt-3/flk-2 receptors. It is present on a number of cell types, including mast cells, melanocytes, hematopoietic stem cells, immature myeloid cells, and myeloid and lymphoid progenitors, and in germ cell lineages, and it plays a crucial role in their activation and growth. Constitutively active c-kit has been implicated in the pathogenesis of a number of disorders, including systemic mastocytosis and gastrointestinal stromal tumors, whereas impairment of kinase activity has been implicated in a number of developmental disorders (55,56). Increased c-kit expression has been seen on malignant cells from many acute myeloid leukemia subtypes and chronic myelogenous leukemia; in addition, a number of solid tumor cells have been shown to express high-affinity c-kit receptors, including breast, lung, and gastric carcinoma, as well as some melanomas, especially of the acral, lentigo maligna, and ocular subtypes.

CD1a

CD1a is a transmembrane glycoprotein, structurally related to major histocompatibility class I, and it is found as a heterodimer associated to β_2-microglobin (57). CD1a is localized to the plasma membrane, with a small fraction of internalized CD1a restricted to the perinuclear recycling vesicles of endosomal sorting machinery. Like other members of the CD1 family, CD1a functions to mediate the presentation of lipid and glycolipid antigens to T cells. In pathology, CD1a has become a marker of Langerhans cells (Fig. 4-9) and blood monocyte–derived dendritic cells. CD1a is also expressed on double-positive ($CD4^+CD8^+$) cortical thymocytes and with less intense expression on CD4 or CD8 single-positive thymocytes. As a diagnostic tool, it has been used together with S100 to define dendritic cell populations in tumors and other tissues, as well as for the diagnosis of Langerhans cell histiocytosis (histiocytosis X) (58).

Antibodies Against Leukocyte Common Antigen (CD45)

This antibody helps to distinguish between undifferentiated lymphomas and carcinomas. Leukocyte common antigen (LCA) is found on all leukocytes, including granulocytes,

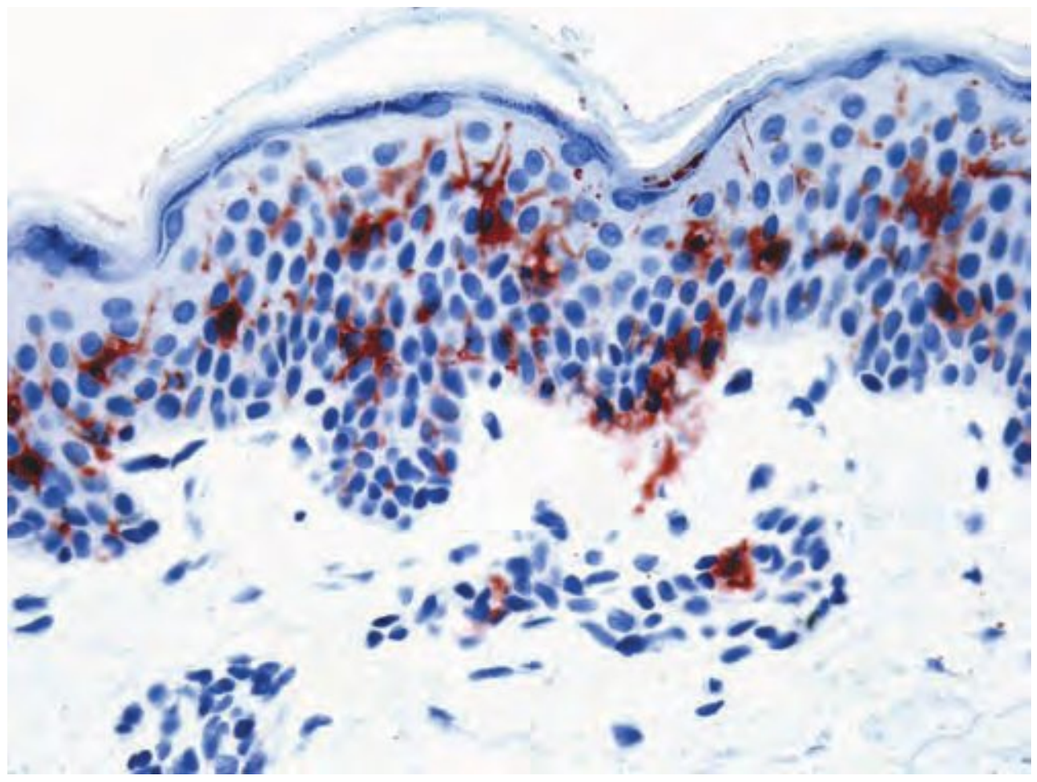


FIGURE 4-9. CD1a immunoperoxidase stain highlights Langerhans cells in the epidermis.

lymphocytes, monocytes, macrophages, mast cells, and Langerhans cells. The lymphomas and leukemias react with the antibody against LCA; carcinomas and melanomas are negative. In addition to LCA, lysozyme and chloroacetate esterase aid in the diagnosis of leukemia cutis (59). LCA is particularly useful in the evaluation of tumors composed of small atypical basophilic cells in the dermis (Table 4-6). Other antigens useful in the analysis of suspected lymphomas include the B- and T-cell markers L-26 (CD20, B cells) or CD79a (B cells) and UCHL-1 (CD45-RO, T cells) (see Chapter 31).

Diagnosis of Lymphomas

The application of monoclonal antibodies for the diagnosis of lymphomas is expanding. However, there is no antibody that distinguishes between benign and malignant lymphocytes. Hence, the difficult distinction between lymphoma and pseudolymphoma remains.

Although many antibodies are best used on frozen sections, an increasing number of commonly available antibodies can be used on formalin-fixed, paraffin-embedded tissue. The quality of certain markers, such as κ and λ light chains, has been variable in paraffin sections and is more reliable on frozen sections or utilizing in situ hybridization. Monoclonal antibodies can determine the cell types in a lymphoma or pseudolymphoma: helper or suppressor T cells, B cells, plasma cells, or macrophages. A confusing issue is that B-cell lymphomas may contain reactive T-cell infiltrates, which can outnumber the B cells. The predominance of a T-helper lymphocytic infiltrate with epidermotropism of the T-helper subtype is highly suggestive of cutaneous T-cell lymphoma. In contrast, a mixture of T-helper and T-suppressor phenotypes is most consistent with a reactive profile (e.g., spongiotic dermatitis). In dense nodular infiltrates, the presence of germinal center formation with B-lymphocyte aggregates surrounded by a mantle of T cells favors lymphocytoma cutis over lymphoma. A detailed discussion of antibodies helpful in the diagnosis of lymphoma is found in Chapter 31.

Molecular studies can provide additional information in the evaluation of atypical lymphoid infiltrates. Detection of a characteristic gene rearrangement coding for B- and T-cell antigen receptors will identify the presence or absence of a clonal population of lymphocytes (60). These applications are an important supplement to routinely available technology; however they must always be interpreted in the context of the clinical presentation and findings on routine histology. Although clonality studies can assist in early detection of cutaneous T-cell lymphoma, nonneoplastic processes such as pityriasis lichenoides, pseudolymphoma, and lichen planus occasionally show T-cell clonality (61–63).

Electron Microscopy

Transmission electron microscopy may be beneficial in the diagnosis of poorly differentiated skin neoplasms for which immunohistochemistry is negative (64). Using electron microscopy, the identification of intercellular junctions (epithelial tumors), melanosomes (melanocytic tumors), or Weibel-Palade bodies (endothelial cells) can provide an important diagnostic aid. Other uses of diagnostic electron microscopy include the subtype determination of epidermolysis bullosa and the diagnosis of metabolic storage diseases (e.g., Fabry disease) or amyloidosis. For optimum results, fresh tissue

TABLE 4-6 Immunohistochemistry of Basophilic Small Cells in the Dermis

Diagnosis	S100	Synaptophysin	LCA	Keratin
Lymphoma	−	−	+	−
Merkel cell carcinoma	−	+	−	+*
Carcinoma	±	−	−	+
Melanoma	+	−	−	−

LCA, leukocyte common antigen.
*Perinuclear staining.
Note: Few if any of these reagents are perfectly specific for their target antigens. Every test must be interpreted in the context of all of the available histologic and clinical information. Poorly differentiated carcinoma may be keratin negative or only positive with low–molecular weight keratin antibodies.

should be fixed in Karnovsky medium (paraformaldehyde-glutaraldehyde) and stored in the refrigerator until processing; although electron microscopy rarely can be performed from paraffin-embedded tissue, there may be extensive distortion precluding valuable interpretation.

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CHAPTER 5

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Outline of Cutaneous Pathology

INTRODUCTION

The diagnosis of disease concerns the ability to classify disorders into categories that predict clinically important attributes such as prognosis and response to therapy. This permits appropriate interventions to be planned for particular patients. Understanding this process involves mastery of the stages of disease, the mechanisms of changes in morphology over time, and the molecular, cellular, gross clinical, and epidemiologic reasons for the differences among diseases.

The process of cutaneous diagnosis at its simplest level might involve the matching of a large number of attributes contained in classical descriptions of skin diseases with the presence or absence of the same attributes in a particular case under consideration. Because there are hundreds of potential diagnostic categories, each having potentially scores of attributes, it is evident that an efficient strategy must be used to enable diagnoses to be considered, dismissed, or retained for further consideration. Observation of an experienced dermatopathologist reveals a rapidity of accurate diagnosis that precludes the simultaneous consideration of more than a few variables. Indeed, the process of diagnosis by an experienced observer is quite different from that employed by the novice and is based on the rapid recognition of combinations or patterns of criteria (1,2). Just as the recognition of an old friend occurs by a process that does not require the serial enumeration of particular facial features, this process of pattern recognition occurs almost instantly and is based on broad parameters that do not, at least initially, require detailed evaluation.

In clinical medicine, patterns may present as combinations of symptoms and signs or even of laboratory values, but in dermatopathology, the most predictive diagnostic patterns are recognized through the scanning lens of the microscope or even before microscopy as the microscopist holds the slide up to the light to evaluate its profile and distribution of colors. Occasionally, a specific diagnosis can be made during this initial stage of pattern recognition by a process of "gestalt"-based or instant recognition, but this should be tempered with a subsequent moment of healthy analytic scrutiny. More often, the scanning magnification pattern suggests a small list of possible diagnoses, a "differential diagnosis." Then, features that are more readily recognized at higher magnification may be used to differentiate among the possibilities. Put in the language of science, the scanning magnification pattern suggests a series of hypotheses, which are then tested by additional observations (1). The tests may be observations made at higher magnification, the results of special studies such as immunohistochemistry, or external findings such as the clinical appearance of the patient or the results of laboratory investigations. For example, a broad, plaquelike configuration of small blue dots near the dermal–epidermal junction could represent a lichenoid dermatitis or a lichenoid actinic keratosis. At higher magnification, the blue dots may be confirmed to be lymphocytes, and one might seek evidence of parakeratosis, atypical keratinocytes, and plasma cells in the lesion, a combination that would rule out lichen planus and establish a diagnosis of actinic keratosis.

Most diagnoses in dermatopathology are established either by the gestalt method or by the process of hypothesis generation and testing (differential diagnosis and investigation) just described, but in either case the basis of the method is the identification of simple patterns recognizable with the scanning lens that suggest a manageably short list of differential diagnostic considerations. This *pattern recognition method* was first developed in a series of lectures given in Boston by Wallace Clark (3) and was refined for inflammatory skin disease by Ackerman (4) and for inflammatory and neoplastic skin disease by Mihm (5). Additional work was done by Murphy (6), Barnhill (7), Maize and colleagues (8), Weedon (9), and McKee (10). These authors published texts based more or less extensively on pattern classification. The present work, however, is organized along more traditional lines, in which diseases are discussed on the basis of pathogenesis (mechanisms) or etiology, as well as on reaction patterns. Such a classification has the advantage of placing disorders such as infections in a common relationship to one another, facilitating the description of their many common attributes. From a histopathologic point of view, however, the novice must learn that some infections, such as syphilis, can resemble disorders as disparate as psoriasis, lichen planus, cutaneous lymphoma, and granulomatous dermatitis.

Because there is a limited number of reaction patterns in the skin, morphologic simulants of disparate disease processes are common in the skin, as elsewhere. For this reason, classification methods based on patterns and those based on pathogenesis are incompatible with each other. To partially circumvent

this problem, the present section of this book presents a pattern-based classification of cutaneous pathology based on *location in the skin, reaction patterns,* and, where applicable, *cell type,* indexed to the more detailed descriptions of the disease entities discussed in other sections of the book. The section is based (with permission) on the original lecture notes prepared by Wallace H. Clark Jr., MD, in 1965, and on the published works cited previously, especially that of Hood et al. (5).

The classification is presented here in tabular form and is redundant, in that a particular disease entity may appear in several positions in the table because of the morphologic heterogeneity of disease processes, which are often based on evolutionary or involutional morphologic changes as a disease waxes and wanes. The order of presentation of particular entities in any given position in the table reflects the authors' rough opinion of the relative frequency of the entities in the list as encountered in a typical dermatopathology practice. For example, lichenoid drug eruption may be more common than lichen planus in most hospital-based practices. However, lichen planus is the "prototypic" lichenoid dermatitis, whereas drug eruptions may adopt any of a number of morphologies as reflected by their appearance in the psoriasiform, lichenoid, perivascular, and bullous categories, as well as elsewhere. The "prototypic" member of each category is italicized for easy reference to the detailed descriptions because such entities constitute the descriptive standard in a given category and they are also the standard against which other entities are evaluated. For example, a "naked" epithelioid cell granuloma may suggest sarcoidosis, whereas the presence of lymphocytes and necrosis in addition to granulomas might suggest tuberculosis, plasma cells might suggest syphilis, and neuritis might suggest leprosy.

The classification tables may be used as the basis of an algorithmic approach to differential diagnosis and as a guide to the descriptions in the other sections of this book. For example, a psoriasiform dermatitis with plasma cells may represent syphilis or mycosis fungoides, whose descriptions are to be found in Chapters 22 and 31, respectively. Terms such as "psoriasiform" and "lichenoid" are defined briefly, and appropriate page references are provided in this section so that the reader may review more specific criteria for the distinctions among morphologic simulants. This system of hypothesis generating and testing not only should lead to more efficient use of this book in the evaluation and diagnosis of an unknown case, but also should facilitate the development of pattern recognition skills as more subtle diagnostic clues are absorbed into the diagnostic repertoire to allow for "tempered gestalt" diagnosis in an increasing percentage of cases. The classification presented here is also the basis of the classification presented in the *Synopsis and Atlas of Lever's Histopathology of the Skin,* which is intended to be a more richly illustrated companion to the present volume, with a more synoptic text relating to the disease entities illustrated (11).

This chapter is intended as a guide to differential diagnosis but should not be construed as an infallible diagnostic tool. Diagnosis should be based not only on the diagnostic considerations presented here, but also on those discussed elsewhere in this book and in the literature, all considered in a clinical and epidemiologic context appropriate to the individual patient.

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PART 1. SITE CATEGORIES OF CUTANEOUS PATHOLOGY

In this part, the major categories of cutaneous disease are briefly discussed based on their location in the skin and subcutis.

I. DISORDERS MOSTLY LIMITED TO THE STRATUM CORNEUM

The stratum corneum is usually arranged in a delicate meshlike or "basket-weave" pattern. It may be shed (exfoliated) or thickened (hyperkeratosis) with or without retention of nuclei (parakeratosis or orthokeratosis, respectively). Usually, alterations in the stratum corneum result from inflammatory or neoplastic changes that affect the whole epidermis and, more often than not, the superficial dermis. Only a few conditions, mentioned in this section, show pathology mostly or entirely limited to the stratum corneum.

II. NEOPLASTIC LOCALIZED EPITHELIAL OR MELANOCYTIC PROLIFERATIONS

Localized proliferations may be reactive but are often neoplastic. The epidermis (keratinocytes) may proliferate without extension into the dermis, extend into the dermis, and be squamous or basaloid. Melanocytes within the epidermis may proliferate with or without cytologic atypia (nevi, dysplastic nevi, melanoma *in situ*) in a proliferative epidermis (superficial spreading melanoma *in situ*, Spitz nevi) or an atrophic epidermis (lentigo maligna); they can also extend into the dermis as proliferative infiltrates (invasive melanoma with or without vertical growth phase). There may be an associated variably cellular, often mixed inflammatory infiltrate, or inflammation may be essentially absent.

III. INFLAMMATION OF THE SUPERFICIAL CUTANEOUS REACTIVE UNIT

The epidermis, papillary dermis, and superficial capillary-venular plexus in the superficial reticular dermis react together in many dermatologic conditions and were termed the "superficial cutaneous reactive unit" by Clark. Many dermatoses are associated with infiltrates of lymphocytes around the superficial vessels with or without other cell types. The epidermis in pathologic conditions can be thinned (atrophic), thickened (acanthosis), edematous (spongiosis), and/or infiltrated by inflammatory cells (exocytosis). The epidermis may proliferate in response to chronic irritation or infection (bacterial, yeast, deep fungal, or viral). The epidermis may proliferate in response to dermatologic conditions (psoriasis, atopic dermatitis, prurigo). The papillary dermis and superficial vascular plexus may have a variety of inflammatory cells, can be edematous, may have increased ground substance (hyaluronic acid), or may be sclerotic or homogenized.

IV. ACANTHOLYTIC, VESICULAR, AND PUSTULAR DISORDERS

Keratinocytes may separate from each other, resulting in separation and rounding up of keratinocyte cell bodies (acantholysis). This may occur on the basis of immunologic antigen/antibody–mediated damage, edema and inflammation (spongiosis), infections (impetigo or herpes viral infection), or structural deficiencies of cell adhesion (Darier's disease). These processes produce spaces within the epidermis (vesicles, bullae, pustules).

V. INFLAMMATION OF THE RETICULAR DERMIS

The dermis serves as a reaction site for a variety of inflammatory, infiltrative, and desmoplastic (fibrogenic) processes. These include infiltrations of a variety of cells (lymphocytes, histiocytes, eosinophils, plasma cells, melanocytes, etc.); perivascular and vascular reactions; infiltration with organisms and foreign bodies; and proliferations of dermal fibers and precursors of dermal fibers as reactions to a variety of stimuli. The infiltrates may be characterized as perivascular, diffuse, or granulomatous.

VI. NEOPLASTIC NODULES AND CYSTS OF THE RETICULAR DERMIS

Neoplasms of the reticular dermis may arise from any of the tissues included in the dermis —lymphoreticular tissue, connective tissue, and epithelial tissue of the skin appendages. In addition, metastases commonly present in the dermis.

VII. INFLAMMATORY DISORDERS OF SKIN APPENDAGES

The hair, sebaceous glands, eccrine glands, apocrine glands, and nails may be involved in inflammatory processes (hidradenitis, folliculitis). Some neoplasms may masquerade as inflammatory processes.

VIII. DISORDERS OF THE SUBCUTIS

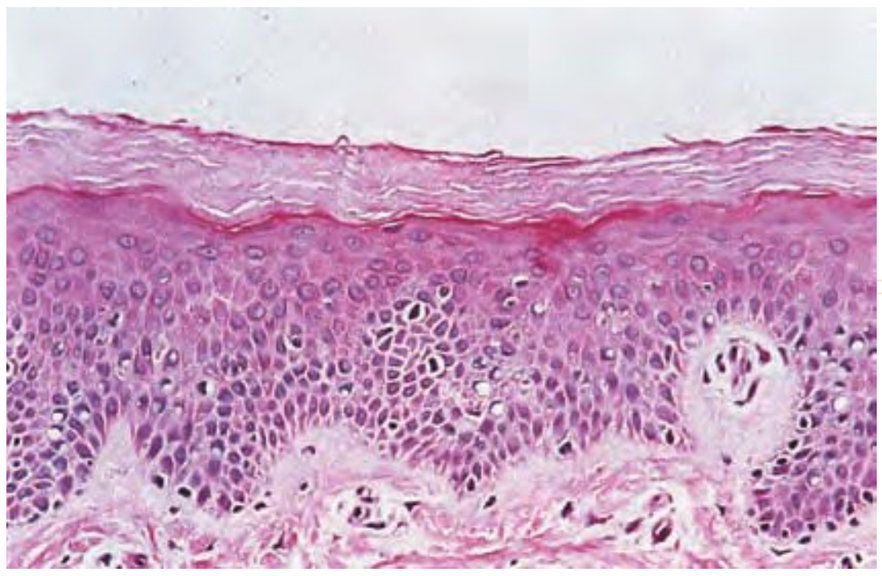
The reactions in the subcutis are mostly inflammatory, although neoplastic proliferations of the subcutis do occur (lipoma). Pathologic conditions centered in the dermis may infiltrate the subcutis.

PART 2. SITE, PATTERN, AND CYTOLOGIC CATEGORIES OF CUTANEOUS PATHOLOGY

The following listings give the categories of cutaneous disease based on location in the skin (categories I, II, III, etc.), architectural pattern (categories A, B, C, etc.), and cytology (categories 1, 2, 3, etc.). A single prototypic example of each disease category is listed, and a prototypic example of each major pattern category is illustrated.

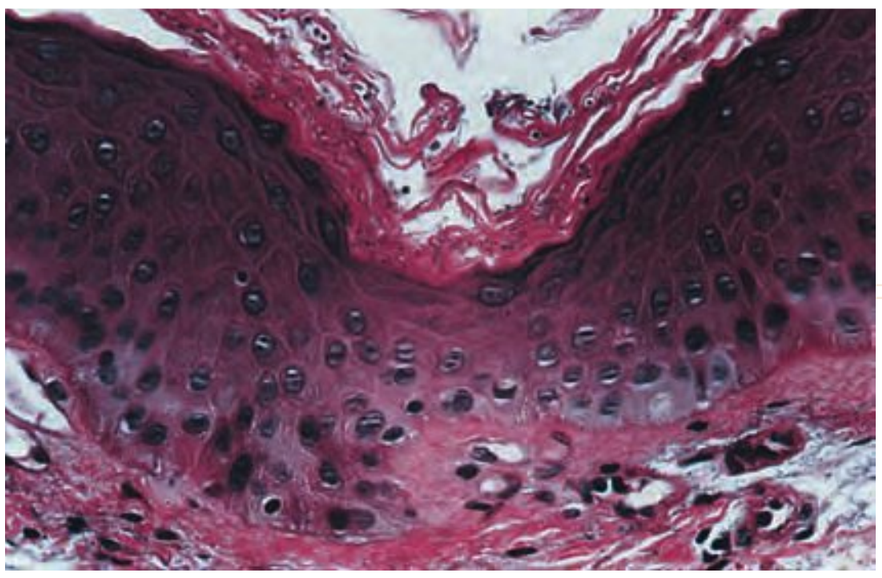
I. DISORDERS MOSTLY LIMITED TO THE EPIDERMIS & STRATUM CORNEUM

A. Hyperkeratosis with Hypogranulosis



1. No Inflammation
   ichthyosis vulgaris

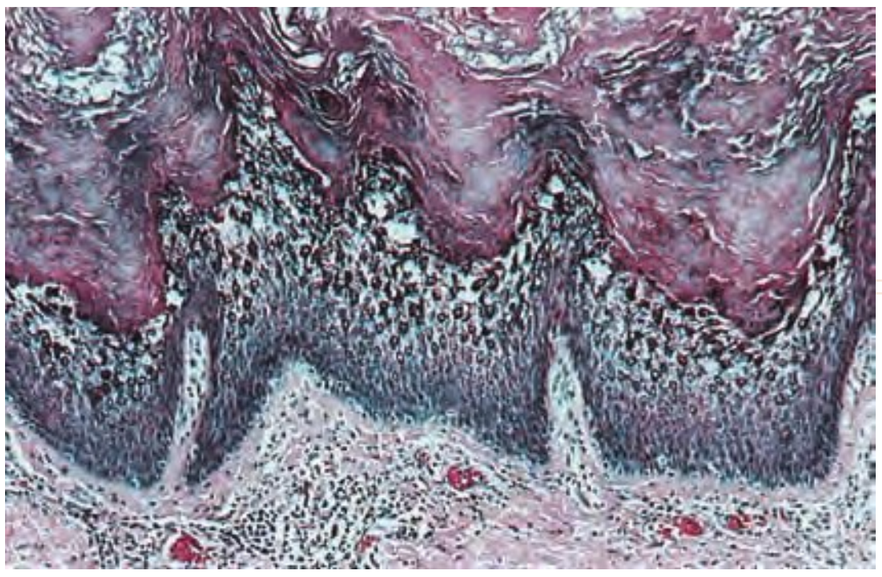
B. Hyperkeratosis with Normal or Hypergranulosis



1. No Inflammation
   lamellar ichthyosis

2. Scant Inflammation
   dermatophytosis

C. Hyperkeratosis with Parakeratosis

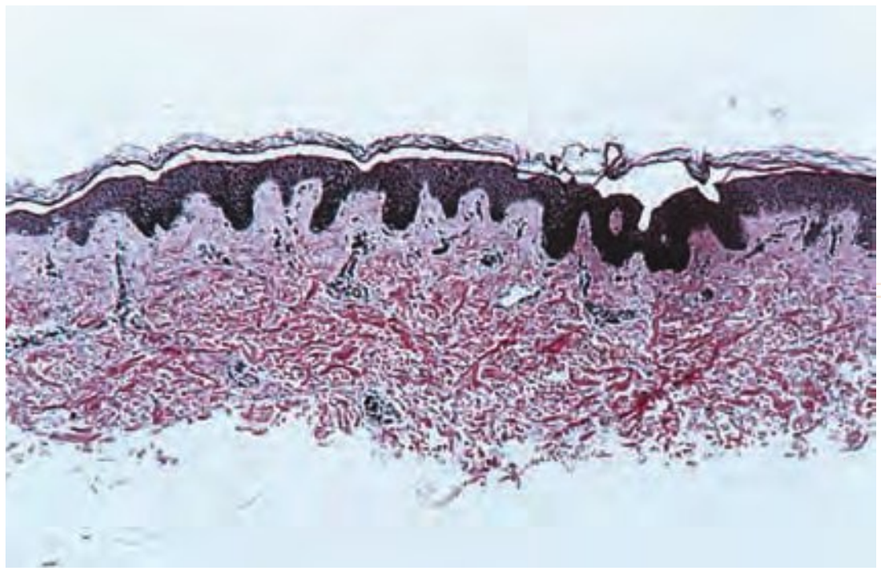


1. No Inflammation
   epidermolytic hyperkeratosis

2. Scant Inflammation
   scurvy

3. With Epidermal Pallor or Necrosis (“Nutritional Dermatosis”)
   pellagra

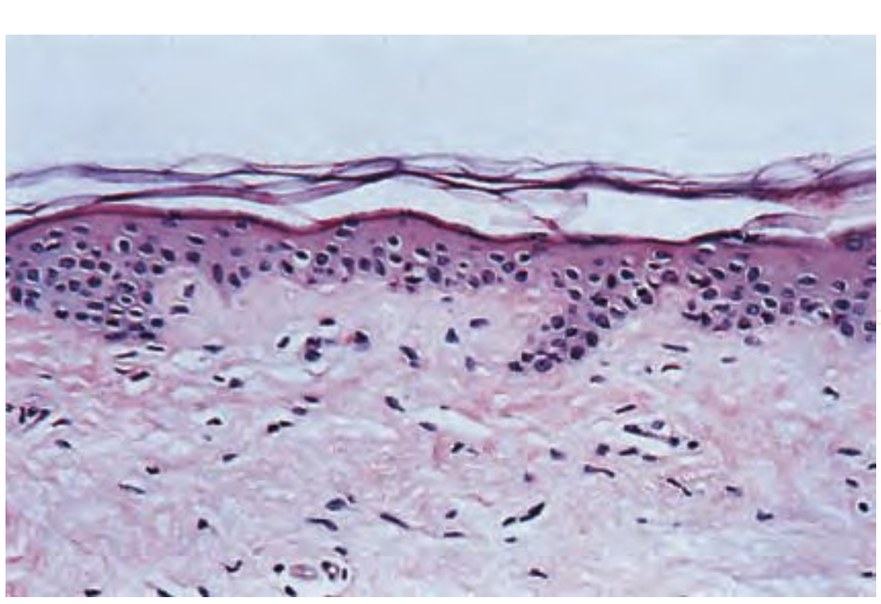
D. Localized or Diffuse Hyperpigmentations



1. No Inflammation
   actinic lentigo

2. Scant Inflammation
   postinflammatory hyperpigmentation

E. Localized or Diffuse Hypopigmentation/ Depigmentation



1. With or Without Slight Inflammation
   vitiligo

II. LOCALIZED SUPERFICIAL EPIDERMAL OR MELANOCYTIC PROLIFERATIONS

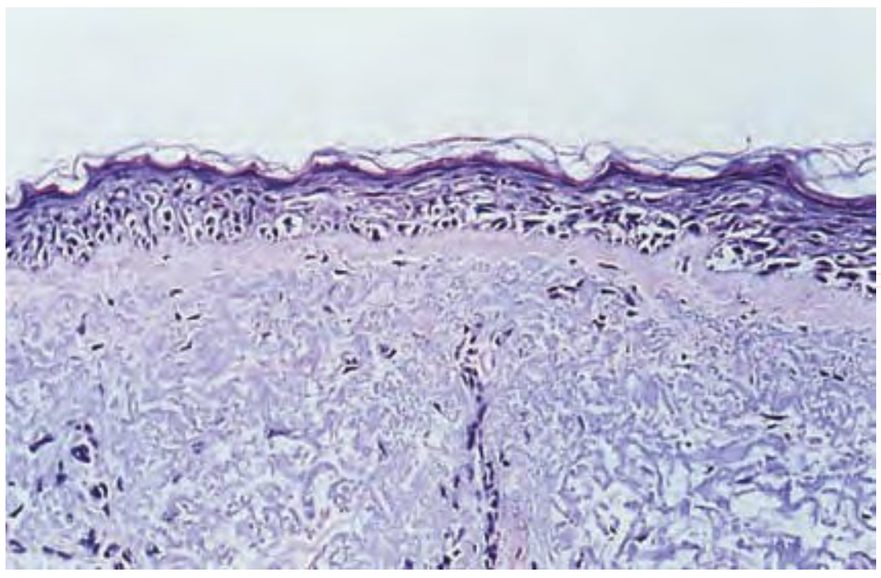
A. Localized Irregular Thickening of the Epidermis



1. Localized Epidermal Proliferations
   seborrheic keratosis

2. Superficial Melanocytic Proliferations
   melanoma *in situ* (superficial spreading type)

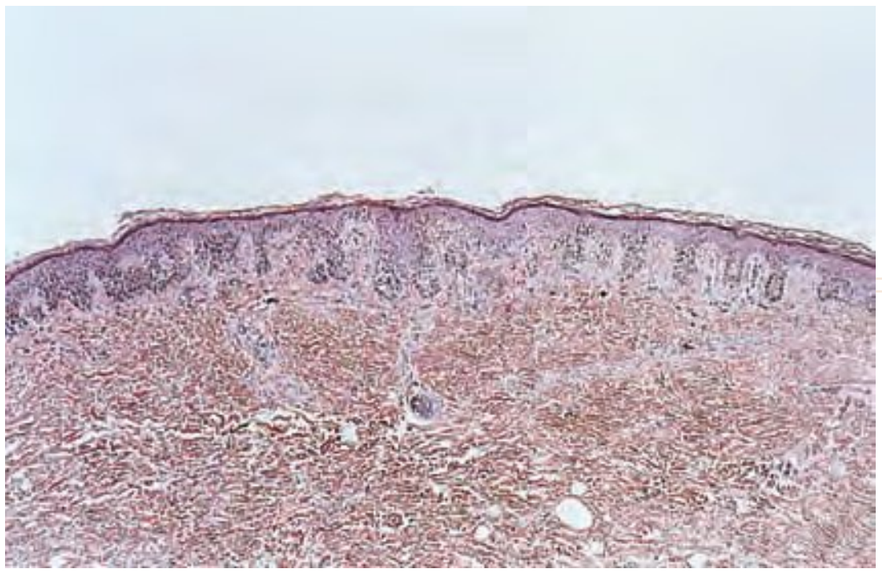
B. Localized Lesions with Thinning of the Epidermis



1. With Melanocytic Proliferation
   melanoma in situ (lentigo maligna type)

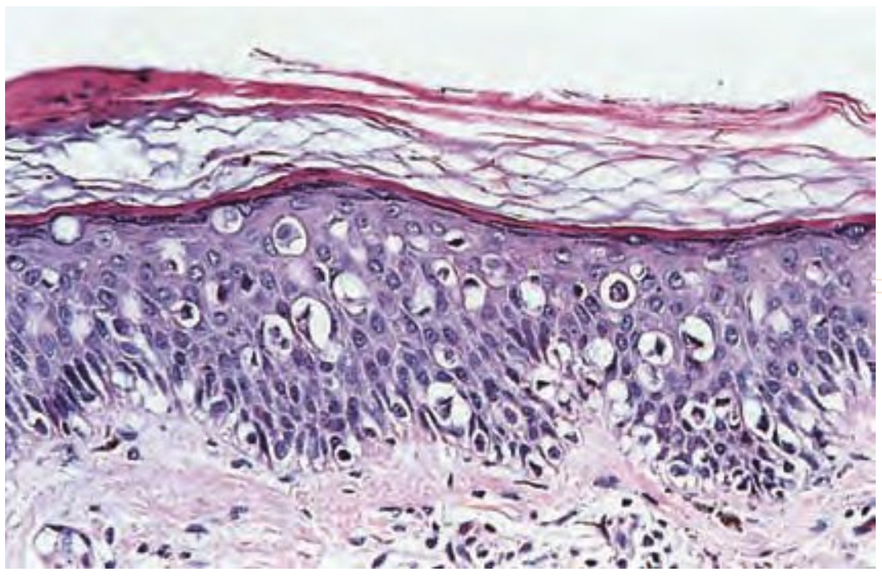
2. Without Melanocytic Proliferation
   actinic keratosis

C. Localized Lesions with Elongated Rete Ridges



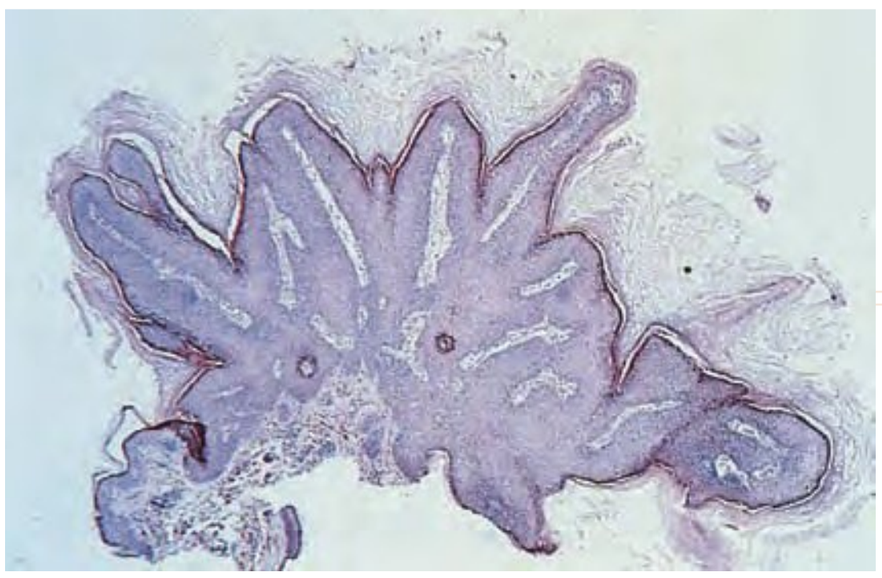
1. With Melanocytic Proliferation
   lentiginous junctional nevus
2. Without Melanocytic Proliferation
   epidermal nevi

D. Localized Lesions with Pagetoid Epithelial Proliferation



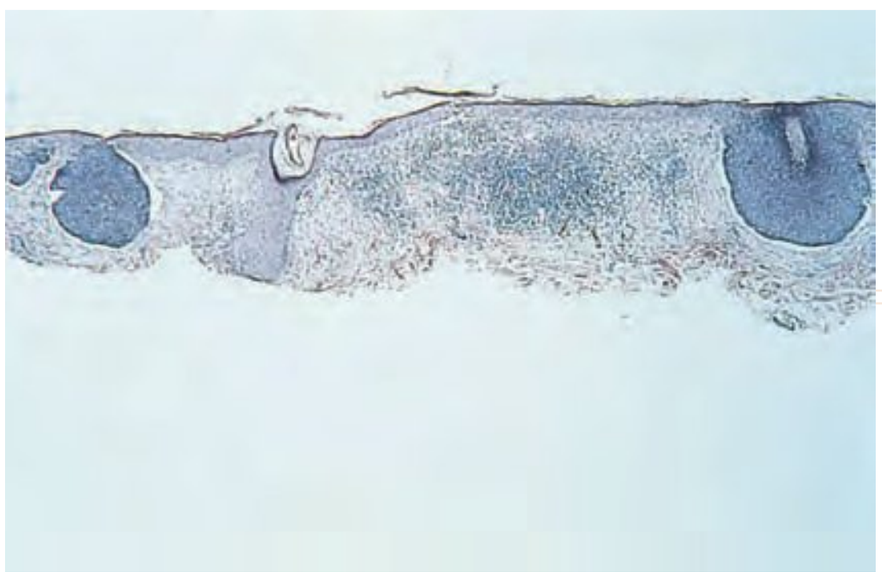
1. Keratinocytic Proliferations
   pagetoid squamous cell carcinoma *in situ*
2. Melanocytic Proliferation
   melanoma in situ (superficial spreading type)
3. Glandular Epithelial Proliferations
   Paget's disease (mammary or extramammary)
4. Lymphoid Proliferations
   Pagetoid reticulosis, localized (Woringer-Kolopp)

E. Localized Papillomatous Epithelial Lesions



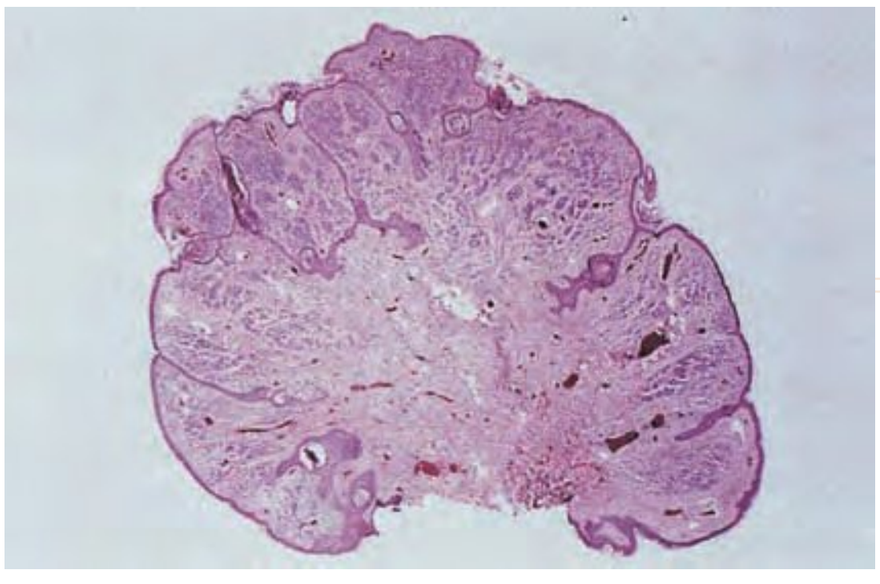
1. With Viral Cytopathic Effects
   verruca vulgaris
2. No Viral Cytopathic Effect
   seborrheic keratosis

F. Irregular Proliferations Extending into the Dermis



1. Squamous Differentiation
   squamous cell carcinoma, superficial
2. Basaloid Differentiation
   basal cell carcinoma, superficial types

G. Superficial Polypoid Lesions

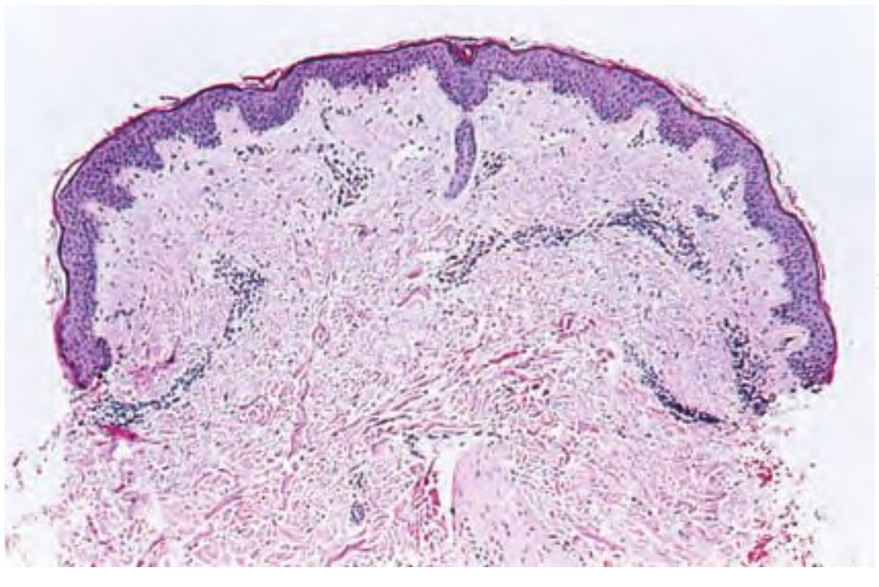


1. Melanocytic Lesions
   polypoid dermal and compound nevi

2. Stromal Lesions
   soft fibroma

III. DISORDERS OF THE SUPERFICIAL CUTANEOUS REACTIVE UNIT

A. Superficial Perivascular Dermatitis



1. Lymphocytes Predominant
   morbilliform viral exanthem
   a. With Eosinophils
      arthropod-bite reaction
   b. With Neutrophils
      erysipelas
   c. With Plasma Cells
      secondary syphilis
   d. With Extravasated Red Cells
      pigmented purpuric dermatosis
   e. Melanophages Prominent
      postinflammatory pigmentation

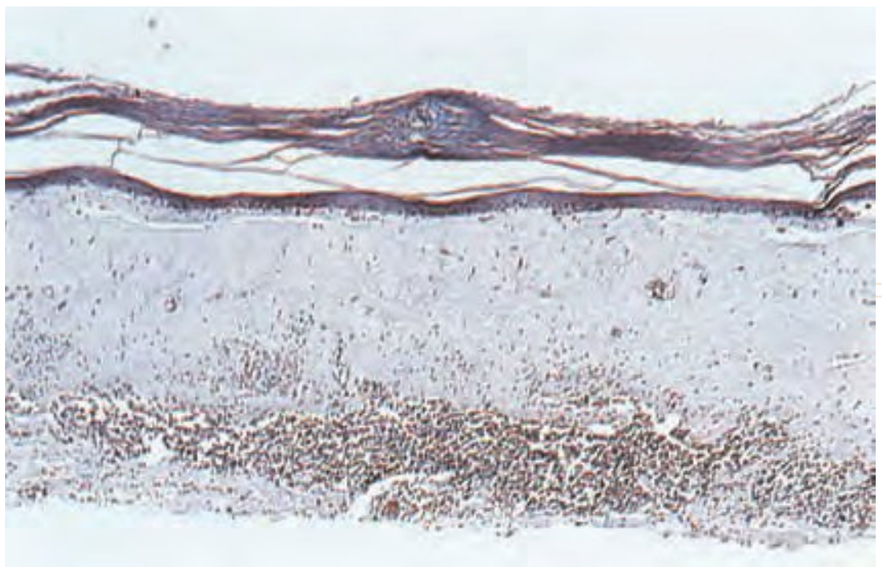
2. Mast Cells Predominant
   telangiectasia macularis eruptiva perstans

B. Superficial Perivascular Dermatitis with Spongiosis (Spongiotic Dermatitis)



1. Lymphocytes Predominant
   nummular eczema
   a. With Eosinophils
      allergic contact dermatitis
   b. With Plasma Cells
      syphilis, primary or secondary lesions
   c. With Neutrophils
      seborrheic dermatitis

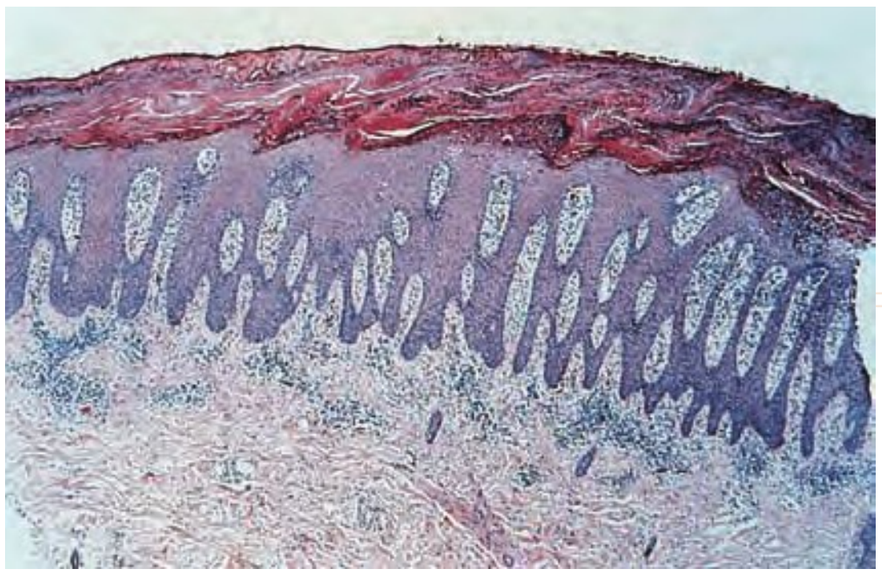
C. Superficial Perivascular Dermatitis with Epidermal Atrophy (Atrophic Dermatitis)



1. Scant Inflammatory Infiltrates
   radiation dermatitis

2. Lymphocytes Predominant
   parapsoriasis/early mycosis fungoides
   a. With Papillary Dermal Sclerosis
      lichen sclerosis et atrophicus

D. Superficial Perivascular Dermatitis with Psoriasiform Proliferation (Psoriasiform Dermatitis)

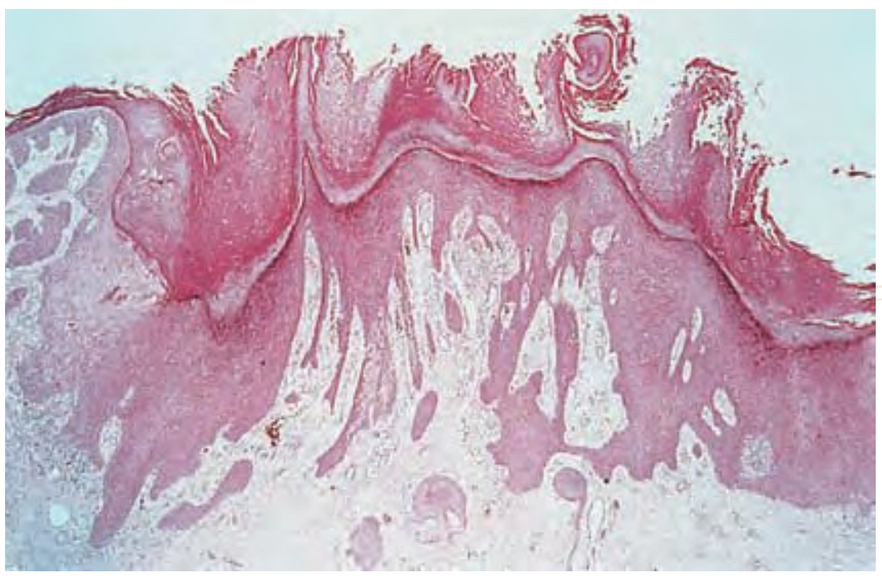


1. Lymphocytes Predominant
   chronic atopic dermatitis
   a. With Plasma Cells
      secondary syphilis
   b. With Eosinophils
      chronic allergic dermatitis

2. Neutrophils Prominent
   psoriasis vulgaris

3. Psoriasiform Epidermal Proliferation, with Epidermal Pallor or Necrosis ("Nutritional Dermatosis")
   pellagra

E. Superficial Perivascular Dermatitis with Irregular Epidermal Proliferation (Hypertrophic Dermatitis)

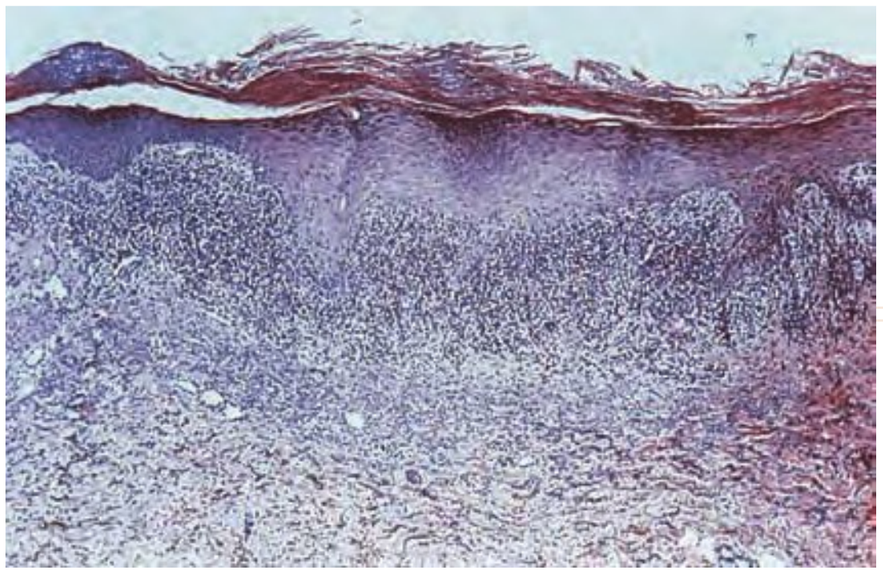


1. Lymphocytes Predominant
   prurigo nodularis
   a. Plasma Cells Present
      rupial secondary syphilis, condyloma lata

2. Neutrophils Prominent
   impetigo contagiosa

3. Neoplastic
   malignant melanoma ("verrucous" pattern)

F. Superficial Dermatitis with Lichenoid Infiltrates (Lichenoid Dermatitis)

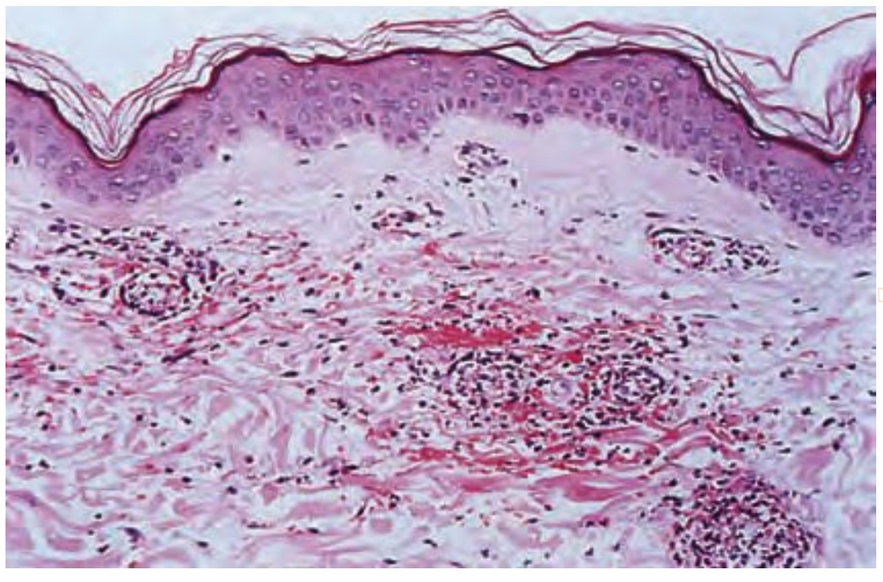


1. Lymphocytes Exclusively
   lichen planus

2. Lymphocytes Predominant
   lichen planus–like keratosis (benign lichenoid keratosis)
   a. Eosinophils Present
      lichenoid drug eruptions
   b. Plasma Cells Present
      secondary syphilis
   c. With Melanophages
      postinflammatory hyperpigmentation
   d. With Lymphocytic Atypia
      mycosis fungoides

3. Histiocytes Predominant
   lichen nitidus

G. Superficial Vasculitis and Vasculopathies



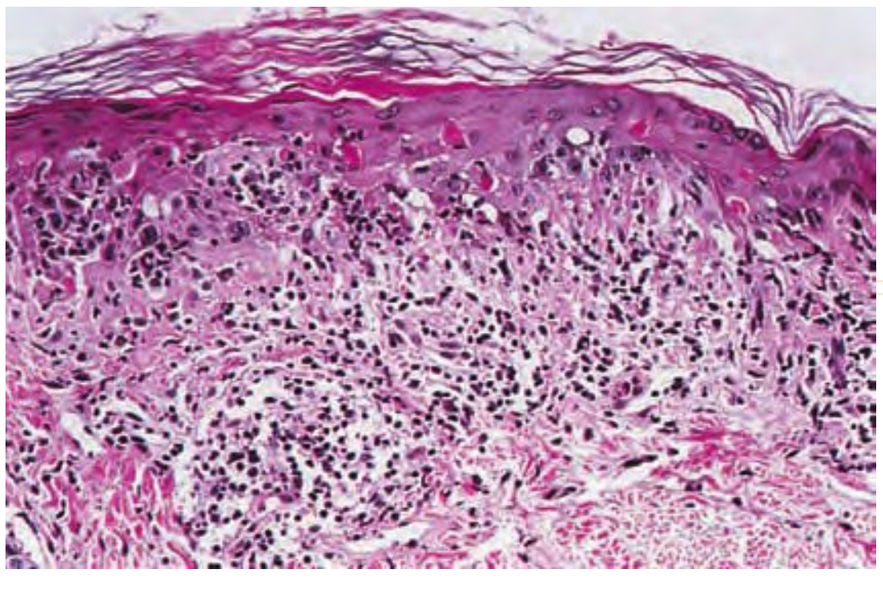
1. Neutrophilic Vasculitis
   cutaneous necrotizing (leukocytoclastic) vasculitis

2. Mixed Cell and Granulomatous Vasculitis
   Churg-Strauss vasculitis

3. Vasculopathies with Scant Inflammation
   malignant atrophic papulosis (Degos)

4. Thrombotic, Embolic, and Other Microangiopathies
   disseminated intravascular coagulation

H. Superficial Perivascular Dermatitis with Interface Vacuoles (Interface Dermatitis)



1. Apoptotic Cells Prominent (Cytotoxic Dermatitis)
   erythema multiforme

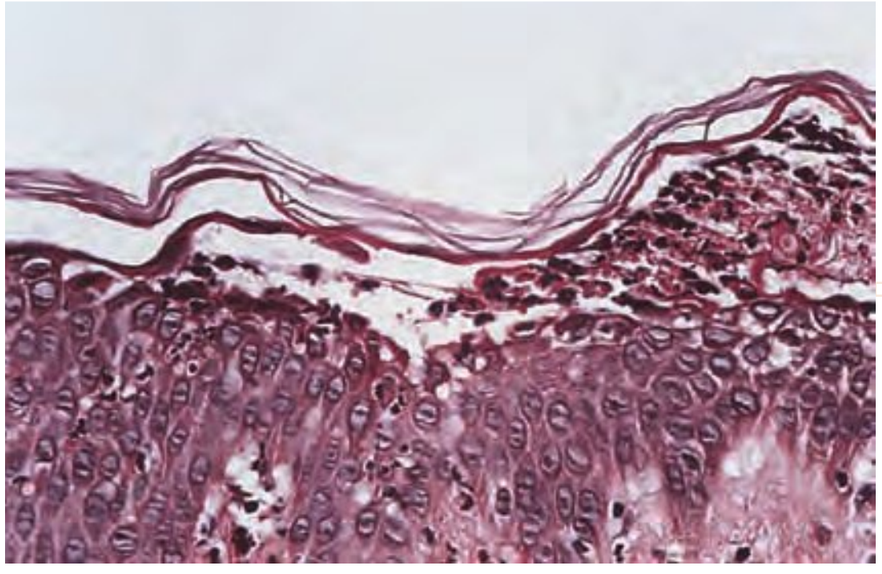
2. Apoptotic Cells Usually Absent
   dermatomyositis

3. Variable Apoptosis
   cytotoxic drug eruptions

4. Basement Membranes Thickened
   lupus erythematosus

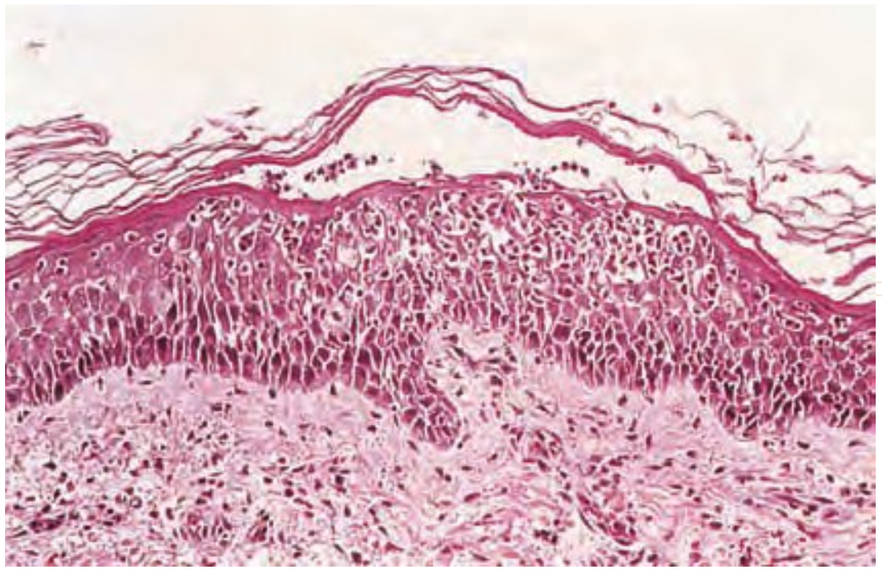
IV. ACANTHOLYTIC, VESICULAR, AND PUSTULAR DISORDERS

A. Subcorneal or Intracorneal Separation



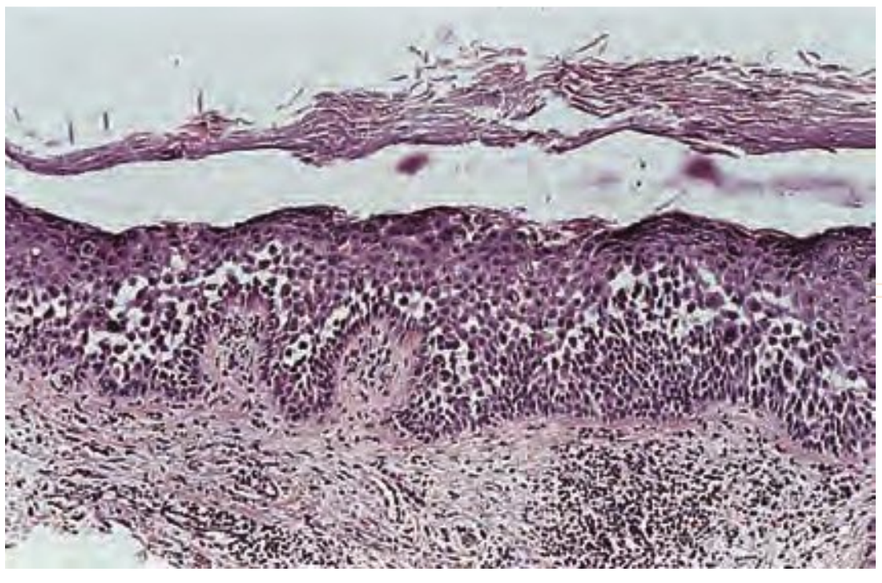
1. Scant Inflammatory Cells
   staphylococcal scalded skin
2. Neutrophils Prominent
   impetigo contagiosa
3. Eosinophils Predominant
   erythema toxicum neonatorum

B. Intraspinous Keratinocyte Separation, Spongiotic



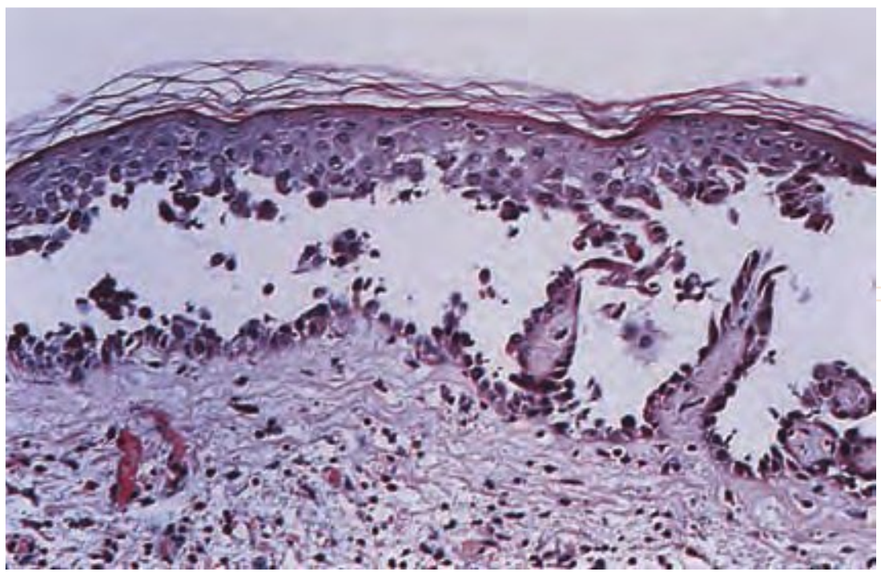
1. Scant Inflammatory Cells
   focal acantholytic dyskeratosis
2. Lymphocytes Predominant
   nummular eczema
   a. Eosinophils Present
      allergic contact dermatitis
3. Neutrophils Predominant
   pustular psoriasis

C. Intraspinous Keratinocyte Separation, Acantholytic



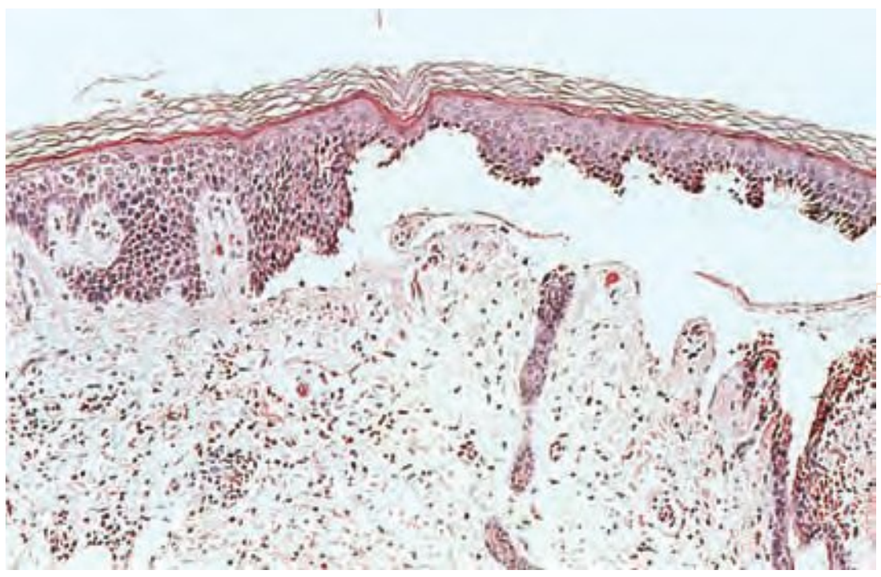
1. Scant Inflammatory Cells
   Hailey-Hailey disease
2. Predominant Lymphocytes
   herpes simplex, varicella-zoster
   a. Eosinophils Present
      pemphigus vegetans
3. Mixed Cell Types
   acantholytic solar keratosis

D. Suprabasal Keratinocyte Separation



1. Scant Inflammatory Cells
   transient acantholytic dermatosis (Grover)
2. Lymphocytes and Plasma Cells
   acantholytic solar keratosis
3. Lymphocytes and Eosinophils
   pemphigus vulgaris

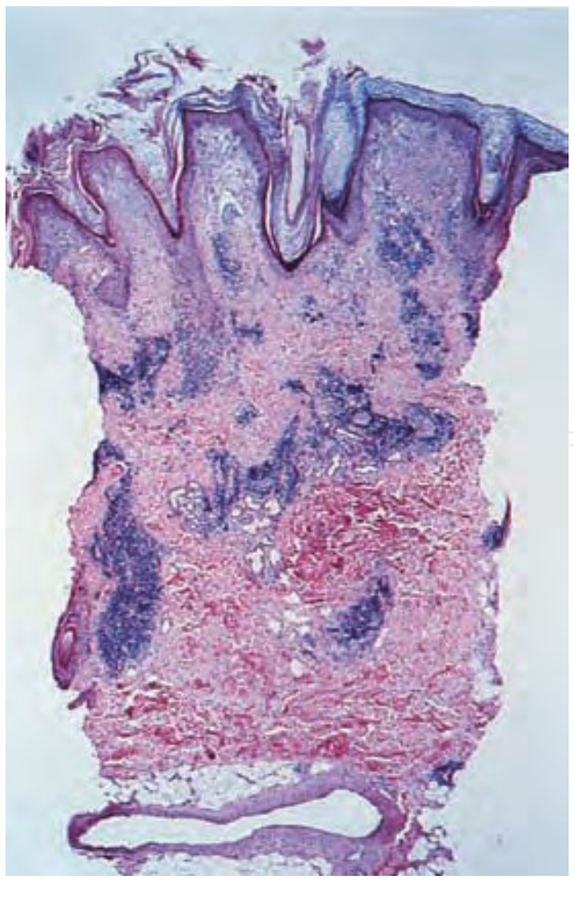
E. Subepidermal Vesicular Dermatitis



1. Scant /No Inflammation
   porphyria cutanea tarda
2. Lymphocytes Predominant
   bullous lichen planus
3. Eosinophils Prominent
   bullous pemphigoid
4. Neutrophils Prominent
   dermatitis herpetiformis
5. Mast Cells Prominent
   bullous mastocytosis

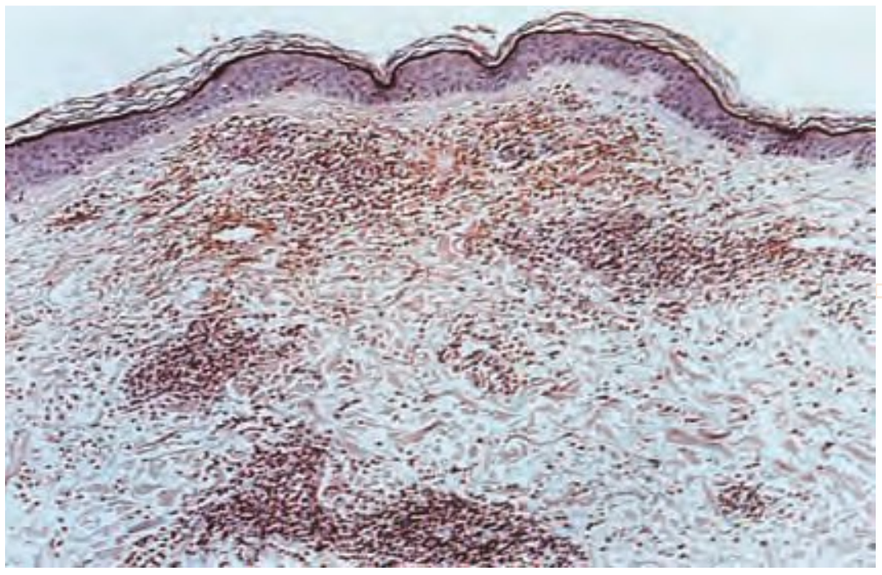
V. PERIVASCULAR, DIFFUSE, AND GRANULOMATOUS INFILTRATES OF THE RETICULAR DERMIS

A. Superficial and Deep Perivascular Infiltrates without Vascular Damage or Vasculitis



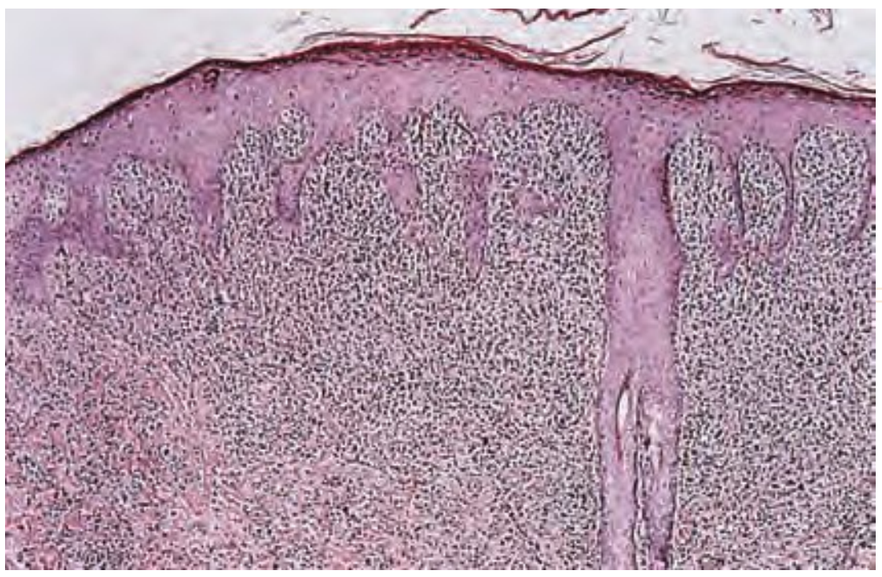
1. Lymphocytes Predominant
   discoid lupus erythematosus (DLE)
2. Neutrophils Predominant
   acute febrile neutrophilic dermatosis (Sweet's syndrome)
3. Lymphocytes and Eosinophils
   papular urticaria
4. With Plasma Cells
   scleroderma/morphea
5. Mixed Cell Types
   erythema chronicum migrans

B. Vasculitis and Vasculopathies



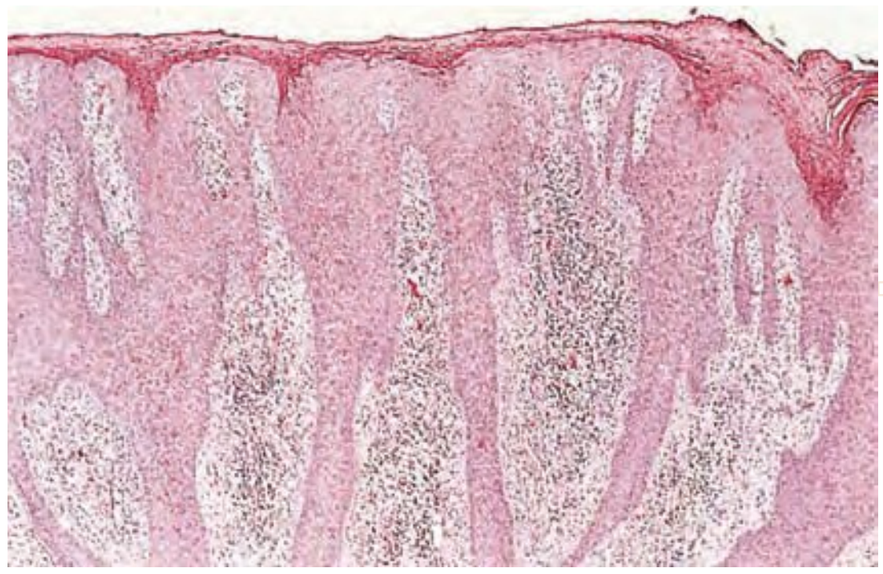
1. Scant Inflammatory Cells
   Degos' disease (malignant atrophic papulosis)
2. Lymphocytes Predominant
   "lymphocytic vasculitis"
3. Neutrophils Prominent
   leukocytoclastic vasculitis
4. Mixed Cell Types and/or Granulomas
   allergic granulomatosis (Churg-Strauss)
5. Thrombotic and Other Microangiopathies
   disseminated intravascular coagulation

C. Diffuse Infiltrates of the Reticular Dermis



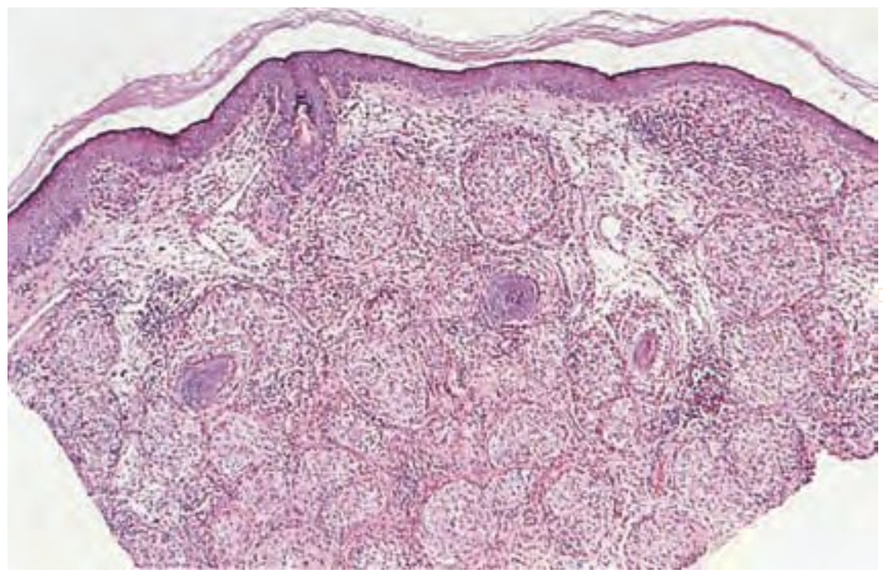
1. Lymphocytes Predominant
   cutaneous lymphoid hyperplasia/lymphocytoma cutis
2. Neutrophils Predominant
   acute neutrophilic dermatosis (Sweet's syndrome)
3. "Histiocytoid" Cells Predominant
   lepromatous leprosy
4. Plasma Cells Prominent
   plasmacytoma, myeloma
5. Mast Cells Predominant
   urticaria pigmentosa
6. Eosinophils Predominant
   eosinophilic cellulitis (Wells' syndrome)
7. Mixed Cell Types
   syphilis, primary, secondary or tertiary
8. Pigment Cells
   nevus of Ota, nevus of Ito
9. Extensive Necrosis
   calciphylaxis

D. Diffuse or Nodular Infiltrates of the Reticular Dermis with Epidermal Proliferation



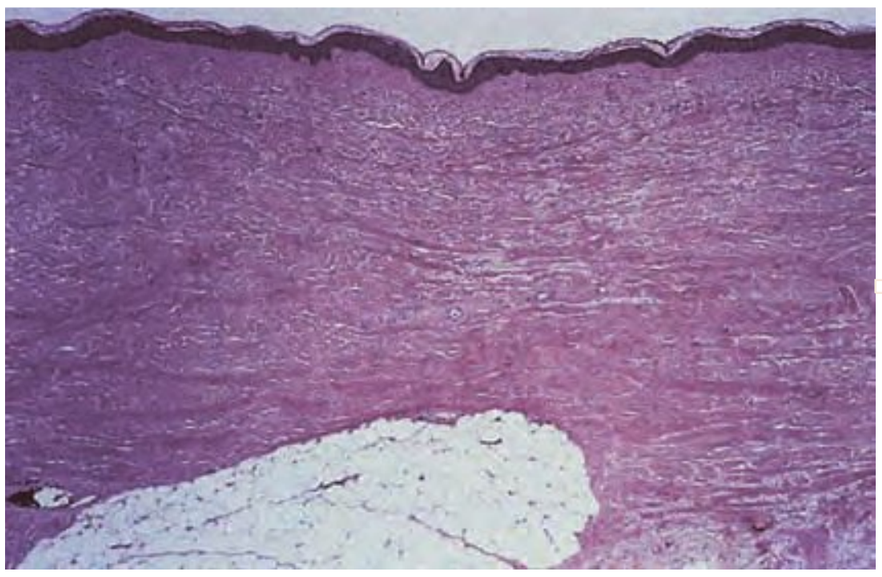
1. Epidermal Proliferation with Mixed Cellular Infiltrates
   deep fungal infection (pseudoepitheliomatous hyperplasia)

E. Nodular Inflammatory Infiltrates of the Reticular Dermis: Granulomas, Abscesses, and Ulcers



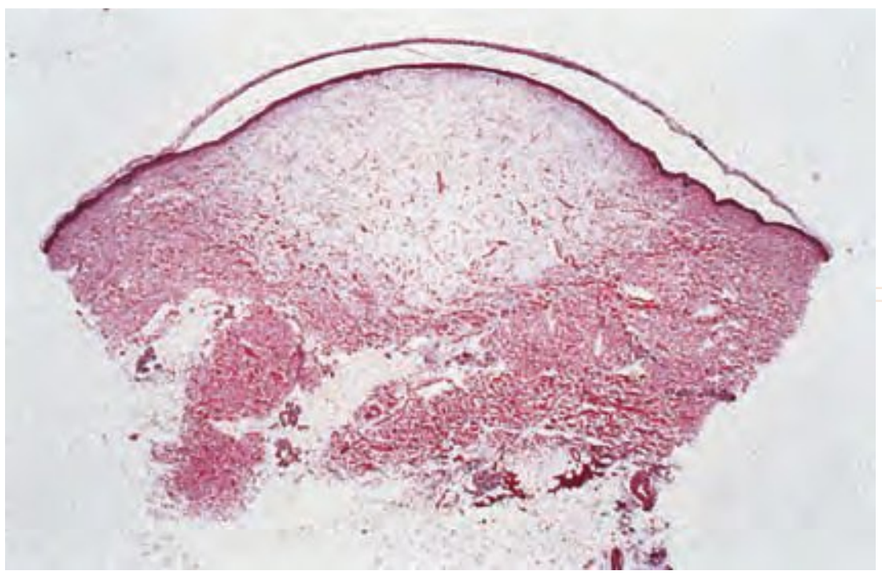
1. Epithelioid Cell Granulomas without Necrosis
   sarcoidosis (lupus pernio and other types)
2. Epithelioid Cell Granulomas with Necrosis
   tuberculosis (lupus vulgaris and other types)
3. Palisading Granulomas
   granuloma annulare
4. Mixed Cell Granulomas
   keratin granuloma (ruptured cyst)
5. Inflammatory Nodules with Prominent Eosinophils
   angiolymphoid hyperplasia with eosinophils
6. Inflammatory Nodules with Mixed Cell Types
   sporotrichosis
7. Abscesses
   acute or chronic bacterial abscesses
8. Inflammatory Nodules with Prominent Necrosis
   aspergillosis
9. Chronic Ulcers and Sinuses
   pyoderma gangrenosum

F. Dermal Matrix Fiber Disorders



1. Collagen Increased
   scleroderma/morphea
2. Collagen Reduced
   scleroderma/morphea
3. Elastin Increased or Prominent
   pseudoxanthoma elasticum
4. Elastin Reduced
   cutis laxa
5. Perforating
   elastosis perforans serpiginosa

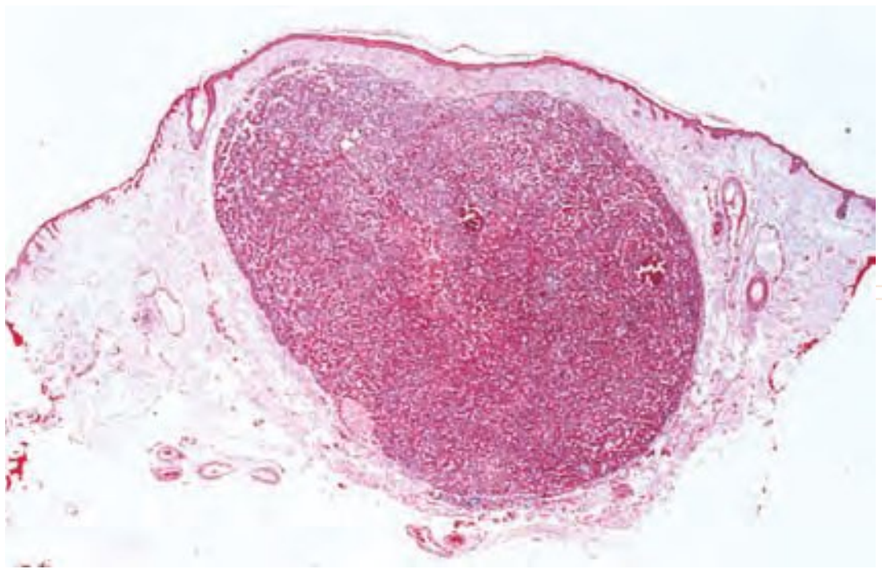
G. Deposition of Material in the Dermis



1. Increased Normal Matrix Constituents
   focal dermal mucinosis
2. Material Not Normally Present in the Dermis
   gout
3. Parasitic Infestations of the Dermis and/or Subcutis
   Myiasis

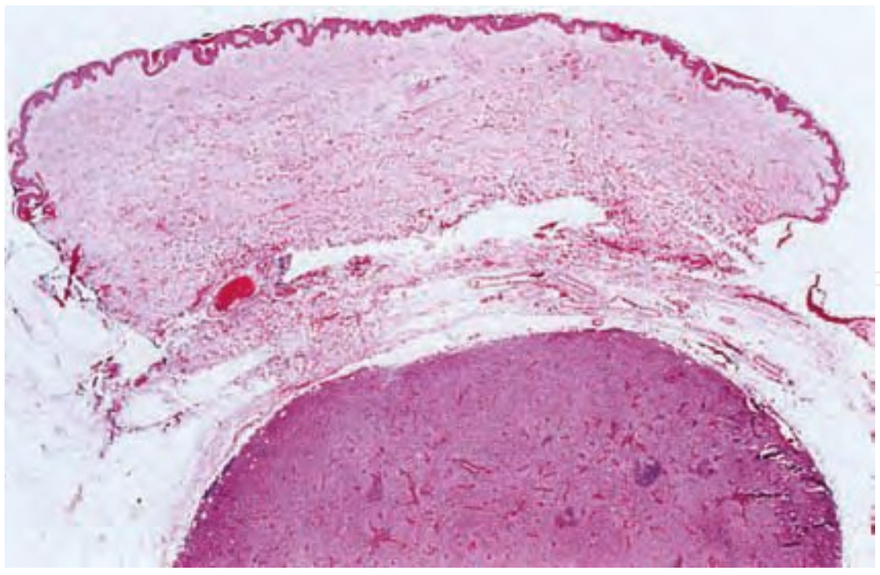
VI. TUMORS AND CYSTS OF THE DERMIS AND SUBCUTIS

A. Small Cell Tumors



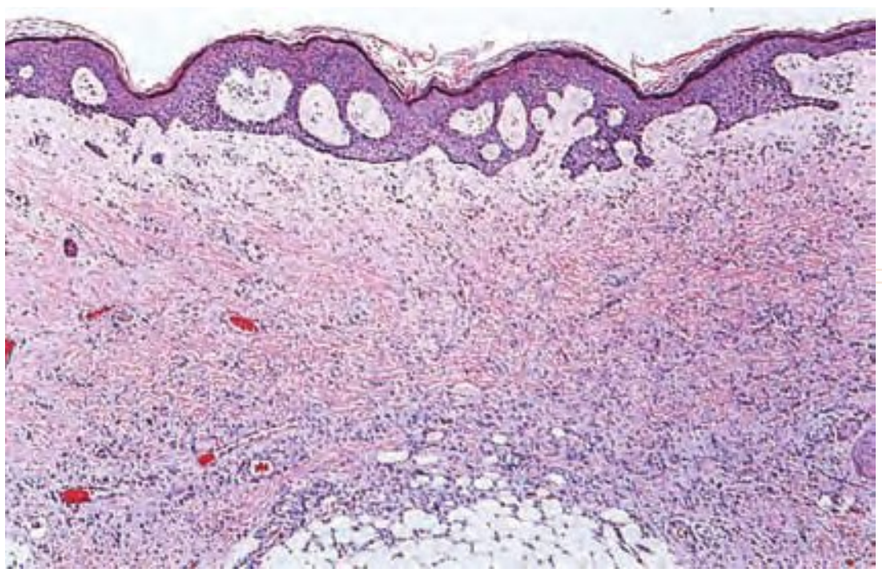
1. Tumors of Lymphocytes or Hemapoietic Cells
   tumor-stage mycosis fungoides
2. Tumors of Lymphocytes and Mixed Cell Types
   cutaneous lymphoid hyperplasia/lymphocytoma cutis
3. Tumors of Plasma Cells
   cutaneous plasmacytoma and myeloma
4. Small Round Cell Tumors
   eccrine spiradenoma

B. Large Polygonal and Round Cell Tumors



1. Squamous Cell Carcinomas
   primary squamous cell carcinoma
2. Adenocarcinomas
   metastatic adenocarcinoma
3. Melanocytic Tumors
   metastatic melanoma
4. Eccrine Tumors
   nodular hidradenoma (eccrine acrospiroma)
5. Apocrine Tumors
   hidradenoma papilliferum
6. Pilar Tumors
   trichoepithelioma
7. Sebaceous Tumors
   sebaceous adenoma and epithelioma
8. "Histiocytoid" Tumors
   xanthomas—eruptive, plane, tuberous, tendon
9. Tumors of Large Lymphoid Cells
   cutaneous anaplastic large cell lymphoma (Ki-1)
10. Mast Cell Tumors
    mastocytosis
11. Tumors with Prominent Necrosis
    epithelioid sarcoma
12. Miscellaneous and Undifferentiated Epithelial Tumors
    undifferentiated carcinoma (large cell, small cell)

C. Spindle Cell, Pleomorphic, and Connective Tissue Tumors



1. Fibrohistiocytic Spindle Cell Tumors
   benign fibrous histiocytoma (dermatofibroma)
2. Schwannian/Neural Spindle Cell Tumors
   neurofibromas
3. Spindle Cell Tumors of Muscle
   leiomyoma
4. Melanocytic Spindle Cell Tumors
   desmoplastic melanoma, including amelanotic
5. Tumors and Proliferations of Angiogenic Cells
   pyogenic granuloma
6. Tumors of Adipose Tissue
   nevus lipomatosus superficialis
7. Tumors of Cartilaginous Tissue
   soft tissue chondroma
8. Tumors of Osseous Tissue
   osteoma cutis

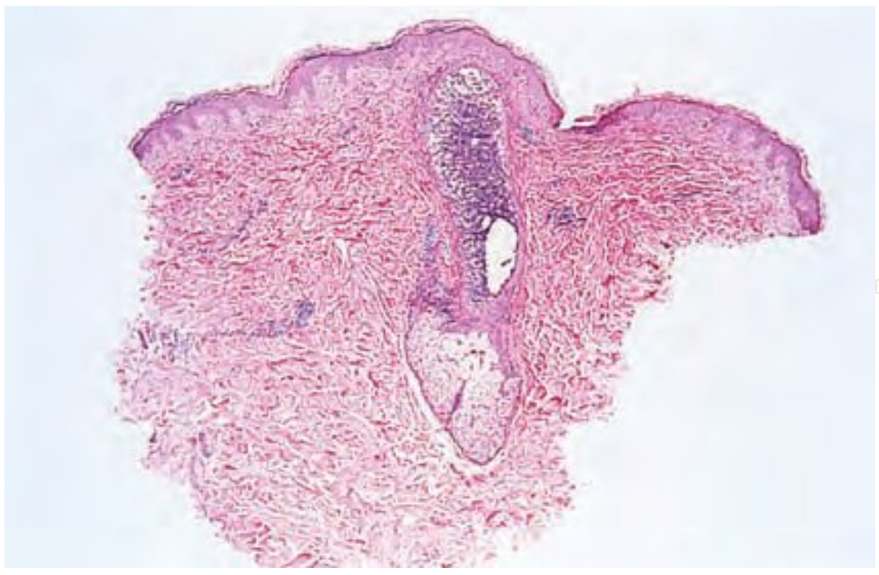
D. Cysts of the Dermis and Subcutis



1. Pilar Differentiation
   epidermal cyst
2. Eccrine and Similar Differentiation
   eccrine hidrocystoma
3. Apocrine Differentiation
   apocrine hidrocystoma

VII. INFLAMMATORY DISORDERS OF SKIN APPENDAGES

A. Pathology Involving Hair Follicles



1. Scant Inflammation
   androgenic alopecia

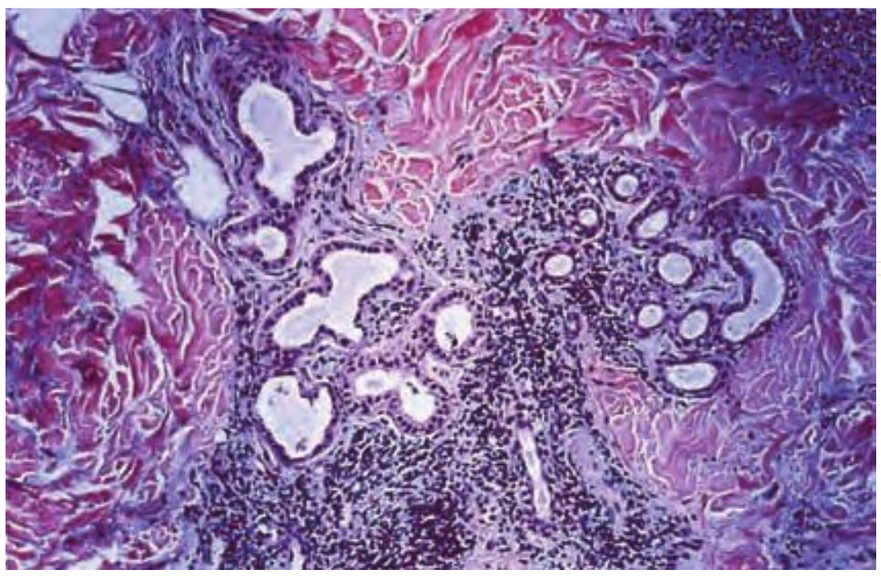
2. Lymphocytes Predominant
   alopecia areata
   a. With Eosinophils Present
      eosinophilic pustular folliculitis

3. Neutrophils Prominent
   acute bacterial folliculitis

4. Plasma Cells Prominent
   acne keloidalis

5. Fibrosing and Suppurative Follicular Disorders
   hidradenitis suppurativa

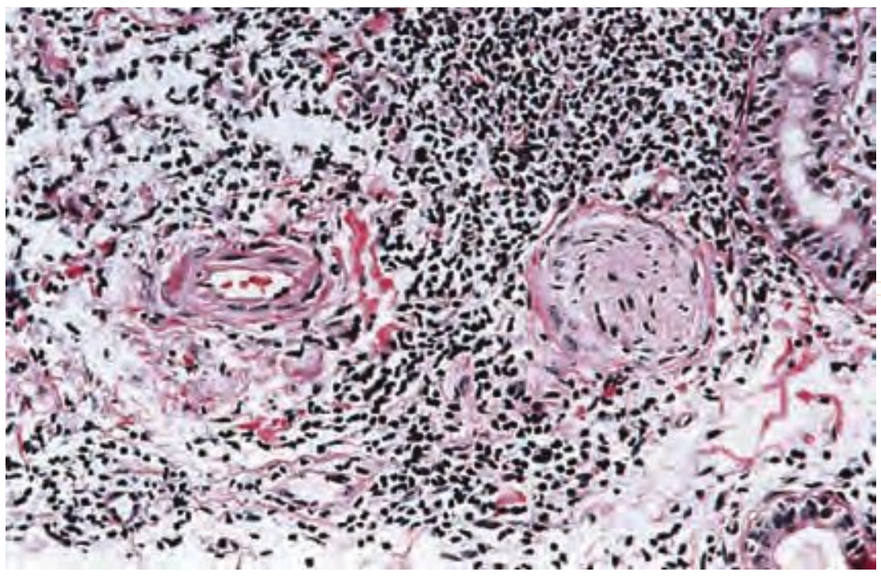
B. Pathology Involving Sweat Glands



1. Scant Inflammation
   eccrine nevus

2. Lymphocytes Predominant
   lupus erythematosus
   a. With Plasma Cells
      cheilitis glandularis
   b. With Eosinophils
      insect bite reactions
   c. With Neutrophils
      neutrophilic eccrine hidradenitis

C. Pathology Involving Nerves



1. Lymphocytic Infiltrates
   neurotropic melanoma

2. Mixed Inflammatory Infiltrates
   leprosy

3. Neoplastic Infiltrates
   neurotropic melanoma

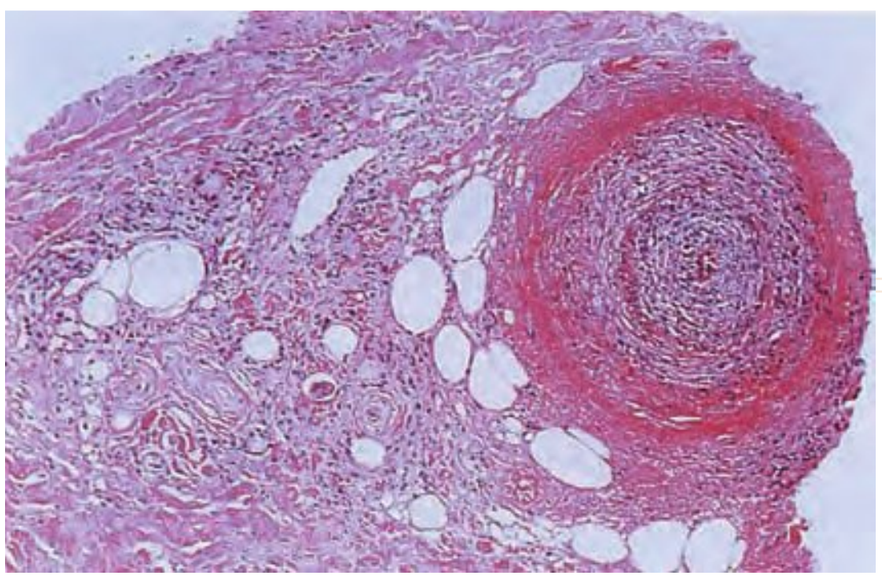
D. Pathology of the Nails



1. Lymphocytic Infiltrates
   melanoma *in situ,* acral-lentiginous type
2. Lymphocytes with Neutrophils
   tinea unguium, onychomycosis
3. Bullous Diseases
   Darier's disease
4. Parasitic Infestations
   scabies

VIII. DISORDERS OF THE SUBCUTIS

A. Subcutaneous Vasculitis and Vasculopathy (Septal or Lobular)



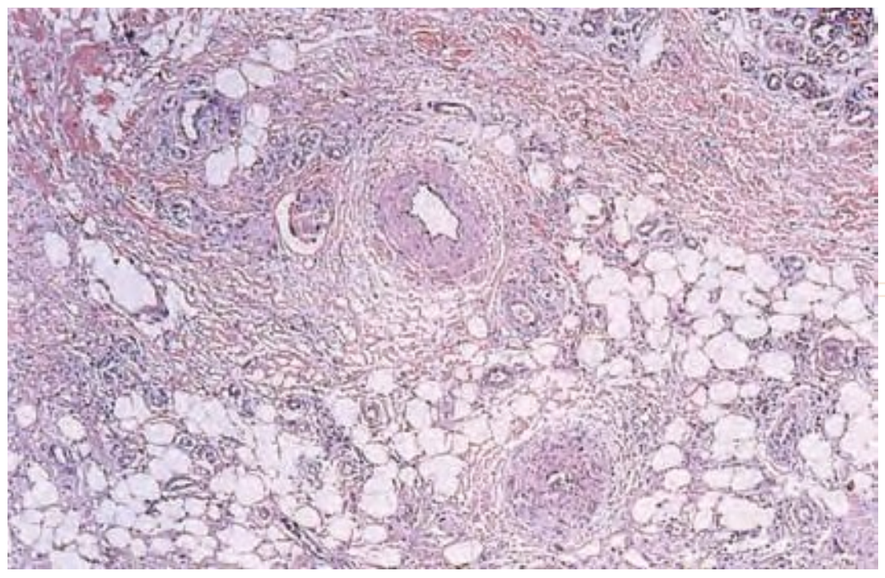
1. Neutrophilic
   subcutaneous polyarteritis nodosa
2. Lymphocytic
   nodular vasculitis
3. Granulomatous
   Churg-Strauss vasculitis

B. Septal Panniculitis without Vasculitis



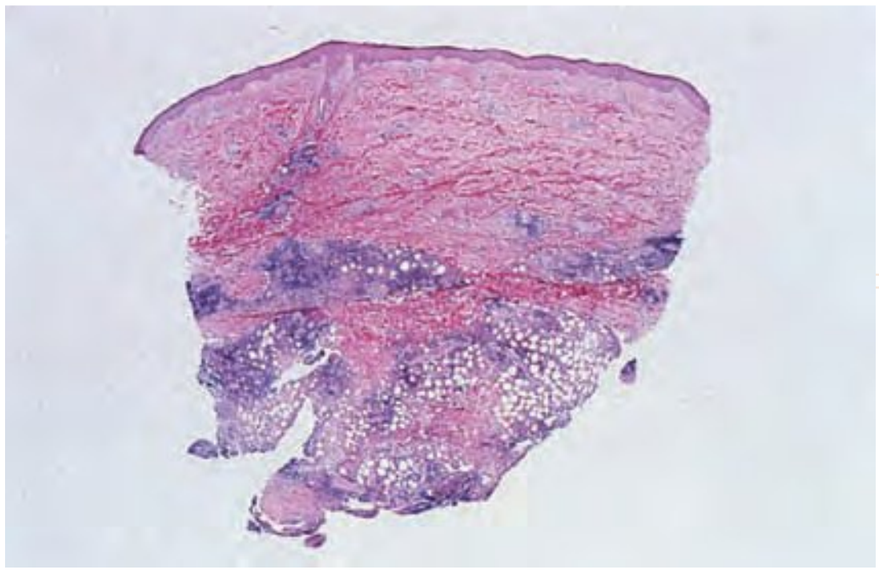
1. Lymphocytes and Mixed Infiltrates
   erythema nodosum and variants
2. Granulomatous
   subcutaneous granuloma annulare
3. Sclerotic
   scleroderma, morphea

C. Lobular Panniculitis without Vasculitis



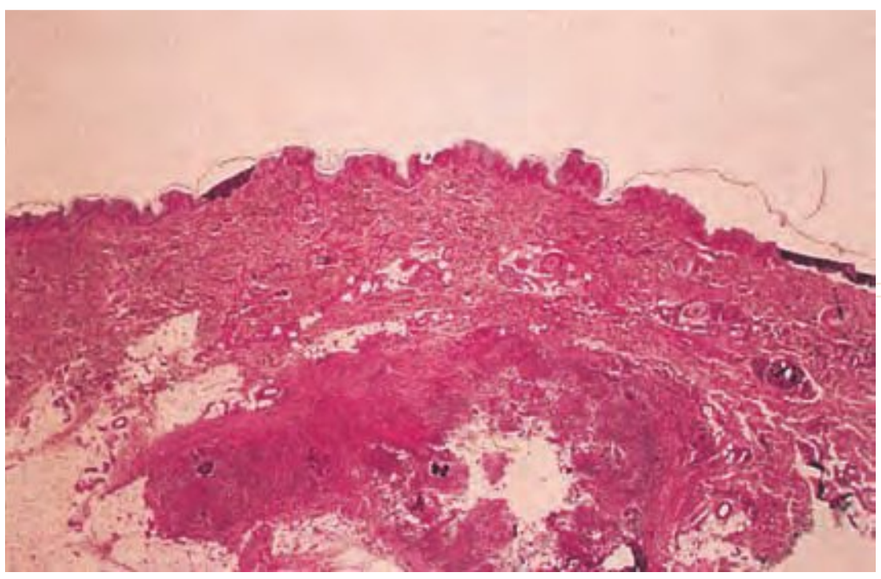
1. Lymphocytes Predominant
   lupus panniculitis
2. Lymphocytes and Plasma Cells
   scleroderma
3. Neutrophilic
   infection (cellulitis)
4. Eosinophils Prominent
   eosinophilic fasciitis
5. Histiocytes Prominent
   cytophagic histiocytic panniculitis
6. Mixed with Foam Cells
   Weber-Christian Disease
7. Granulomatous
   subcutaneous sarcoidosis
8. Crystal Deposits, Calcifications
   sclerema neonatorum
9. Necrosis Prominent
   pancreatic panniculitis
10. Embryonic Fat Pattern
    lipoatrophy
11. Miscellaneous
    lipomembranous panniculitis

D. Mixed Lobular and Septal Panniculitis



1. With Hemorrhage or Sclerosis
   traumatic panniculitis
2. With Many Neutrophils
   necrotizing fasciitis (bacterial infection)
3. With Many Lymphocytes
   nonspecific panniculitis
4. With Cytophagic Histiocytes
   histiocytic cytophagic panniculitis (late lesion)
5. With Granulomas
   mycobacterial panniculitis

E. Subcutaneous Abscesses (Courtesy Waine Johnson, MD)



1. With Neutrophils
   deep fungus infection

PART 3. DISEASE LISTINGS CATEGORIZED BY SITE, PATTERN, AND CYTOLOGY

In this section, the cutaneous diseases are listed in categories based on their location in the skin, their architectural patterns, and their cytology. The listings may be used as a basis for differential diagnosis generation and for review of material covered elsewhere in this text.

I. DISORDERS MOSTLY LIMITED TO THE EPIDERMIS AND STRATUM CORNEUM[1]

The stratum corneum is usually arranged in a delicate mesh-like or "basket-weave" pattern. It may be shed (exfoliated) or thickened (hyperkeratosis) with or without retention of nuclei (parakeratosis or orthokeratosis; respectively). The granular layer may be normal, increased (hypergranulosis), or reduced (hypogranulosis). Usually, alterations in the stratum corneum result from inflammatory or neoplastic changes that affect the whole epidermis and, more often than not, the superficial dermis. Only a few conditions, mentioned in this section, show pathology mostly or entirely limited to the stratum corneum.

A. Hyperkeratosis with Hypogranulosis 86

1. No Inflammation 86

ichthyosis vulgaris 133

B. Hyperkeratosis with Normal or Hypergranulosis 86

The stratum corneum is thickened, the granular cell layer is normal or thickened, and the dermis shows only sparse perivascular lymphocytes. There is no epidermal spongiosis or exocytosis.

1. No Inflammation 86

The upper dermis contains only sparse perivascular lymphocytes.

lamellar ichthyosis 135
X-linked ichthyosis 133
epidermolytic hyperkeratosis 793
epidermolytic acanthoma 793
oculocutaneous tyrosinosis (tyrosinemia) 451
acanthosis nigricans 447
large cell acanthoma 799
hyperkeratosis lenticularis perstans (Flegel's disease) 397

[1]In the lists that follow, the term "predominant" is used to describe an infiltrate in which the majority of the cells are of a certain type, usually lymphocytes or neutrophils. Many dermatoses are composed of infiltrates that are predominantly lymphocytic, with only an occasional other cell; these are listed as, for example, "1. Lymphocytes predominant." Many other dermatoses contain a diagnostically significant admixture of other cell type(s) as a minority population; these are listed in subsequent sections as, for example, "a. With Eosinophils," "b. With Plasma Cells," and so on, it being understood that lymphocytes predominate in these dermatoses also. Infiltrates in which there is an approximately equal admixture of multiple cell types are listed as "mixed" infiltrates.

confluent and reticulated papillomatosis (Gougerot and Carteau)

2. Scant Inflammation 86

Lymphocytes are minimally increased about the superficial plexus. There may be a few neutrophils in the stratum corneum.

dermatophytosis 592
lichen amyloidosis 427
tinea versicolor
erythrasma

C. Hyperkeratosis with Parakeratosis 86

The stratum corneum is thickened, the granular cell layer is reduced, and there is parakeratosis. The dermis may show only sparse perivascular lymphocytes, although some of these conditions in other instances may show more substantial inflammation. There is no epidermal spongiosis or exocytosis.

1. No Inflammation 86

The upper dermis contains only sparse perivascular lymphocytes.

epidermolytic hyperkeratosis 793
epidermal nevi 791
porokeratotic eccrine duct nevus 793
cutaneous horn 811
oral leukoplakia 811
leukoplakia of the vulva 816

2. Scant Inflammation 86

Lymphocytes are minimally increased about the superficial plexus. There may be a few lymphocytes and/or neutrophils in the stratum corneum.

scurvy 407
vitamin A deficiency 407, 450
pellagra (niacin deficiency) 451
Hartnup's disease 451
acrokeratosis neoplastica (Bazex's syndrome) 419
dermatophytosis 592
epidermal dysmaturation (cytotoxic chemotherapy: variable keratin alterations) 321

3. With Epidermal Pallor or Necrosis ("Nutritional Dermatosis") 86

There may be psoriasiform epidermal hyperplasia, and there is hyperkeratosis with parakeratosis and with pallor, swelling, or necrosis of superficial keratinocytes.

necrolytic migratory erythema 409
necrolytic acral erythema 409
acrodernmatitis enteropathica 410
pellagra 408

D. Localized or Diffuse Hyperpigmentations 87

Increased melanin pigment is present in basal keratinocytes, without melanocytic proliferation.

1. No Inflammation 87

The upper dermis contains only sparse perivascular lymphocytes.

simple ephelis (ephelide) 705
melanotic macules 705
café-au-lait spot 1111
actinic lentigo 706
pigmented actinic keratosis 811
melasma 690
Becker's melanosis 706
congenital diffuse melanosis 689
reticulated hyperpigmentations 689
Addison's disease 690
alkaptonuric ochronosis 439
hemochromatosis 449

2. Scant Inflammation 87

Lymphocytes are minimally increased about the superficial plexus. There may be a few lymphocytes and/or neutrophils in the stratum corneum. Melanophages may be present in the papillary dermis.

lichen amyloidosis 427
postinflammatory hyperpigmentation 690
erythema dyschromicum perstans 172

E. Localized or Diffuse Hypopigmentations 87

Melanin pigment is reduced in basal keratinocytes, with (vitiligo) or without (early stages of chemical depigmentation) a reduction in the number of melanocytes.

1. With or Without Slight Inflammation 87

Lymphocytes may minimally increase about the dermal–epidermal junction, as in the active phase of vitiligo, or may be absent, as in albinism.

vitiligo 694
chemical depigmentation 691
idiopathic guttate hypomelanosis 691
albinism 693
tinea versicolor 596
piebaldism 693
Chediak-Higashi syndrome 694
postinflammatory hypopigmentation

II. LOCALIZED SUPERFICIAL EPIDERMAL OR MELANOCYTIC PROLIFERATIONS

Localized proliferations may be reactive but are often neoplastic. The epidermis (keratinocytes) may proliferate without extension into the dermis or extend into the dermis and may be squamous or basaloid. Melanocytes within the epidermis may proliferate with or without cytologic atypia (nevi, dysplastic nevi, melanoma *in situ*), in a proliferative epidermis (superficial spreading melanoma *in situ*, Spitz nevi) or an atrophic epidermis (lentigo maligna); they can also extend into the dermis as proliferative infiltrates (invasive melanoma with or without vertical growth phase). There may be an associated variably cellular, often mixed, inflammatory infiltrate, or inflammation may be essentially absent.

A. Localized Irregular Thickening of the Epidermis 87

Localized irregular epidermal proliferations are usually neoplastic.

1. Localized Epidermal Proliferations 87

The epidermis is thickened secondary to a localized proliferation of keratinocytes (acanthosis). The proliferation can be cytologically atypical, as in squamous cell carcinoma *in situ*, or bland, as in eccrine poroma.

a. No Cytologic Atypia 87

seborrheic keratosis 795
dermatosis papulosa nigra 799
stucco keratosis 799
large cell acanthoma 799
clear cell acanthoma 799
epidermal nevi 791
eccrine poroma 885
hidroacanthoma simplex 886
oral white sponge nevus 794
leukoedema of the oral mucosa 794
verrucous hyperplasia of oral mucosa (oral florid papillomatosis) 813

b. With Cytologic Atypia 87

actinic keratosis 807
arsenical keratosis 816
squamous cell carcinoma *in situ* 809
Bowen's disease 813
erythroplasia of Queyrat 815
erythroplakia of the oral mucosa 812
bowenoid papulosis 656

c. Pseudoepitheliomatous Hyperplasia 822

halogenodermas (Halogen Eruptions) 326
deep fungal infections 604
epidermis above granular cell tumor 1130
Spitz nevus 718
verrucous melanoma 756

2. Superficial Melanocytic Proliferations 87

The epidermis may be thickened (acanthosis) and is associated with a proliferation of single or nested melanocytic cells. The proliferation can be malignant, as in superficial spreading melanoma, or benign, as in nevi.

junctional nevi 699
recurrent melanocytic nevi 732
Spitz nevi 718
compound or dermal nevi, papillomatous 714
junctional or superficial compound dysplastic nevi 733
melanoma in situ 738

B. Localized Lesions with Thinning of the Epidermis 87

A thinned epidermis is characteristic of aged or chronically sun-damaged skin. The epidermis is thinned secondary to diminished number and to decreased size of keratinocytes.

1. With Melanocytic Proliferation 87

The epidermis is thinned (atrophic), and there is proliferation of single or small groups of atypical melanocytes, resulting in the localization of melanocytes in contiguity with one another, in the basal layer of the epidermis.

melanoma in situ (lentigo maligna type) 738

2. Without Melanocytic Proliferation 87

The epidermis is thinned without proliferation of keratinocytes or melanocytes. Each melanocyte is separated from the next by several keratinocytes.

actinic keratosis. 807
porokeratosis 139
lichen sclerosus et atrophicus 303

C. Localized Lesions with Elongated Rete Ridges 88

Elongation of the rete ridges without melanocytic proliferation is termed "psoriasiform hyperplasia" because this pattern is seen in psoriasis. Elongated rete with melanocytic proliferation and predominance of single cells over nests is termed a "lentiginous" pattern. The prototype of this pattern, also seen in a more exaggerated form in dysplastic nevi and in the "lentiginous" melanomas, is lentigo simplex.

1. With Melanocytic Proliferation 88

The epidermal rete ridges are elongated, and within the rete is melanocytic proliferation.

lentigo simplex 708
nevus spilus 708
lentiginous junctional nevus 711
junctional nevus 711
dysplastic nevus 733
acral-lentiginous melanoma 747
mucosal-lentiginous melanoma 749

2. Without Melanocytic Proliferation 88

The epidermis is thickened (acanthotic). Melanocytes are normal as are keratinocytes. The only change is acanthosis.

epidermal nevi 791
psoriasis 174
lichen simplex chronicus 174, 242
acanthosis nigricans 447

D. Localized Lesions with Pagetoid Epithelial Proliferation 88

A neoplastic proliferation of one cell type distributed as single cells or nests within a benign epithelium is termed "Pagetoid" after Paget's disease of the breast (mammary carcinoma cells proliferating in skin of the nipple).

1. Keratinocytic Proliferation 88

The epidermis has atypical keratinocytes scattered within mature epithelium at all or multiple levels; there is loss of normal maturation. Mitoses are increased, and there may be individual cell necrosis.

pagetoid squamous cell carcinoma in situ 815
intraepithelial epithelioma (Borst-Jadassohn) 832
clonal seborrheic keratosis 832

2. Melanocytic Proliferation 88

Atypical melanocytes are seen at all levels within the otherwise mature but often hyperplastic epidermis.

melanoma in situ (superficial spreading type) 738

3. Glandular Epithelial Proliferations 88

Atypical large clear cells with glandular differentiation (mucin production, occasionally lumen formation) proliferate in a normally maturing epidermis.

Paget's disease (mammary or extramammary) 838

4. Lymphoid Proliferations 88

Atypical, large, clear lymphoid cells proliferate in a normally maturing epidermis.

a. Pagetoid reticulosis 88

localized (Woringer-Kolopp) 940
disseminated (Ketron-Goodman) 940

E. Localized Papillomatous Epithelial Lesions 88

A "papilla" may be likened to a "finger" of stroma with a few blood vessels, collagen fibers, and fibroblasts covered by a "glove" of epithelium, which may be reactive or neoplastic, benign or malignant.

1. With Viral Cytopathic Effects 88

The epidermis is acanthotic with vacuolated cells often having enlarged and somewhat irregular nuclei (koilocytes), the granular cell layer is usually thickened with enlarged keratohyaline granules, and there is parakeratosis in tall columns overlying the thickened epidermis at the tops of the papillae. Large inclusions are seen in molluscum contagiosum.

verruca vulgaris 650
orf 637
condyloma acuminatum 654

molluscum contagiosum 659
bowenoid papulosis 656

2. No Viral Cytopathic Effect 88

The epidermis proliferates. The cells may be basophilic or "basaloid" in type (seborrheic keratoses). There may be increased stratum corneum and elongation of the dermal papillae (squamous papilloma), or there may be basilar keratinocyte atypia (actinic keratosis).

seborrheic keratosis 795
acanthosis nigricans 447
confluent and reticulated papillomatosis 449
actinic keratosis, hypertrophic 808
nonspecific squamous papilloma 649, 791
epithelial nevus/epidermal nevus 791
hyperkeratosis of the nipple and areola 792
verruciform xanthoma 685
verrucous melanoma 756

F. Irregular Proliferations Extending into the Dermis 88

Irregular or asymmetric proliferations of keratinocytes extending into the dermis are usually neoplastic. The differential diagnosis includes reactive pseudoepitheliomatous hyperplasia, which may be seen around chronic ulcers or in association with other inflammatory conditions.

1. Squamous Differentiation 88

The epidermis is irregularly thickened, the maturation is abnormal, and there may be keratinocyte atypia (squamous cell carcinoma). The proliferation is often associated with a thick parakeratotic scale.

lichen simplex chronicus 182, 242
squamous cell carcinoma, superficial 817
keratoacanthoma 835
prurigo nodularis 173
actinic prurigo 335
inverted follicular keratosis 795
verrucous carcinoma 656, 822
of oral mucosa 813
of anogenital region (giant condyloma of Buschke and Lowenstein) 656, 822
of plantar skin (epithelioma cuniculatum) 822
pseudoepitheliomatous hyperplasia 822
deep fungal infection 604
halogenoderma 326
chronic ulcers 539, 604, 625
granular cell tumor 1131
Spitz nevus 718
verrucous melanoma 756

2. Basaloid Differentiation 88

The proliferation is of basal cells from the epidermis, extending into the dermis. The epidermis can be thickened, normal, or atrophic.

basal cell carcinoma, superficial types 817
dermatofibroma with basaloid induction 969

G. Superficial Polypoid Lesions 89

A polyp is any lesion that protrudes from a surface. Whereas a papilloma consists of elongated papillae representing a "finger" of stroma covered by a "glove" of epithelium, a polyp is more like a hand within which the papillae ("fingers") may be elongated or, more usually, normal or attenuated. Thus, polypoid lesions may also be papillomatous, or not. Many of the neoplasms listed in Section VI may also present as polypoid neoplasms.

1. Melanocytic Lesions 89

polypoid dermal and compound nevi, including Spitz nevi 756
polypoid melanoma 756

2. Stromal Lesions 89

neurofibroma 1109
soft fibroma (fibroepithelial polyp, acrochordon, skin tag) 981

3. Other Neoplasms 89

See Section VI on tumor and cysts of the dermis and subcutis.

III. DISORDERS OF THE SUPERFICIAL CUTANEOUS REACTIVE UNIT

The epidermis, papillary dermis, and superficial capillary-venular plexus react together in many dermatologic conditions and were termed the *superficial cutaneous reactive unit* by Clark. Many dermatoses are associated with infiltrates of lymphocytes, with or without other cell types, around the superficial vessels. The epidermis in pathologic conditions can be thinned (atrophic), thickened (acanthosis), edematous (spongiosis), and/or infiltrated (exocytosis). The epidermis may proliferate in response to chronic irritation or infection (bacterial, yeast, deep fungal, or viral). The epidermis may proliferate in response to dermatologic conditions (psoriasis, atopic dermatitis, prurigo). The papillary dermis and superficial vascular plexus may have a variety of inflammatory cells, can be edematous, may have increased ground substance (hyaluronic acid), or may be sclerotic or homogenized.

A. Superficial Perivascular Dermatitis 89

Many dermatoses are associated with infiltrates of lymphocytes around the vessels of the superficial capillary-venular plexus with or without other cell types. The vessel walls may be quite unremarkable, or there may be slight to moderate endothelial swelling. Eosinophilic change ("fibrinoid necrosis"), a hallmark of true vasculitis, is not seen. The term "lymphocytic vasculitis" may encompass some of the conditions mentioned here, but is of doubtful validity in the absence of vessel wall damage. The epidermis is variable in its thickness, amount, and type of exocytotic cells and in the integrity of the basal cell zone (liquefaction

degeneration). In some of the entities listed here, the perivascular infiltrate may in some examples also involve vessels of the mid and deep vessels. These conditions are also listed in Section V.

1. Superficial Perivascular Dermatitis, Lymphocytes Predominant 89

Lymphocytes are seen about the superficial vascular plexus. Other cell types are rare or absent.

morbilliform viral exanthem 659
papular acrodermatitis (Gianotti-Crosti) 184, 418
stasis dermatitis 1034
pityriasis lichenoides et varioliformis acuta (PLEVA), early 196
Jessner's lymphocytic infiltrate 291
candidiasis 597
superficial gyrate erythemas 171
lupus erythematosus, early 287
mixed connective tissue disease 292
dermatomyositis 293
early herpes simplex, zoster 638
morbilliform drug eruption 311
cytomegalovirus inclusion disease 644
polymorphous drug eruption 314
progressive pigmented purpura 169, 952
parapsoriasis, small-plaque type (digitate dermatosis) 182
mucocutaneous lymph node syndrome (Kawasaki's disease) 184
secondary syphilis 579

a. Superficial Perivascular Dermatitis with Eosinophils 89

In addition to lymphocytes, eosinophils are present in varying numbers, with both a perivascular and interstitial distribution.

arthropod-bite reaction 634
allergic urticarial reaction (drug) 311
bullous pemphigoid, urticarial phase 256
erythema toxicum neonatorum 267
Wells' syndrome 467
mastocytosis/telangiectasia macularis eruptiva perstans 159
angiolymphoid hyperplasia with eosinophilia 1007
Kimura's disease 1025
Langerhans cell histiocytosis (early lesions) 668

b. Superficial Perivascular Dermatitis with Neutrophils 89

In addition to lymphocytes, neutrophils are present in varying numbers, with both a perivascular and interstitial distribution.

cellulitis
erysipelas
urticaria
Still's disease
if vasculitis is present, refer to Section III.G

c. Superficial Perivascular Dermatitis with Plasma Cells 89

Plasma cells are seen about the dermal vessels as well as in the interstitium. They are most often admixed with lymphocytes.

secondary syphilis 579
arthropod-bite reaction 634
Kaposi's sarcoma, nonspecific patch stage 1031
actinic keratoses and Bowen's disease 815
Zoon's plasma cell balanitis circumscripta 815
erythroplasia of Queyrat 815

d. Superficial Perivascular Dermatitis, with Extravasated Red Cells 89

A perivascular lymphocytic infiltrate is associated with extravasation of erythrocytes, without fibrinoid necrosis of vessels.

pityriasis rosea 184
lupus erythematosus, subacute 283
lupus erythematosus, early 289
postinflammatory hyperpigmentation 691
stasis dermatitis 1034
Kaposi's sarcoma, patch stage 1031
pityriasis lichenoides et varioliformis acuta (PLEVA) 196
pityriasis lichenoides chronica 196
pigmented purpuric dermatoses (Schamberg's) 225

e. Superficial Perivascular Dermatitis, Melanophages Prominent 89

There is a perivascular infiltrate of lymphocytes with an admixture of pigment-laden melanophages, indicative of prior damage to the basal layer and "pigmentary incontinence." Some degree of residual interface damage may also be evident.

postinflammatory hyperpigmentation 691
postchemotherapy hyperpigmentation 322
chlorpromazine pigmentation 319
amyloidosis 425
regressed pigmented lesion
resolved lichenoid reaction including fixed drug eruption

2. Superficial Perivascular Dermatitis, Mast Cells Predominant 89

Mast cells are the main infiltrating cells seen in the dermis. Lymphocytes are also present, and there may be a few eosinophils.

urticaria pigmentosa, nodular type 158
telangiectasia macularis eruptiva perstans (TMEP), adult mast cell disease 159

B. Superficial Dermatitis with Spongiosis (Spongiotic Dermatitis) 89

Spongiotic dermatitis is characterized by intercellular edema in the epidermis. In mild or early lesions, the intercellular space is increased with stretching of desmosomes but the integrity of the epithelium is intact. In more severe spongiotic conditions, there is separation of keratinocytes to form spaces (vesicles). For this reason, the spongiotic dermatoses are also discussed later in Section IV.

1. Spongiotic Dermatitis, Lymphocytes Predominant 89

There is marked intercellular edema (spongiosis) within the epidermis. In the dermis, perivascular lymphocytes are predominant.

eczematous dermatitis 236
atopic dermatitis 242
allergic contact dermatitis 242
photoallergic drug eruption 318, 241
irritant contact dermatitis 240
nummular dermatitis (eczema) 241
dyshidrotic dermatitis 240
parapsoriasis, small-plaque type (digitate dermatosis) 182
polymorphous light eruption 333
lichen striatus 193
chronic actinic dermatitis (actinic reticuloid) 333
actinic prurigo, early lesions 335
"id" reaction 241
seborrheic dermatitis 243
stasis dermatitis 243
erythroderma 244
miliaria 244
pityriasis rosea 183
Sézary's syndrome 944
papular acrodermatitis (Gianotti-Crosti) 184, 418

a. Spongiotic Dermatitis, with Eosinophils 89

There is marked intercellular edema (spongiosis) within the epidermis. In the dermis, lymphocytes are predominant. Eosinophils can be found in most examples of atopy and allergic contact dermatitis and are numerous in incontinentia pigmenti.

spongiotic (eczematous) dermatitis 237
atopic dermatitis 242
allergic contact dermatitis 242
photoallergic drug eruption 318
incontinentia pigmenti, vesicular stage 161
eczematous nevus (Meyerson's nevus) 730
erythema gyratum repens 171
scabies 626
erythema toxicum neonatorum 267

b. Spongiotic Dermatitis with Plasma Cells 89

There is marked intercellular edema (spongiosis) within the epidermis. In the dermis, perivascular lymphocytes are predominant, and plasma cells are present.

syphilis, primary or secondary lesions 579
pinta, primary or secondary lesions 584
seborrheic dermatitis in HIV infection 243

c. Spongiotic Dermatitis with Neutrophils 89

There is marked intercellular edema (spongiosis) within the epidermis. Lymphocytes are present in the dermis. There is focal and shoulder parakeratosis, with a few neutrophils in the stratum corneum.

dermatophytosis 592
seborrheic dermatitis 243
toxic shock syndrome 546

C. Superficial Dermatitis with Epidermal Atrophy (Atrophic Dermatitis) 90

Most inflammatory dermatoses are associated with epithelial hyperplasia. Only a few chronic conditions exhibit epidermal atrophy.

1. Epidermal Atrophy, Scant Inflammatory Infiltrates 90

The epidermis is thinned—only a few cell layers thick. There is a scanty lymphocytic infiltrate about the superficial capillary-venular plexus.

aged skin 691
chronic actinic damage 691
radiation dermatitis 348
porokeratosis 139
acrodermatitis chronica atrophicans 586
malignant atrophic papulosis 232
poikiloderma atrophicans vasculare 295

2. Epidermal Atrophy, Lymphocytes Predominant 90

The epidermis is thinned but not as marked as in aged or irradiated skin. In the dermis there are many lymphocytes about the superficial capillary-venular plexus.

parapsoriasis/early mycosis fungoides 182, 944
lupus erythematosus 279
mixed connective tissue disease 292
pinta, tertiary lesions 584
dermatomyositis 293

a. Epidermal Atrophy with Papillary Dermal Sclerosis/Matrix Changes 90

The epidermis is thinned, and there can be hyperkeratosis. The dermis is homogenized and edematous; inflammation is minimal.

lichen sclerosus et atrophicus 296
thermal burns 274, 345
parapsoriasis/early mycosis fungoides 183, 944
poikiloderma vasculare atrophicans 295
radiation dermatitis

D. Superficial Dermatitis with Psoriasiform Proliferation (Psoriasiform Dermatitis) 90

Psoriasiform proliferation is a form of epithelial hyperplasia characterized by uniform elongation of rete ridges. Although the surface may be slightly raised to form a plaque, the epidermal proliferation tends to extend downward into the dermis, in contrast to a papillomatous pattern, in which the rete ridges are elongated upward above the plane of the epidermal surface and a papilloma (such as a wart) is formed. The prototype is psoriasis, in which the suprapapillary plates are thinned. In most other psoriasiform conditions, the suprapapillary plates are thickened but not as much as the elongated rete. Because of the increased epithelial turnover, there is often associated hypogranulosis and parakeratosis.

1. Psoriasiform Epidermal Proliferation, Lymphocytes Predominant 90

The epidermis is evenly and regularly thickened in a psoriasiform pattern, spongiosis is variable (rare to absent in psoriasis, common in seborrheic and inflammatory dermatoses). There is an infiltrate of lymphocytes about dermal vessels.

chronic spongiotic dermatitis 237
atopic dermatitis 242
seborrheic dermatitis 243
nummular dermatitis (eczema) 241
lichen simplex chronicus 173, 242
prurigo nodularis 173
psoriasis 174
psoriasiform drug eruptions 322
pityriasis rosea 183
exfoliative dermatitis 175
pityriasis rubra pilaris 195
parapsoriasis/early mycosis fungoides 182, 944
verrucous hyperkeratotic mycosis fungoides 936
inflammatory linear verrucous epidermal nevus (ILVEN) 194
pellagra 408
necrolytic migratory erythema (chronic lesions) 409
acrodermatitis enteropathica 410
kwashiorkor 410
reticulated hyperpigmentations (e.g., Dowling-Degos disease) 689

a. Psoriasiform Epidermal Proliferation, with Plasma Cells 90

The epidermis is evenly thickened and may be spongiotic. There may be exocytosis of lymphocytes. The stratum corneum is variable, often parakeratotic. Plasma cells are found about the superficial vessels in varying numbers admixed with lymphocytes.

arthropod-bite reactions 634
secondary syphilis 579
cutaneous T-cell lymphoma (mycosis fungoides) 936
prurigo nodularis 173

b. Psoriasiform Epidermal Proliferation, with Eosinophils 90

The epidermis is evenly thickened and may be spongiotic, and there may be exocytosis of inflammatory cells, including eosinophils. Eosinophils are easily identified in the dermis and may be numerous in some conditions (e.g., incontinentia pigmenti).

chronic spongiotic dermatitis
chronic allergic dermatitis 237
chronic atopic dermatitis 237
exfoliative dermatitis 175
cutaneous T-cell lymphoma 935
incontinentia pigmenti, verrucous stage 160

2. Psoriasiform Epidermal Proliferation, Neutrophils Prominent (Neutrophilic/Pustular Psoriasiform Dermatitis) 90

The epidermis is evenly thickened, and there is exocytosis (migration of inflammatory cells through the epidermis) of neutrophils. These may collect into abscesses in the epidermis at the level of the stratum corneum (Munro microabscess). The stratum corneum is thickened and parakeratotic and contains neutrophils.

psoriasis vulgaris 174
pustular psoriasis 174
Reiter's syndrome, keratoderma blenorrhagicum 181
pustular drug eruption 326
acute generalized exanthematous pustulosis 314
geographic tongue (lingua geographica) 187, 795
candidiasis 597
pustular secondary syphilis (rare) 582
dermatophytosis 592

3. Psoriasiform Epidermal Proliferation, with Epidermal Pallor or Necrosis ("Nutritional Dermatosis") 90

There may be psoriasiform epidermal hyperplasia, and there is hyperkeratosis with parakeratosis and with pallor, swelling, or necrosis of superficial keratinocytes.

necrolytic migratory erythema 409
necrolytic acral erythema 409
acrodermatitis enteropathica 410
pellagra 408

E. Superficial Dermatitis with Irregular Epidermal Proliferation (Hypertrophic Dermatitis) 90

Irregular thickening and thinning of the epidermis is seen in some reactive conditions, but the possibility of squamous cell carcinoma should also be considered. As in other conditions

associated with increased epithelial turnover, there may be hypogranulosis and parakeratosis.

1. Irregular Epidermal Proliferation, Lymphocytes Predominant 90

The epidermis is irregularly thickened, with areas of normal thickness, acanthosis, and thinning. Lymphocytes are the predominant inflammatory cell about the dermal vessels.

lichen simplex chronicus 173, 242
inflammatory linear verrucous nevus (ILVEN, psoriasiform category) 194
prurigo nodularis 173
incontinentia pigmenti, verrucous stage 160
pellagra (niacin deficiency) 451
Hartnup's disease 451

a. Irregular Epidermal Proliferation, Plasma Cells Present 90

The epidermis is irregularly acanthotic. Plasma cells are found about the dermal vessels admixed with lymphocytes.

squamous cell carcinoma *in situ* (Bowen's disease) 813
erythroplasia of Queyrat 815
rupial secondary syphilis, condyloma lata 582
yaws, primary or secondary 583
pinta, primary or secondary lesions 584
actinic keratosis 807
pseudoepitheliomatous hyperplasia 822
pemphigus vegetans 245

2. Irregular Epidermal Proliferation, Neutrophils Prominent 90

The epidermis has focal areas of acanthosis, and neutrophils can be seen as exocytotic cells and are found in the dermis in abscesses and about dermal vessels without there being a primary vasculitis.

deep fungal infections (superficial biopsy; see later) 604
halogenodermas (Halogen Eruptions) 326
botryomycosis 573
keratoacanthoma 835
impetigo contagiosa 539
granuloma inguinale 570

3. Irregular Epidermal Proliferation, Neoplastic 90

The epidermis is irregularly acanthotic. There is an associated neoplastic infiltrate in the epidermis or dermis or in both.

squamous cell carcinoma
malignant melanoma ("verrucous" pattern) 738
granular cell tumor 1130

F. Superficial Dermatitis with Lichenoid Infiltrates (Lichenoid Dermatitis) 91

Lichenoid inflammation is a dense, "bandlike" infiltrate of small lymphocytes clustered about the dermal–epidermal junction and obscuring the interface. The epidermis is variable in its thickness, amount of exocytotic lymphocytes, and integrity of the basal cell zone (liquefaction degeneration). Hypergranulosis due to delayed epidermal maturation is a commonly associated feature. For the same reason, there may be orthokeratotic hyperkeratosis. Apoptotic or necrotic keratinocytes are often present. In lichen planus, these are called Civatte bodies. Pigmentary incontinence (melanin-laden macrophages in the papillary dermis) is common, as in any condition in which there is destruction of basal keratinocytes.

1. Lichenoid Dermatitis, Lymphocytes Exclusively 91

The bandlike infiltrate is composed almost exclusively of lymphocytes. Eosinophils and plasma cells are essentially absent.

lichen planus–like keratosis (benign lichenoid keratosis) 186
lichen planus 185
pityriasis lichenoides chronica
lupus erythematosus, lichenoid forms 279
mixed connective tissue disease 292
acrodermatitis chronica atrophicans 586
poikiloderma atrophicans vasculare 295
pigmented purpuric dermatitis, lichenoid type (Gougerot-Blum) 226
graft-versus-host disease (GVHD), lichenoid stage 270
erythema multiforme 268
pityriasis lichenoides et varioliformis acuta (PLEVA), early lesions 196
parapsoriasis/mycosis fungoides, patch/plaque stage 182, 936
Sézary's syndrome 944

2. Lichenoid Dermatitis, Lymphocytes Predominant 91

The bandlike lichenoid infiltrate is composed almost exclusively of lymphocytes. A few plasma cells and eosinophils may also be present.

lichen planus–like keratosis (benign lichenoid keratosis) 186
parapsoriasis/mycosis fungoides, patch/plaque stage 182, 936
Sézary's syndrome 944
paraneoplastic pemphigus 254
secondary syphilis 579
halo nevus 730
lichenoid tattoo reaction 361
lichen striatus 193

a. Lichenoid Dermatitis, Eosinophils Present 91

Eosinophils are found in the lichenoid dermal infiltrate, about the dermal vessels, and in some instances around the adnexal structures.

lichenoid drug eruptions 313
lichenoid actinic keratoses 187
lichen planus, hypertrophic 185
arthropod-bite reactions 634
cutaneous T-cell lymphoma, mycosis fungoides, patch/plaque stage 182, 936
histiocytosis X (Letterer-Siwe) 668
mastocytosis/telangiectasia eruptiva macularis perstans 159

b. Lichenoid Dermatitis, Plasma Cells Present 91

Plasma cells are found in the lichenoid infiltrate; their number is variable, but they do not as a rule comprise the major portion of the dermal infiltrate.

lichenoid actinic keratosis 808
lichenoid keratosis (lichen planus–like keratosis) 187
Bowen's disease 813
erythroplasia of Queyrat 815
keratosis lichenoides chronica 192
secondary syphilis 579
pinta, primary or secondary lesions 584
arthropod-bite reaction 634
cutaneous T-cell lymphoma, mycosis fungoides, patch/plaque stage 182, 936
zoon plasma cell balanitis 815
lichen striatus 193

c. Lichenoid Dermatitis, with Melanophages 91

Most of the conditions listed as lichenoid dermatoses may be associated with release of pigment from damaged basal keratinocytes into the papillary dermis—"pigmentary incontinence." If a specific dermatosis cannot be identified, the appearances may be classified as postinflammatory hyperpigmentation.

postinflammatory hyperpigmentation 689

3. Lichenoid Dermatitis, Histiocytes Predominant 91

Histiocytes are the predominant cell type in the dermal infiltrate.

lichen nitidus 192
actinic reticuloid/chronic actinic dermatitis 338
histiocytosis X (Letterer-Siwe, Hand-Schüller-Christian) 669
granulomatous slack skin 936

G. Superficial Vasculitis and Vasculopathies 91

Endothelial swelling, eosinophilic degeneration of the vessel wall ("fibrinoid necrosis"), and infiltration of the vessel wall by neutrophils, with nuclear fragmentation or leukocytoclasia resulting in "nuclear dust," define true vasculitis. There are extravasated red cells in the vessel walls and adjacent dermis. If the vasculitis is severe, ulceration or subepidermal separation ("bullous vasculitis") can occur. "Lymphocytic vasculitis" in which there is no vessel wall damage is a controversial term and is discussed under lymphocytic infiltrates. A "vasculopathy" includes any abnormality of the vessel wall that does not meet the foregoing criteria for vasculitis, such as fibrosis or hyalinization of the vessel wall without inflammation or necrosis.

1. Neutrophilic Vasculitis 91

In the dermis, vessels are necrotic, fibrinoid is present, and there are perivascular and intravascular neutrophils with leukocytoclasia and nuclear dust.

cutaneous necrotizing (leukocytoclastic) vasculitis 205
Henoch-Schönlein purpura 218
cryoglobulinemia 219
connective tissue associated (rheumatoid arthritis, lupus erythematosus) 220
septicemia, especially meningococcemia/gonococcemia 546
urticarial vasculitis 169, 219
erythema elevatum diutinum 221
miscellaneous 228
polyarteritis nodosa 209
vasculitis in exanthemic pustulosis (drug induced) 315

2. Mixed Cell and Granulomatous Vasculitis 91

There is vessel wall damage and a mixed infiltrate in the dermis that includes eosinophils, plasma cells, histiocytes, and giant cells.

Churg-Strauss vasculitis 213
Wegener granulomatosis 214
giant-cell arteritis 207
granuloma faciale 222
Buerger's disease 209

3. Vasculopathies with Scant Inflammation 91

There is fibrosis or hyalinization of the vessel walls, with few inflammatory cells.

atrophie blanche (segmental hyalinizing vasculitis) 231
malignant atrophic papulosis (Degos) 232
Mondor's disease 209
pigmented purpuric dermatoses (Majocchi-Schamberg-Gougerot-Bloom) 225

4. Thrombotic, Embolic, and Other Microangiopathies 91

There are thrombi or emboli within the lumens of small vessels. In other microangiopathies, the vessel walls may be thickened with compromise of the lumen (amyloidosis, calciphylaxis).

disseminated intravascular coagulation 228
thrombotic thrombocytopenic purpura 228

cryoglobulinemia/macroglobulinemia 219
antiphospholipid syndrome 288
lupus anticoagulant and antiocardiolipin syndromes 288
connective tissue disease (rheumatoid, mixed) 220, 286
calciphylaxis 435
amyloidosis 425
porphyria cutanea tarda and other porphyrias 432
cholesterol emboli 230

H. Superficial Dermatitis with Interface Vacuoles (Interface Dermatitis) 91

1. Vacuolar Dermatitis, Apoptotic/Necrotic Cells Prominent 91

Lymphocytes approximate the dermal–epidermal junction. Vacuolar degeneration is present in the basal cell zone. Apoptotic keratinocytes are found in the epidermis in variable numbers, visualized as round, eosinophilic anuclear structures. The dermis usually has perivascular lymphocytes and may show pigment incontinence.

erythema multiforme 268
toxic epidermal necrolysis (Lyell) 268
Stevens-Johnson syndrome 268
fixed drug eruption 314
phototoxic drug eruption 318
radiation dermatitis 270, 348
sunburn reaction 692
thermal burn 343
pityriasis lichenoides et varioliformis acuta (PLEVA) 196
graft-versus-host disease (GVHD), acute 270
eruption of lymphocyte recovery 272
bullous vasculitis 205

2. Vacuolar Dermatitis, Apoptotic Cells Usually Absent 91

There is basilar keratinocyte vacuolar destruction; apoptotic cells are rare or absent. The dermis has perivascular lymphocytes and may show pigment incontinence.

dermatomyositis 293
morbilliform viral exanthem 659
poikiloderma vasculare atrophicans 295
paraneoplastic pemphigus 254
erythema dyschromicum perstans 172
pinta, tertiary stage 584

3. Vacuolar Dermatitis, Variable Apoptosis 91

Vacuolar degeneration is associated with variable numbers of apoptotic cells in the epidermis. The dermis may have increased ground substance, and there may be pigmentary incontinence.

cytotoxic drug eruptions 318
lupus erythematosus 279
drug-induced lupus 318, 287

4. Vacuolar Dermatitis, Basement Membranes Thickened 91

Vacuolar degeneration is associated with variable numbers of apoptotic cells in the epidermis. The basement membrane zone is thickened by deposition of eosinophilic hyaline material.

lupus erythematosus 279

IV. ACANTHOLYTIC, VESICULAR, AND PUSTULAR DISORDERS

Keratinocytes may separate from each other on the basis of immunologic antigen/antibody–mediated damage, resulting in separation and rounding up of keratinocyte cell bodies (acantholysis) on the basis of edema and inflammation (spongiosis) or perhaps on the basis of structural deficiencies of cell adhesion (Darier's disease). These processes produce intraepidermal spaces (vesicles, bullae, pustules).

A. Subcorneal or Intracorneal Separation 92

There is separation within or just below the stratum corneum. Inflammatory cells may be sparse or may consist predominantly of neutrophils.

1. Sub/Intracorneal Separation, Scant Inflammatory Cells 92

There is separation within or just below the stratum corneum, associated with scant inflammation, usually lymphocytic.

staphylococcal scalded skin 539
bullous impetigo 539
miliaria crystallina 244
exfoliative dermatitis 178
pemphigus foliaceus 250
pemphigus erythematosus 252
necrolytic migratory erythema 409
pellagra 408
acrodermatitis enteropathica 410

2. Sub/Intracorneal Separation, Neutrophils Prominent 92

There is separation in or just below the stratum corneum. Neutrophils are prominent in the stratum corneum and in the superficial epidermis and can often be found in the dermis.

impetigo contagiosa 539
epidermis adjacent to folliculitis 542
impetiginized dermatitis 539
candidiasis 597
subcorneal pustular dermatosis (Sneddon-Wilkinson) 267
immunoglobulin A pemphigus 253
secondary syphilis 579
acropustulosis of infancy 267
transient neonatal pustular melanosis 267

3. Sub/Intracorneal Separation, Eosinophils Predominant 92

There is separation in or just below the stratum corneum, with (pemphigus) or without acantholytic keratinocytes. Eosinophils are present in the epidermis, and occasionally there is eosinophilic spongiosis. The separation is associated with a dermal infiltrate that contains eosinophils.

erythema toxicum neonatorum 267
pemphigus foliaceus 250
pemphigus erythematosus 252
immunoglobulin A pemphigus 253
eosinophilic pustular folliculitis 466
incontinentia pigmenti, vesicular 160
exfoliative dermatitis, drug induced 320

B. Intraspinous Keratinocyte Separation, Spongiotic 92

There are spaces within the epidermis (vesicles, bullae). There may be dyskeratosis or acantholysis, and a few eosinophils may be present in the epidermis.

1. Intraspinous Spongiosis, Scant Inflammatory Cells 92

The infiltrate in the dermis is scant, and lymphocytic or eosinophilic.

early spongiotic dermatitis 237
epidermolytic hyperkeratosis 793
epidermolytic acanthoma 793
miliaria rubra 244
transient acantholytic dermatosis 273
bullous dermatitis of diabetes and of uremia 273
coma bulla 316
friction blisters 274

2. Intraspinous Spongiosis, Lymphocytes Predominant 92

In the dermis, lymphocytes predominate. Eosinophils can be found in most examples of atopy and allergic contact dermatitis.

spongiotic (eczematous) dermatitis 237
atopic dermatitis 242
allergic contact dermatitis 273
photoallergic drug eruption 318, 241
irritant contact dermatitis 240
nummular dermatitis (eczema) 318
dyshidrotic dermatitis 240
"id" reaction 241
seborrheic dermatitis 243
stasis dermatitis 243
erythroderma 244
miliaria rubra 244
pityriasis rosea 183

a. Intraspinous Spongiosis, Eosinophils Present 92

The number of eosinophils seen is variable, from many in incontinentia pigmenti and pemphigus vegetans to few in atopic dermatitis.

spongiotic (eczematous) dermatitis 237
atopic dermatitis 242
allergic contact dermatitis 273
photoallergic drug eruption 318
incontinentia pigmenti, vesicular stage

3. Intraspinous Spongiosis, Neutrophils Predominant 92

Neutrophils are seen in the epidermis, stratum corneum, and dermis. Aggregations of neutrophils in the superficial spinous layer constitute the spongiform pustules of Kogoj that are characteristic of psoriasis.

pustular psoriasis 174
Reiter's syndrome 181
immunoglobulin A pemphigus 253
subcorneal pustular dermatosis (Sneddon-Wilkinson) 267
exanthemic pustular drug eruptions 314
impetiginized dermatosis 539
dermatophytosis 592
rupial secondary syphilis 482
seborrheic dermatitis 243
epidermis adjacent to folliculitis 542
impetigo contagiosa 539
hydroa vacciniforme 337
mucocutaneous lymph node syndrome (Kawasaki's disease, pustular variant) 184
if vasculitis is present, refer to Section III.G or Section V.B

C. Intraspinous Keratinocyte Separation, Acantholytic 92

There are spaces within the epidermis (vesicles, bullae). The process of separation is acantholysis. Keratinocytes within the spinous layer detach or separate from each other or from basal keratinocytes. There may be dyskeratosis, and a few eosinophils may be present in the epidermis. The infiltrate in the dermis is variable, composed of lymphocytes with or without eosinophils.

1. Intraspinous Acantholysis, Scant Inflammatory Cells 92

The infiltrate in the dermis is scant, and lymphocytic or eosinophilic.

epidermolytic hyperkeratosis 793
epidermolytic acanthoma 793
Darier's disease 149
isolated keratosis follicularis (warty dyskeratoma) 794
Hailey-Hailey disease 148
transient acantholytic dermatosis 273
focal acantholytic dyskeratosis 794
acantholytic actinic keratosis 808
pemphigus erythematosus 252
pemphigus foliaceus 250
friction blister (cytolytic blister) 274

2. Intraspinous Acantholysis, Predominant Lymphocytes 92

In the dermis, lymphocytes are predominant. In erythema multiforme and related lesions, there is necrosis of individual cells (apoptosis) that may become confluent.

erythema multiforme (with vacuolar and apoptotic changes) 268
Stevens-Johnson syndrome 268
toxic epidermal necrolysis (TEN) 268
herpes simplex, varicella-zoster 637
hydroa vacciniforme (epidermal necrosis) 337
cowpox 646
hand-foot-and-mouth disease (coxsackievirus) 658
orf 647
paraneoplastic pemphigus 254

a. Intraspinous Acantholysis, Eosinophils Present 92

The number of eosinophils seen is variable, from many in incontinentia pigmenti and pemphigus vegetans to few in atopic dermatitis.

pemphigus vegetans 250
pemphigus vulgaris 247
drug-induced pemphigus 253, 317
paraneoplastic pemphigus 254

3. Intraspinous Separation, Neutrophils or Mixed Cell types 92

Inflammatory cells in the dermis include lymphocytes and plasma cells, with or without eosinophils, neutrophils, mast cells, and histiocytes.

acantholytic actinic keratosis 808
acantholytic squamous cell carcinoma 810
hydroa vacciniforme (epidermal necrosis) 337
immunoglobulin A pemphigus 253
herpesvirus infection

D. Suprabasal Keratinocyte Separation 93

There is separation between the keratinocytes of the basal layer and those of the spinous layer.

1. Suprabasal Vesicles, Scant Inflammatory Cells 93

The suprabasal separation may be associated with scant inflammation and frequently with dyskeratotic or atypical keratinocytes.

transient acantholytic dermatosis (Grover) 794
benign familial pemphigus (Hailey-Hailey) 148
Darier's disease (keratosis follicularis) 149
acantholytic actinic keratosis 808
acantholytic squamous cell carcinoma 810
focal acantholytic dyskeratosis

2. Suprabasal Separation, with Keratinocytes Atypia, Lymphocytes, and Often Plasma Cells 93

Suprabasal separation is associated with keratinocyte atypia.

acantholytic actinic keratosis 808
acantholytic squamous cell carcinoma 810

3. Suprabasal Vesicles, Lymphocytes, Eosinophils 92

There is suprabasal separation with eosinophils in the epidermis (eosinophilic spongiosis) and in the dermis.

pemphigus vulgaris 247
pemphigus vegetans 250

E. Subepidermal Vesicular Dermatitis 93

A subepidermal blister refers to separation of the epidermis from the dermis. The roof of the blister is composed of an intact or (partially) necrotic epithelium.

1. Subepidermal Vesicles, Scant/No Inflammation 93

The infiltrate in the dermis in most of these conditions is scant (few lymphocytes, eosinophils, neutrophils).

porphyria cutanea tarda and other porphyrias 432
drug-induced pseudoporphyria 320
bullous pemphigoid, cell poor 256
epidermolysis bullosa simplex 145
epidermolysis bullosa letalis 145
epidermolysis bullosa acquisita (classic) 261
graft-versus-host disease (GVHD), acute 187
acute radiation dermatitis 630
bullous dermatosis of diabetes 273, 395
bullous dermatosis of uremia 435
electrical burn (polarized epidermis) 274
thermal burn (epidermal necrosis) 274, 343
suction blister 275
Vibrio vulnificus septicemia (necrotic bullae) 548

2. Subepidermal Vesicles, Lymphocytes Predominant 93

The epidermis is separated from the dermis, predominantly due to liquefaction of the basal cell layer. In polymorphous light eruption, massive papillary dermal edema is the cause. The infiltrate in the dermis is primarily lymphocytic.

bullous lichen planus (more often histologic than clinical) 185
erythema multiforme 268
fixed drug eruption 314
lichen sclerosus et atrophicus 303
bullous lupus erythematosus, mononuclear type 279
graft-versus-host disease 270
polymorphous light eruption 333
epidermolysis bullosa acquisita (usually neutrophils) 261

3. Subepidermal Vesicles, Eosinophils Prominent 93

The subepidermal blister is associated with a dermal infiltrate rich in eosinophils. Eosinophils may extend into the overlying epidermis.

bullous pemphigoid 235
cicatricial pemphigoid 259
bullous drug eruption 317
herpes gestationis 260
bullous insect-bite reaction 634
dermatitis herpetiformis
(certain old bullae) 259

4. Subepidermal Vesicles, Neutrophils Prominent 93

A neutrophilic infiltrate is seen often in dermal papillae at the dermal–epidermal junction adjacent to the subepidermal blister or in the blister.

dermatitis herpetiformis 259
bullous lupus erythematosus,
neutrophilic type 261, 279
bullous vasculitis 205
linear immunoglobulin A dermatosis
(adult, childhood, drug associated) 236
epidermolysis bullosa acquisita (inflammatory) 261
vesiculopustular eruption of hepatobiliary disease 266
toxic shock syndrome 546
cutis laxa 157

5. Subepidermal Vesicles, Mast Cells Prominent 93

The epidermis is separated from the dermis. There is an infiltrate in the superficial dermis composed almost entirely of mast cells, with or without a few eosinophils. This may be associated with separation of the epidermis from the dermis.

bullous mastocytosis 158

V. PERIVASCULAR, DIFFUSE, AND GRANULOMATOUS INFILTRATES OF THE RETICULAR DERMIS

The dermis serves as a reaction site for a variety of inflammatory, infiltrative, and desmoplastic processes. These include infiltrations of a variety of cells (lymphocytes, histiocytes, eosinophils, plasma cells, melanocytes, etc.); perivascular and vascular reactions; infiltration with organisms and foreign bodies; proliferations of dermal fibers and precursors of dermal fibers as reactions to a variety of stimuli.

A. Superficial and Deep Perivascular Infiltrates without Vascular Damage or Vasculitis 93

In some of the diseases considered here, the infiltrates are predominantly in the upper reticular dermis (urticarial eruptions), whereas others are both superficial and deep (gyrate erythemas). Most of these also involve the superficial plexus. A few diseases are mainly deep (e.g., lupus erythematosus, scleroderma).

1. Perivascular Infiltrates, Lymphocytes Predominant 93

In the dermis there is no vasculitis, only a perivascular surround of lymphocytes as the predominant cell.

pityriasis lichenoides et varioliformis
acuta (PLEVA) 196
stasis dermatitis 1034
acne rosacea 462
discoid lupus erythematosus (DLE) 280
polymorphous light eruption 333
deep gyrate erythemas 171
erythema annulare centrifugum 191
erythema chronicum migrans 926
Jessner's lymphocytic infiltrate 291
reticulated erythematous
mucinosis (REM) 444
perioral dermatitis 462
papular acrodermatitis
(Gianotti-Crosti) 184, 418
leprosy, indeterminate 550
"tumid" lupus erythematosus 280
perniosis (chilblains) 526

2. Perivascular Infiltrates, Neutrophils Predominant 93

Neutrophils are seen in perivascular or perivascular and diffuse patterns in the dermis. Edema is prominent in some instances (Sweet's syndrome).

acute febrile neutrophilic dermatosis
(Sweet's syndrome) 223
cellulitis/erysipelas 541
necrotizing fasciitis 541
pyoderma gangrenosum (early) 411
ecthyma gangrenosum 547
neutrophil-rich urticaria 169
solar urticaria 340
rheumatoid neutrophilic dermatosis
if vasculitis is present, refer to Section V.B

3. Perivascular Infiltrates, Lymphocytes and Eosinophils 93

Lymphocytes and eosinophils are mixed in the infiltrate. Lymphocytes are always seen; eosinophil numbers may vary, being greatest in bite reactions and often (though variable and sometimes very few) in eosinophilic fasciitis.

urticaria/angioedema 169
pruritic and urticarial papules and
plaques of pregnancy (PUPPP) 170
prurigo simplex 173
papular urticaria 634
morbilliform drug eruption 311

photoallergic reaction 338
eosinophilic fasciitis/scleroderma 295
angiolymphoid hyperplasia with eosinophilia (AHLE) 1022
insect-bite reaction 634
if vasculitis is present, refer to Section V.B

4. Perivascular Infiltrates, with Plasma Cells 93

In addition to lymphocytes, plasma cells are found in the dermal infiltrate.

primary syphilitic chancre 580
erythema chronicum migrans 586
acne rosacea 463
perioral dermatitis 462
scleroderma/morphea 295
secondary syphilis 581
Kaposi's sarcoma, early lesions 1029

B. Vasculitis and Vasculopathies 94

True vasculitis is defined by eosinophilic degeneration of the vessel wall ("fibrinoid necrosis"), infiltration of the vessel wall by neutrophils, with neutrophils, nuclear dust, and extravasated red cells in the vessel walls and adjacent dermis. Some of the conditions mentioned here lack these prototypic findings and may be termed "vasculopathies" (e.g., Degos' disease)

1. Vascular Damage, Scant Inflammatory Cells 94

Although there is significant vascular damage, there is little early inflammatory response.

Degos' disease (malignant atrophic papulosis) 232
atrophie blanche 231

2. Vasculitis, Lymphocytes Predominant 94

The term "lymphocytic vasculitis" is controversial, but there are some conditions in which perivascular and intramural lymphocytes may be associated with some degree of vasculopathy, not usually including frank fibrinoid necrosis. Most of these conditions are discussed elsewhere as "perivascular lymphocytic infiltrates." In angiocentric lymphomas, the cells infiltrating the vessel walls are neoplastic, but the process may be mistaken for an inflammatory reaction.

"lymphocytic vasculitis" 224
lupus erythematosus 279
lymphomatoid papulosis 935
pityriasis lichenoides et varioliformis acuta (PLEVA) 196
pityriasis lichenoides chronica 196
purpura pigmentosa chronica 225
morbilliform viral infections 659
Lyme disease 585
perniosis (chilblains) 526
angiocentric mycosis fungoides 936
angiocentric T-cell lymphoma/lymphomatoid granulomatosis 933
cytomegalovirus inclusion disease 644
Behçet's syndrome 412

3. Vasculitis, Neutrophils Prominent 94

Neutrophils are prominent in the infiltrate, with fibrinoid necrosis and nuclear dust; eosinophils and lymphocytes are also found.

small-vessel leukocytoclastic vasculitis 215
neutrophilic dermatoses 333
Sweet's syndrome 223
granuloma faciale 221
bowel-associated dermatosis-arthrosis syndrome 224, 412
septic/embolic lesions of gonococcemia/meningococcemia 548
Rocky Mountain spotted fever (*Rickettsia rickettsii*) 568
polyarteritis nodosa 209
erythema elevatum diutinum 221
Behçet's syndrome 412
papulonecrotic tuberculid 554
mixed cryoglobulinemia

4. Vasculitis, Mixed Cell Types and/or Granulomas 94

Histiocytes and giant cells are a part of the infiltrate. Lymphocytes and eosinophils can also be found, depending on the diagnosis. Giant cell arteritis is a true inflammation of the artery wall (true arteritis), although there is no fibrinoid necrosis.

allergic granulomatosis (Churg-Strauss syndrome) 213
Wegener granulomatosis 214
giant cell arteritis (temporal arteritis) 207
erythema chronicum migrans 586
erythema nodosum leprosum 564
some insect-bite reactions 234
"secondary vasculitis" at the base of ulcers of diverse etiology 205
Behçet's syndrome 412
Granuloma faciale 222

5. Thrombotic and Other Microangiopathies 94

The dermal vessels contain fibrin, red cells, and platelet thrombi and/or eosinophilic protein precipitates.

septicemia 221
disseminated intravascular coagulation 228
coumarin necrosis 228
amyloidosis 425
porphyria cutanea tarda and other porphyrias 431
calciphylaxis 230, 543
thrombophlebitis and superficial migratory thrombophlebitis 209
Lucio reaction 565
cryoglobulinemia, type I
anticardiolipin antibodies

C. Diffuse Infiltrates of the Reticular Dermis 94

Diffuse infiltrates of the reticular dermis may show some relation to vessels or to skin appendages or may be randomly distributed in the reticular dermis.

1. Diffuse Infiltrates, Lymphocytes Predominant 94

Lymphocytes are seen almost to the exclusion of other cell types.

cutaneous lymphoid hyperplasia/ lymphocytoma cutis 915
Jessner's lymphocytic infiltrate 291
leukemia cutis (lymphocytic lymphoma, chronic lymphocytic leukemia) 957

2. Diffuse Infiltrates, Neutrophils Predominant 94

Neutrophils are the main infiltrating cell although lymphocytes can be found.

cellulitis 541
dermis adjacent to folliculitis 542
abscess 542
acute neutrophilic dermatosis (Sweet's syndrome) 223
rheumatoid neutrophilic dermatosis 223
granuloma faciale 222
pyoderma gangrenosum 411
neutrophilic dermatosis of the dorsal hands 223
cutaneous reaction to cytokines especially granulocyte colony-stimulating factor 322
bowel arthrosis dermatosis syndrome 412
erythema elevatum diutinum 221
Behçet's syndrome 412

3. Diffuse Infiltrates, "Histiocytoid" Cells Predominant 94

Histiocytes or histiocytoid cells are found in great numbers in the dermal infiltrate. Some may be foamy; others may contain organisms. The leukemic cells of myeloid leukemia may be easily mistaken for histiocytes and may have histiocytic differentiation (myelomonocytic leukemia).

xanthelasma, xanthomas (usually nodular) 681
atypical mycobacteria
Mycobacterium avium-intracellulare (MAI) 555
deep fungus infection
cryptococcosis 609
histoplasmosis 611
paraffinoma 374
silicone granuloma 374
talc and starch granuloma 375
annular elastolytic giant cell granuloma (actinic granuloma) 364
"histiocytoid" Sweet's syndrome 223
lepromatous leprosy 560
histoid leprosy 562
cutaneous leishmaniasis 621
rhinoscleroma (*Klebsiella rhinoscleromatis*) 570
histiocytosis X 667
leukemia cutis (myeloid, myelomonocytic) 958
anaplastic large cell lymphoma (Ki-1) 952
reticulohistiocytic granuloma 948
malakoplakia 549
Rosai-Dorfman disease 678

4. Diffuse Infiltrates, Plasma Cells Prominent 94

Plasma cells are found in the diffuse dermal infiltrate, although they may not be the predominant cell type.

insect-bite reaction 634
plasmacytoma, myeloma 922
circumorificial plasmacytosis 922
syphilis, secondary or tertiary 579
yaws, primary or secondary 583
acne keloidalis nuchae 544

5. Diffuse Infiltrates, Mast Cells Predominant 94

Mast cells compose almost the entire dermal infiltrate. There may be an admixture of eosinophils.

urticaria pigmentosa 158

6. Diffuse Infiltrates, Eosinophils Predominant 94

Eosinophils are prominent, although they are not the only infiltrating cell type. Lymphocytes are also found, and plasma cells may also be present.

eosinophilic cellulitis (Wells' syndrome) 467
insect-bite reaction 634
granuloma faciale 222

7. Diffuse Infiltrates, Mixed Cell Types 94

The diffuse infiltrate contains plasma cells, lymphocytes, histiocytes, and a variety of acute inflammatory cells.

syphilis, primary, secondary, or tertiary 579
acrodermatitis chronica atrophicans 586
cutaneous reactions to cytokines 322
chronic actinic dermatitis (actinic reticuloid) 333
rhinosporidiosis 615
rhinoscleroma 622
histoplasmosis 611
dermal hematopoiesis (extramedullary hematopoiesis) 956
cutaneous leishmaniasis 621
granuloma inguinale 570
granuloma gluteale infantum 381
persistent nodular scabies 627

8. Diffuse Infiltrates, Pigment Cells 94

The diffuse infiltrate contains bipolar, cuboidal, or dendritic cells with brown cytoplasmic pigment.

Mongolian spot 699
nevus of Ota, nevus of Ito 700
dermal melanocytic hamartoma 700

9. Diffuse Infiltrates, Extensive Necrosis 94

Vascular and dermal necrosis is found secondary to vascular occlusion or to destruction by organisms.

tertiary syphilis 583
sporotrichosis 612
deep fungus 591
atypical mycobacteria 549
infarcts 230
vasculitis and deep vasculitis 205
thrombi and deep thrombi 205
calciphylaxis (cutaneous necrosis/
calcification syndrome) 230, 435
gangrenous ischemic necrosis 230

D. Diffuse or Nodular Infiltrates of the Reticular Dermis with Epidermal Proliferation 95

Ill-defined nodules or diffuse infiltrates of inflammatory cells, usually including lymphocytes, plasma cells, and neutrophils, are present in the dermis, and the epidermis is irregularly thickened.

1. Epidermal Proliferation with Mixed Cellular Infiltrates 95

squamous cell carcinoma 817
pseudoepitheliomatous hyperplasia 822
halogenodermas (Halogen Eruptions) 326
deep fungus infections
North American blastomycosis 603
paracoccidioidomycosis 605
chromoblastomycosis 607
coccidioidomycosis 608
rhinosporidiosis 615
protothecosis 615
verrucous cutaneous leishmaniasis 621
verrucous lupus vulgaris 551
tuberculosis verrucosa cutis 551
Mycobacterium marinum 555
granuloma inguinale
(*Calymmatobacterium* granulomatis) 570
pyoderma vegetans 546
verruciform xanthoma 685
verrucose sarcoidosis 370
granuloma gluteale infantum 381
verrucous lupus erythematosus 280

E. Nodular Inflammatory Infiltrates of the Reticular Dermis: Granulomas, Abscesses, and Ulcers 95

A granuloma is defined as a collection of histiocytes, which may have abundant cytoplasm and confluent borders ("epithelioid histiocytes"), often with Langhans type giant cells. Granulomas may be associated with necrosis or may palisade around areas of necrobiosis, may be mixed with other inflammatory cells, may include foreign-body giant cells, and may contain ingested foreign material or pathogens (acid-fast bacilli, fungi). An abscess is a localized area of suppurative necrosis containing abundant neutrophils mixed with necrotic debris and usually surrounded by a reaction of granulation tissue and fibrosis.

1. Epithelioid Cell Granulomas without Necrosis 95

Large epithelioid histiocytes are common in the infiltrate, as are giant cells. The infiltrate may also contain a few plasma cells as well as lymphocytes.

sarcoidosis (lupus pernio and other types) 370
lichen scrofulosorum 554
granulomatous granuloma annulare 361
foreign-body granulomas 365
syphilis, secondary or tertiary 581
granulomatous rosacea 463
cheilitis granulomatosa
(Miescher-Melkersson-Rosenthal) 380
tuberculoid leprosy 563
tuberculosis
lupus vulgaris 551
Crohn's disease 415
allergic granulomatous reactions to chemical
agents (silica, zirconium, aluminum,
beryllium granulomas) 373
collagen implant granuloma 378
granulomatous mycosis fungoides 941
chronic cutaneous leishmaniasis 623

2. Epithelioid Cell Granulomas with Necrosis 95

The presence of necrosis in an epithelioid cell granuloma of the skin strongly suggests tuberculosis except in lesions of the face. Epithelioid sarcoma may simulate a necrotizing granuloma.

tuberculosis 550
tuberculosis verrucosa cutis 551
miliary tuberculosis 551
lupus vulgaris (necrosis usually
slight or absent) 551
nontuberculosis mycobacteria 555
lupus miliaris disseminatus faciei 465
granulomatous rosacea 373
tertiary syphilis 583
epithelioid sarcoma 995
cryptococcosis 609
histoplasmosis 611

3. Palisading Granulomas 95

There are foci of altered collagen ("necrobiosis") surrounded by histiocytes and lymphocytes. Histiocytic giant cells may also be seen in the infiltrate. The lesions of epithelioid sarcoma are associated with true tumor necrosis but may superficially resemble rheumatoid nodules.

granuloma annulare 361
rheumatoid nodule 367
necrobiosis lipoidica 365
subcutaneous granuloma annulare 361

annular elastolytic giant-cell granuloma
(actinic granuloma) 364
rheumatic nodule 368
epithelioid sarcoma 995
occasional examples of deep fungus infections 363
necrobiotic xanthogranuloma 683
palisading necrotizing granuloma 213
palisaded neutrophilic and
granulomatosis (PNGD) 368

4. Mixed Cell Granulomas 95

Lymphocytes and plasma cells are present in addition to epithelioid histiocytes, which may form loose clusters, and giant cells, which may be quite inconspicuous. Organisms are found in many of these granulomatous infiltrates. Keratin granuloma is the most common mixed granuloma. Flakes of keratin may be appreciated as fibers, often gray rather than pink, in the cytoplasm of giant cells.

keratin granuloma
ruptured cyst 373, 801
folliculitis with rupture 542
sporotrichosis 612
persistent arthropod bite 634
syphilis, secondary and tertiary 581
cryptococcosis 609
candidal granuloma 598
nontuberculosis mycobacteria 555
cat-scratch disease 571
North American blastomycosis 603
South American blastomycosis 605
chromomycosis 607
phaeohyphomycosis 601
coccidioidomycosis 608

5. Inflammatory Nodules with Prominent Eosinophils 95

The nodular dermal infiltrates contain many eosinophils, often admixed with lymphocytes.

angiolymphoid hyperplasia with eosinophils 1022
Kimura's disease 1025
scabietic nodule 626

6. Inflammatory Nodules with Mixed Cell Types 95

There is a variety of cells in the infiltrate, including neutrophils, histiocytes, plasma cells, giant cells, and lymphocytes.

chronic bacterial infections 555
keratin granuloma
ruptured cyst 373, 801
folliculitis 542
sporotrichosis 612
rhinoscleroma (*Klebsiella rhinoscleromatis*) 570
atypical mycobacteria 549
Mycobacterium avium-intracellulare 555
Mycobacterium marinum 555
nocardiosis 574
lobomycosis 606
protothecosis 615

7. Inflammatory Nodules with Necrosis and Neutrophils (Abscesses) 95

Inflammatory nodules are characterized by central suppurative necrosis, with neutrophils adjacent to the necrosis and often with granulation tissue, mixed inflammatory cells including epithelioid histiocytes and giant cells, and fibrosis at the periphery.

acute or chronic bacterial abscesses 567
deep fungal infections 604
phaeohyphomycotic cyst 602
North American blastomycosis 603
chromoblastomycosis 607
cutaneous alternariosis 603
paracoccidioidomycosis 605
coccidioidomycosis 608
sporotrichosis 612
botryomycosis 573
actinomycosis 574
nocardiosis 574
cat-scratch disease 571
erythema nodosum leprosum
(type 2 leprosy reaction) 564
scrofuloderma 552
tuberculous gumma 552
protothecosis 615

8. Inflammatory Nodules with Prominent Necrosis 95

Necrosis is a striking feature along with variable but sometimes sparse infiltrates of inflammatory cells, which may include plasma cells, epithelioid histiocytes, neutrophils, lymphocytes, and hemorrhage. Organisms may be demonstrable. Epithelioid sarcoma may simulate an inflammatory lesion.

tertiary syphilis 583
tertiary yaws 584
aspergillosis 599
zygomycosis (mucormycosis) 599
tuberculosis 550
atypical mycobacteria 549
infarcts 230
deep vasculitis 205
deep thrombi 205
calciphylaxis 230, 435
frostbite 352
necrobiotic xanthogranuloma with
paraproteinemia 367, 683
gangrenous ischemic
necrosis 230
epithelioid sarcoma 995

9. Chronic Ulcers and Sinuses Involving the Reticular Dermis 95

A chronic ulcer is characterized by central suppurative necrosis, with neutrophils adjacent to the necrosis and often with granulation tissue, fibrosis, and reactive epithelium at the periphery. A sinus extends deeper into the dermis than most ulcers, in a serpentine fashion. A fistula is an abnormal communication between two epithelial-lined surfaces. The histologic architecture of fistulas and sinuses is similar to that of chronic ulcers.

pyoderma gangrenosum 411
ecthyma gangrenosum 547
deep fungal infection
North American blastomycosis 603
eumycetoma 614
tuberculosis cutis orificialis 553
enterocutaneous fistula 415
chondrodermatitis nodularis helicis 492
ecthyma 541
papulonecrotic tuberculid 554
Buruli ulcer (*Mycobacterium ulcerans*) 556
chancroid (*Haemophilus ducreyi*) 569
granuloma inguinale
(*Calymmatobacterium granulomatis*) 570
lymphogranuloma venereum
(*Chlamydia trachomatis*) 571
follicular occlusion disorder
pilonidal sinus 545
hidradenitis suppurativa 544
acne conglobata 544
perifolliculitis capitis abscedens et suffodiens
(dissecting cellulitis of the scalp) 544
anthrax (*Bacillus anthracis*) 567
tularemia (*Francisella tularensis*) 568
cutaneous leishmaniasis 621
necrotizing sialometaplasia of the hard palate 813
eosinophilic ulcer of the tongue 813

F. Dermal Matrix Fiber Disorders 96

The dermis serves as a reaction site for a variety of inflammatory, infiltrative, and desmoplastic processes. These may include accumulations or deficiencies of dermal fibrous and nonfibrous matrix constituents as reactions to a variety of stimuli.

1. Fiber Disorders, Collagen Increased 96

Dermal collagen is increased with production at the dermal–subcutaneous interface. Inflammation is seen at this site. The inflammatory cells are lymphocytes, plasma cells, and eosinophils. In some instances fibroblasts are increased.

scar, keloid 979
scleroderma/morphea 295
phytonadione-induced pseudoscleroderma 316
necrobiosis lipoidica 365
eosinophilic fasciitis 303
radiation fibrosis 349
nephrogenic systemic fibrosis (nephrogenic
fibrosing dermopathy) 301, 316
fibroblastic rheumatism 307
sclerodermoid graft-versus-host
disease (GVHD) 270
acrodermatitis chronica atrophicans 586
facial hemiatrophy 588
chronic lymphedema 527, 1029
necrobiosis lipoidica 365
acro-osteolysis 401

2. Fiber Disorders, Collagen Reduced 96

Collagen may be reduced focally or diffusely as part of an inborn error of collagen fiber metabolism or as an acquired phenomenon.

Ehlers-Danlos syndrome 155
Marfan's syndrome 394
penicillamine-induced atrophy 325
striae distensae 398
aplasia cutis 142
focal dermal hypoplasia (Goltz) 142
atrophoderma (Pasini and Pierini) 301
relapsing polychondritis (type II collagen
degeneration of cartilage) 493

3. Fiber Disorders, Elastin Increased or Prominent 96

Abnormal elastic fibers are increased focally in the dermis and may become calcified (pseudoxanthoma elasticum), or there may be diffuse elastosis in the superficial reticular dermis of sun-exposed skin.

pseudoxanthoma elasticum 152
penicillamine-induced elastosis perforans 325
solar elastosis 390
erythema ab igne 347
annular elastolytic giant cell granuloma
(actinic granuloma) 364

4. Fiber Disorders, Elastin Reduced 96

Elastin may be reduced focally or diffusely as part of an inborn error of metabolism or as an acquired phenomenon.

cutis laxa 157
anetoderma 399
middermal elastolysis 399
annular elastolytic giant cell granuloma
(actinic granuloma) 364

5. Fiber Disorders, Perforating 96

Abnormal elastin or collagen fibers may be extruded through the epidermis, which may form channels that extend down into the dermis.

elastosis perforans serpiginosa 393
Kyrle's disease 392
perforating folliculitis 392
reactive perforating collagenosis 395
perforating disorder of renal failure
and diabetes 395

perforating calcific elastosis 396
perforating granuloma annulare 361

G. Deposition of Material in the Dermis 96

The dermis serves as a reaction site for a variety of inflammatory, infiltrative, and desmoplastic processes, which may include accumulations of matrix molecules that may be indigenous to the normal dermis or foreign to it.

1. Increased Normal Nonfibrous Matrix Constituents 96

Ground substance (hyaluronic acid) is increased, associated with a varying inflammatory infiltrate that can include lymphocytes, plasma cells, and eosinophils.

granuloma annulare 361
pretibial myxedema 441
generalized myxedema 441
juvenile cutaneous mucinosis 445
papular mucinosis (lichen myxedematosus) 441
scleromyxedema 444
reticular erythematous mucinosis (REM) 444
scleredema 445
focal dermal mucinosis 997
digital mucous cyst/myxoid cyst 997
cutaneous myxoma 997
mucocele, mucinous mucosal cyst 997
lupus erythematosus 279
hereditary progressive mucinous histiocytosis 677
nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy) 301

2. Deposition of Material Not Normally Present in the Dermis 96

Materials not present in substantial amounts in the normal dermis are deposited as crystals (gout), amorphous deposits (calcinosis), hyaline material (colloid milium, amyloidosis, porphyria), or pigments.

gout 438
colloid milium 429
calcinosis cutis 299, 435
calcinosis universalis, circumscripta (scleroderma) 436
tumoral calcinosis 437
idiopathic calcinosis of the scrotum 437
subepidermal calcified nodule 437
amyloidosis 425
dermal pigments 319
minocycline 324
argyria 327
chrysiasis 327
mercury pigmentation 327
hemochromatosis 449
endogenous ochronosis (alkaptonuria) 439
calcaneal petechiae (hemoglobin) 356
lipoid proteinosis (hyalinosis cutis et mucosae, Urbach-Wiethe) 430
cryoglobulinemia 219
porphyria cutanea tarda 432
foreign material: dirt, glass, paraffin, grease, etc. 373
tattoo reactions 377
silicone, talc, starch 374
cactus, sea urchin, hair granulomas 375
intralesional steroids 380
vaccines, aluminum 376
Hunter's syndrome (lysosomal granules) 447

3. Parasitic Infestations of the Dermis and/or Subcutis 96

Macroscopically visible parasitic agents may infest the dermis and subcutis.

subcutaneous dirofilariasis 628
onchocerciasis 629
strongyloidiasis 628
schistosomiasis 631
subcutaneous cysticercosis 632
myiasis 632

VI. TUMORS AND CYSTS OF THE DERMIS AND SUBCUTIS

Neoplasms in the reticular dermis may arise from any of the tissues included in the dermis—lymphoreticular tissue, connective tissue, and epithelial tissue of the skin appendages. In addition, metastases commonly present in the dermis and subcutis.

A. Small Cell Tumors 96

A neoplastic nodule is a circumscribed collection of neoplastic cells in the dermis. Abscesses, granulomas, and cysts may also present as nodules. Cysts are considered separately. In general, neoplastic nodules can be differentiated from reactive and inflammatory nodules by the presence of a monotonous population of cells consistent with a clonal proliferation, whereas inflammatory nodules are composed of inflammatory cell types (lymphocytes, neutrophils, histiocytes, etc.), generally in a heterogeneous mixture.

1. Tumors of Lymphocytes or Hemapoietic Cells 96

Nodular infiltrates or extensive diffuse infiltrates of normal and/or atypical lymphocytes are found in the dermis.

cutaneous T-cell lymphoma
lymphoblastic lymphoma, T-cell type 955
tumor-stage mycosis fungoides 936
adult T-cell leukemia/lymphoma 953
cutaneous B-cell lymphoma
lymphoblastic lymphoma, B-cell type 922
small lymphocytic lymphoma 925
immunocytoma (lymphoplasmacytoid lymphoma) 925

primary cutaneous follicle center lymphoma 917
diffuse large B-cell lymphoma (centroblastic/immunoblastic) 930
leukemia cutis 957
drug-induced pseudolymphoma 320
aluminum granuloma 376
pseudolymphomatous tattoo reaction 377

2. Tumors of Lymphocytes and Mixed Cell Types 96

Nodular infiltrates or extensive diffuse infiltrates of normal lymphocytes are found in the dermis. Other reactive cell types (plasma cells, histiocytes) are admixed.

cutaneous lymphoid hyperplasia/lymphocytoma cutis 915
Lennert's (lymphoepithelial) lymphoma 951
chronic myleogenous leukemia 957
angioimmunoblastic lymphadenopathy 952
borrelial lymphocytoma cutis 588

3. Tumors of Plasma Cells 96

Nodular plasma cell infiltrates, with scattered lymphocytes.

cutaneous plasmacytoma and myeloma 923

4. Small Round Cell Tumors 96

Tumors of small cells with scant cytoplasm and with small dark nuclei constitute a group of tumors that can usually be distinguished from one another with appropriate immunohistochemical investigations in conjunction with light microscopic and clinical information. Some of these tumors arise in the deep soft tissue, but they may rarely present in a deep skin biopsy.

primitive neuroepithelial tumors (PNET)
peripheral neuroblastoma/neuroepithelioma . .1139
Ewing's sarcoma 995
cutaneous small cell undifferentiated carcinoma (CSCUC/Merkel's cell tumor) 1138
melanotic neuroectodermal tumor of infancy 1141
lymphoma/leukemia 911
rhabdomyosarcoma 1084
metastatic neuroectodermal carcinoma 1158
small cell melanoma 749
small cell carcinoma (squamous or adenocarcinoma) 1153
eccrine spiradenoma 888
lymphoepithelioma-like carcinoma 819

B. Large Polygonal and Round Cell Tumors 97

1. Squamous Cell Carcinomas 97

Proliferations of atypical cells with more or less abundant cytoplasm, contiguous cell borders, evidence of keratinization, and/or desmosomes occupy the dermis as nodular masses. Most primary squamous cell carcinomas show evidence of epidermal origin, often with associated squamous cell carcinoma *in situ*.

primary squamous cell carcinoma. 817
metastatic squamous cell carcinoma 1154

2. Adenocarcinomas 97

Proliferations of atypical cells with more or less abundant cytoplasm and with evidence of gland formation and/or mucin production occupy the dermis as nodular masses. The possibility of metastatic adenocarcinoma must be considered and differentiated from the possibility of a primary cutaneous adenocarcinoma of skin appendages (refer to the eccrine, apocrine, pilar, and sebaceous tumor sections that follow).

primary adenocarcinoma of skin adnexal origin (see later discussion) 896
mucin-producing squamous cell carcinoma simulating adenocarcinoma 821
mucoepidermoid carcinoma 821
adenosquamous carcinoma 821
metastatic adenocarcinoma 1155

3. Melanocytic Tumors 97

The proliferations in the dermis are melanocyte derived, pigmented or amelanotic, benign, atypical, or malignant. Superficial lesions may involve the epidermis (junctional component). There may be a fibrous and inflammatory host response. S100 and HMB-45 stains may be of value in recognizing melanocytic differentiation in amelanotic tumors.

superficial melanocytic nevi
compound melanocytic nevus 712
dermal melanocytic nevus, acquired type 714
dermal recurrent melanocytic nevus 717
dysplastic nevi, compound 717
nevus of genital skin 717
nevus of acral skin 716
halo nevus 730
combined nevus 704
pigmented spindle cell nevus of Reed 724
balloon cell nevus 715
superficial and deep melanocytic nevi
small congenital nevus 727
intermediate and giant congenital nevi 728
deep penetrating nevus 729
spindle and epithelioid cell nevus (Spitz nevus) 729
pigment-synthesizing dermal neoplasms
metastatic melanoma 774
common blue nevus 701
cellular blue nevus 702
combined nevus 704
deep penetrating nevus 729
malignant blue nevus 771
proliferative nodules in congenital melanocytic nevi 729
malignant melanomas in congenital melanocytic nevi 728

malignant melanocytic
schwannoma 753, 1116
pigmented epithelioid melanocytoma 757
dermal melanocytic tumors of uncertain
malignant potential (MELTUMP) 772
nevus of Ota 700
melanotic neuroectodermal tumor of infancy .1141
tumorigenic primary melanomas
nodular melanomas 749
complex primary melanomas with radial growth
phase and vertical growth phase 739
superficial spreading melanoma with
vertical growth phase 743
lentigo maligna and lentigo maligna
melanoma 745
acral lentiginous melanoma 747
mucosal-lentiginous melanoma 749
desmoplastic melanoma 753
neurotropic melanoma 753
minimal deviation melanoma 757
metastatic malignant melanoma
epidermotropic metastatic melanoma 775
satellites and in-transit metastatic
melanoma 768
dermal and subcutaneous metastatic
melanoma 767

4. Eccrine Tumors 97

Proliferations of eccrine ductal (small, dark cells usually forming tubules at least focally) or glandular tissue or both occur in a hyalinized or sclerotic dermis. The inflammatory infiltrate is mainly lymphocytic.

circumscribed, symmetric
eccrine nevus 883
papillary eccrine adenoma 890
clear cell (nodular) hidradenoma
(eccrine acrospiroma) 891
syringoma 884
chondroid syringoma 893
eccrine spiradenoma 888
cylindroma (some consider apocrine) 881
eccrine syringofibroadenoma 888
mucinous syringometaplasia 888
infiltrative, asymmetric
microcystic adnexal carcinoma (sclerosing
sweat duct carcinoma) 896
malignant chondroid syringoma 894
malignant clear cell (nodular) hidradenoma
(malignant acrospiroma) 891
malignant eccrine spiradenoma 890
malignant eccrine poroma
(porocarcinoma) 887
eccrine adenocarcinoma 896
mucinous eccrine carcinoma 898
adenoid cystic eccrine carcinoma 899
aggressive digital papillary adenoma/
adenocarcinoma 899
syringoid eccrine carcinoma 831, 896

5. Apocrine Tumors 97

Tumors in the dermis are composed of proliferations of apocrine ductal and glandular epithelium (large, pink cells with decapitation secretion). The stroma is sclerotic and well vascularized, and the inflammatory cells are mainly lymphocytes.

circumscribed, symmetric
apocrine nevus 876
tubular apocrine adenoma
('tubulopapillary hidradenoma") 880
cylindroma (some consider eccrine) 881
hidradenoma papilliferum 878
syringocystadenoma papilliferum 878
apocrine hidrocystoma 877
infiltrative, asymmetric
apocrine adenocarcinoma 895
malignant cylindroma 883
erosive adenomatosis of the nipple
(florid papillomatosis) 881

6. Pilar Tumors 97

The dermal infiltrating tumor is composed of epithelium that differentiates toward hair or is a proliferation of portions of the follicular structure and its stroma. The inflammatory cell infiltrate is mainly lymphocytic, and the dermis is fibrocellular.

follicular infundibular neoplasms
dilated pore of Winer 855
pilar sheath acanthoma 855
trichilemmoma 867
tumor of the follicular infundibulum 869
branching and lobular pilosebaceous neoplasms
trichofolliculoma 854
trichoepithelioma 857
tumor of follicular infundibulum 869
top of nevus sebaceous 870
nodular pilosebaceous neoplasms
hair follicle nevus 853
keratoacanthoma 835
trichoepithelioma 857
desmoplastic trichoepithelioma 859
immature trichoepithelioma 859
hair follicle hamartoma 863
pilomatricoma 864
trichoblastoma 860
trichogenic fibroma 860
trichoadenoma 862
proliferating trichilemmal
cyst (pilar tumor) 866
inverted follicular keratosis 795
tumors of pilosebaceous mesenchyme
trichodiscoma 856
fibrofolliculoma 856
tumors of the arrector pili muscle 1075

infiltrative, asymmetric
pilomatrix carcinoma (malignant pilomatricoma) 864
trichilemmal carcinoma 870
basal cell carcinoma with follicular differentiation 832

7. Sebaceous Tumors 97

The dermal masses are proliferations of the germinative epithelium and of mature sebocytes. The admixture of these cells varies from one tumor to another. The dermis is fibrocellular.

symmetric, circumscribed
sebaceous hyperplasia 465, 872
Fordyce's condition (ectopic sebaceous glands in mucosae) 872
rhinophyma 463
nevus sebaceous 853
sebaceous adenoma 873
sebaceous epithelioma 873
sebaceous trichofolliculoma 855
infiltrative, asymmetric
sebaceous carcinoma 875
basal cell carcinoma with sebaceous differentiation 831

8. "Histiocytoid" Tumors 97

"Histiocytes" may have foamy cytoplasm reflecting the accumulation of lipids or may have eosinophilic or amphophilic cytoplasm surrounding an ovoid nucleus with open chromatin. Some nonhistiocytic lesions whose cells may simulate histiocytes are also included here.

foamy histiocytes
xanthomas: eruptive, plane, tuberous, tendon 680
verruciform xanthoma 685
xanthelasma 681
cholestanolemia, phytosterolemia 680
xanthoma disseminatum 675
diffuse normolipemic plane xanthoma 684
papular xanthoma 673
eruptive normolipemic xanthoma 684
progressive nodular histiocytosis (superficial) 677
Langerhans cell histiocytosis (rare xanthomatous type) 669
lepromatous leprosy 560
dermatofibroma with xanthomatous change
nonfoamy histiocytes
dermatofibroma/histiocytoma
Langerhans cell histiocytosis 669
congenital self-healing reticulohistiocytosis 669
indeterminate cell histiocytosis 678
granuloma annulare 361
eruptive histiocytomas 678
benign cephalic histiocytosis 677
sinus histiocytosis with massive lymphadenopathy 678
juvenile xanthogranuloma 672
epithelioid cell histiocytoma
giant cells prominent
juvenile xanthogranuloma 672
multicentric reticulohistiocytosis 675
giant cell reticulohistiocytoma 675
necrobiotic xanthogranuloma with paraproteinemia 683
xanthoma disseminatum 675
histiocytic simulants
pleomorphic large cell lymphoma (Ki-1, usually T cells) 952
epithelioid sarcoma 995
leukemia cutis 957

9. Tumors of Large Lymphoid Cells 97

Large lymphoid cells may be mistaken for carcinoma or melanoma cells but can be distinguished morphologically by their tendency to exhibit less cohesive growth in large sheets, by the absence of epithelial or melanocytic differentiation, and by immunopathology.

pleomorphic peripheral T-cell lymphoma 950
cutaneous anaplastic large cell lymphoma (CD30 [Ki-1] lymphoma, regressing atypical histiocytosis) . . .952
leukemia cutis 957
cutaneous Hodgkin's disease 933

10. Mast Cell Tumors 97

Mast cells predominate in a nodular dermal infiltrate, with scattered eosinophils.

mastocytosis 158

11. Tumors with Prominent Necrosis 97

Necrosis is a striking feature in epithelioid sarcoma, which as a result may be mistaken for a granulomatous process. In addition, many advanced malignancies, often metastatic, have prominent necrosis.

epithelioid sarcoma 995
some metastatic carcinomas, sarcomas, melanomas 1154
occasional advanced primary malignant tumors 749, 791, 892

12. Miscellaneous and Undifferentiated Epithelial Tumors 97

Proliferations of atypical cells with more or less abundant cytoplasm and contiguous cell borders occupy the dermis as nodular masses.

undifferentiated carcinoma (large cell, small cell) 1154
granular cell nerve sheath tumor (granular cell tumor/schwannoma) 1130

plexiform granular cell nerve
sheath tumor 1131
malignant granular cell tumor 1130
neuroendocrine tumor 1124
cephalic brain-like hamartoma (nasal glioma) 1141
encephalocele 1141
cutaneous meningiomas 1141
epithelial simulants
pleomorphic large cell lymphoma
(Ki-1, usually T cells) 952
epithelioid sarcoma 995
epithelioid angiosarcoma 1043
cellular neurothekeoma (immature
nerve sheath myxoma) 1127
ganglioneuroma 1140

C. Spindle Cell, Pleomorphic, and Connective Tissue Proliferations 98

There is a proliferation of elongated, tapered "spindle cells" in the dermis that may be of fibrohistiocytic, muscle, neural (schwannian), melanocytic, or unknown origin. Immunohistochemistry can be essential in making these distinctions.

1. Fibrohistiocytic Spindle Cell Proliferations 98

There is a proliferation of spindle to pleomorphic cells that may synthesize collagen or be essentially undifferentiated. In the absence of specific markers for fibroblasts, immunohistochemistry is of little diagnostic utility except to rule out nonfibrous spindle cell tumors. Morphology is critical for accurate diagnosis.

benign fibrous histiocytoma (dermatofibroma) 969
aneurysmal fibrous histiocytoma 1035
fibrous papule (angiofibroma) 987
hypertrophic scar, keloid 979
atypical fibroxanthoma 978
juvenile xanthogranuloma, spindle
cell variant 673
dermatofibrosarcoma protuberans 974
nephrogenic fibrosing dermopathy (not a tumor)
fibromatoses
desmoid tumor 992
recurrent infantile digital fibromatosis 986
juvenile hyaline fibromatosis 986
giant cell tumors
giant cell fibroblastoma 976
giant cell tumor of tendon sheath 974
proliferative lesions of the fascia
nodular fasciitis 983
cranial fasciitis of childhood 984
myxoid spindle cell infiltrate
cutaneous myxoma 997
digital mucous cyst 997
mucocele of oral mucosa 997
pseudocyst of the auricle 1100
sarcomas
malignant fibrous histiocytoma 979
angiomatoid fibrous histiocytoma 994
synovial sarcoma 994
fibromas
fibroma of tendon sheath 982
follicular fibroma 989
acquired digital fibrokeratoma 989
elastofibroma 987
dermatomyofibroma 980
progressive nodular histiocytoma
(deep fibrous type) 677
plexiform fibrohistiocytic tumor 977

2. Schwannian/Neural Spindle Cell Tumors 98

These tumors are composed of elongated, narrow spindle cells that tend to have serpentine, S-shaped nuclei and to be arranged in "wavy" fiber bundles. Immunohistochemistry for S100 is useful but not specific.

neurofibromas 1109
sporadic cutaneous neurofibroma
(common neurofibroma) 1109
extraneural (common neurofibroma) 1109
intraneural 1111
neurofibromatosis 1110
plexiform neurofibroma 1110
diffuse neurofibroma 1113
fibrolamellar nerve sheath tumor 1132
storiform nerve sheath tumor 1132
pacinian neurofibroma 1133
neurilemmomas (schwannomas) 1116
cellular schwannoma 1118
atypical schwannoma 1119
transformed (borderline)
schwannoma 1121
epithelioid schwannoma 1119
glandular schwannoma 1120
plexiform schwannoma 1120
infiltrating fascicular schwannoma
of infancy 1121
malignant schwannomas, intraneural
or extraneural 1119
malignant nerve sheath tumor 1122
psammomatous melanotic
schwannoma 1121
epithelioid malignant schwannoma 1121
mature (myxoid) neurothekeoma,
nerve sheath myxoma 1126
perineurioma 1132
extraneural neuromas 1135
traumatic neuroma 1135
intraneural neuromas 1135
palisaded and encapsulated
neuroma (PEN) 1135
intraneural plexiform neuroma 1136
mucosal neuroma syndrome 1137
linear cutaneous neuroma 1137

impingement neurofasciitis (Morton's neuroma) . . .1143
accessory digit 1135
ganglioneuroma 1140

3. Spindle Cell Tumors of Muscle 98

Smooth muscle cells have more abundant cytoplasm than fibroblasts or Schwann cells. The cytoplasm is trichrome positive and reacts with the muscle markers desmin and muscle-specific actin. The nuclei tend to have blunt ends. In neoplasms, the cells tend to be arranged in whorled bundles.

leiomyoma 1076
angioleiomyoma 1076
superficial leiomyosarcoma 1080
infantile myofibromatosis 984
solitary myofibroma 984
dermatomyofibroma 980
benign mixed mesodermal proliferations 1094
malignant mesenchymal tumors
of uncertain origin 1075
smooth muscle hamartoma 1075
rhabdomyosarcoma 1084

4. Melanocytic Spindle Cell Tumors 98

Melanocytic spindle cell tumors may have many attributes of the schwannian tumors described earlier. S100 is positive and HMB-45 is often negative in spindle cell melanomas. Diagnosis of melanoma then depends on recognizing melanocytic differentiation—pigment synthesis—or a characteristic intraepidermal *in situ* or microinvasive component.

desmoplastic melanoma, including amelanotic 753
cellular blue nevus, amelanotic 702
blue nevus, amelanotic 702
desmoplastic Spitz nevus 722
spindle cell metastatic melanoma 755

5. Tumors and Proliferations of Angiogenic Cells 98

There is a dermal proliferation of vascular endothelium. Factor VIII staining may be helpful in demonstrating endothelial differentiation. The many variants of benign hemangiomas should be carefully considered in the differential diagnosis of Kaposi's sarcoma and angiosarcoma.

angiomas 1013
juvenile hemangioendothelioma
(strawberry nevus) 1014
cherry hemangioma 1015
glomeruloid hemangioma 1010
tufted angioma (angioblastoma) 1015
angiokeratoma 1011
cavernous hemangioma 1019
sinusoidal hemangioma 1019
verrucous hemangioma 1020
microvenular hemangioma 1020
targetoid hemosiderotic (hob-nail)
hemangioma 1021
cirsoid aneurysm (arteriovenous
hemangioma) 1026
epithelioid hemangioma 1022
lymphangiomas 1043
cavernous lymphangioma and cystic
hygroma 1044
lymphangioma circumscriptum 1044
progressive lymphangioma (benign
lymphangioendothelioma) 1045
lymphangiomatosis 1045
pyogenic granuloma 1016
bacillary angiomatosis 572
intravascular papillary endothelial hyperplasia 1007
telangiectases 1011
hereditary hemorrhagic telangiectasia 1012
spider nevus 1012
venous lakes 1012
vascular malformations 1010
angioma serpiginosum 1012
glomus tumors
glomus tumor, glomiangioma,
glomangiomyoma 1047
infiltrating glomus tumor 1048
glomangiosarcoma 1047
vascular lipomas
angiomyolipoma 1060
angiolipoma 1064
angiosarcomas 1040
epithelioid angiosarcoma 1043
Kaposi's sarcoma 1029
Kaposi's sarcoma simulants (see also angiomas)
aneurysmal fibrous histiocytoma 1035
spindle cell hemangioendothelioma 1027
Kaposi-like infantile
hemangioendothelioma 1038
acroangiodermatitis (pseudo-
Kaposi's sarcoma) 1035
multinucleate cell angiohistiocytoma 1035
bacillary angiomatosis 1018
angiomatosis 1027
hemangioendotheliomas
epithelioid hemangioendothelioma 1039
retiform hemangioendothelioma 1035
malignant endovascular papillary
angioendothelioma (Dabska's tumor) 1036
spindle cell hemangioendothelioma 1027
Kaposi-like infantile
hemangioendothelioma 1038
hemangiopericytoma 1049
angiolymphoid hyperplasia with eosinophilia 1022
intravascular lymphoma (malignant
angioendotheliomatosis) 932
reactive angioendotheliomatosis 933, 1008

6. Tumors of Adipose Tissue 98

nevus lipomatosus superficialis 1058

lipomas
spindle cell lipoma 1066
pleomorphic lipoma 1066
chondroid lipoma 1067
angiolipoma 1064
liposarcomas
well differentiated 1071
atypical lipomatous tumor 1072
myxoid 1072
round cell 1074
pleomorphic 1074
hibernoma 1068
benign lipoblastoma 1070

7. Tumors of Cartilaginous Tissue 98

chondroid lipoma 1067
soft tissue chondroma 1094
chondrosarcoma 1097

8. Tumors of Osseous Tissue 98

Albright's hereditary osteodystrophy 1086
osteoma cutis 1087
metaplastic ossification 1089
subungual exostosis 1090

D. Cysts of the Dermis and Subcutis 98

A cyst is a space lined by epithelium; its contents are usually a product of its lining. Some cysts are inclusion or retention cysts of normal structures (e.g., hair follicle–related cysts). Others are benign neoplasms. Some malignant neoplasms may be cystic. These tend to be larger and asymmetric, with a poorly circumscribed and infiltrative border. Their epithelial lining is proliferative, with cytologic atypia.

1. Pilar Differentiation 98

Cystic proliferations are present in the dermis; these show spaces surrounded by epithelium of follicular origin and differentiation. Keratin is usually seen in the cystic cavity. Associated cells may be sparse or may include lymphocytes and plasma cells.

epidermal cyst 801
milia 802
trichilemmal cyst 802
steatocystoma multiplex 803
pigmented follicular cyst 804
dermoid cyst 804
bronchogenic and thyroglossal duct cysts 805
eruptive vellus hair cyst 806
pilar sheath acanthoma 855
dilated pore of Winer 855

2. Eccrine and Similar Differentiation 98

Cystic proliferations are present in the dermis; these show spaces surrounded by eccrine epithelium (small, dark epithelial cells). The epithelium of ciliated and bronchogenic cysts is not eccrine but may resemble that of an eccrine cyst.

eccrine hidrocystoma 884
cutaneous ciliated cyst 805
bronchogenic and thyroglossal duct cysts 805
median raphe cyst of the penis 805
cutaneous endometriosis 890

3. Apocrine Differentiation 98

Cystic proliferations are present in the dermis; these show spaces surrounded by apocrine epithelium (large, pink cells with decapitation secretion). There may be lymphocytes and plasma cells (syringocystadenoma).

hidradenoma papilliferum 852
syringocystadenoma papilliferum 878
apocrine hidrocystoma 877

VII. INFLAMMATORY AND OTHER BENIGN DISORDERS OF SKIN APPENDAGES

The hair, sebaceous glands, eccrine glands, apocrine glands, and nails may be involved in inflammatory processes (hidradenitis, folliculitis). Some neoplasms may masquerade as inflammatory processes.

A. Pathology Involving Hair Follicles 99

Inflammatory processes may present as alopecia or as follicular localization of inflammatory rashes. Acne and related conditions present as dilation of follicles, which are filled with keratin.

1. Scant Inflammation 99

There is follicular alteration with a sparse infiltrate of cells, mainly lymphocytes.

follicular maturation disorders
androgenetic alopecia 479
telogen effluvium 478
trichotillomania 476
scurvy 407
vitamin A deficiency (phrynoderma) 407, 450
follicular keratinization disorders
keratosis pilaris 469
lichen spinulosus 469
trichorrhexis invaginata (Netherton's syndrome) 489
trichostasis spinulosa 470
acne vulgaris 459
Favre-Racouchot syndrome (nodular elastosis with cysts and comedones) 390
nevus comedonicus 793
Bazex's syndrome (follicular atrophoderma) 823

2. Lymphocytes Predominant 99

There is follicular alteration with an inflammatory infiltrate, mainly of lymphocytes.

alopecia areata 470
discoid lupus 280, 468
alopecia mucinosa/follicular mucinosis 467, 936
folliculotropic mycosis fungoides 939
lichen planopilaris 470
Fox-Fordyce disease 492
syringolymphoid hyperplasia with alopecia 490
lichen striatus 193
chronic folliculitis 544
rosacea 463
perioral dermatitis 462
disseminated and recurrent
infundibular folliculitis 459
acne varioliformis (acne necrotica) 543

a. With Eosinophils Present 99

Eosinophils are prominent in the infiltrate and may infiltrate the follicular structures.

eosinophilic pustular folliculitis 466
erythema toxicum neonatorum 267, 467
Ofuji's syndrome 466
fungal folliculitis 591

3. Neutrophils Prominent 99

There is a follicular alteration with an inflammatory infiltrate containing neutrophils, which may result in disruption of the follicle.

superficial folliculitis
acute bacterial folliculitis 543
impetigo of Bockhart 542
Pseudomonas folliculitis 542
acne vulgaris 459
alopecia of secondary syphilis 582
deep folliculitis
furuncle, carbuncle 543
folliculitis barbae, decalvans 544
pseudofolliculitis of the beard 544
pyoderma gangrenosum 411
follicular occlusion disorders
dissecting cellulitis/perifolliculitis capitis abscedens
et suffodiens 544
hidradenitis suppurativa 544
acne conglobata 544
fungal folliculitis
Majocchi granuloma (*Trichophyton rubrum*) 593
favus (*Trichophyton schoenleinii*) 593
Pityrosporum folliculitis 596
viral folliculitis 638
acne fulminans 459
Behçet's syndrome, acneiform lesions 412

4. Plasma Cells Prominent 99

Plasma cells are seen in abundance in the infiltrate. In most instances they are admixed with lymphocytes.

acne keloidalis 544
fungal folliculitis 591
alopecia of secondary syphilis 582

5. Fibrosing and Suppurative Follicular Disorders 99

In follicular occlusion disorders and acne keloidalis there is extensive fibrosis of the dermis, often with keratin tunnels of follicular origin and with embedded hairs with associated foreign-body inflammation. Neutrophils and plasma cells are seen in abundance in the infiltrate in addition to lymphocytes. In scarring alopecias the follicles are replaced by a delicate fibrous track.

acne keloidalis 549
follicular occlusion disorders
pilonidal sinus 545
hidradenitis suppurativa 544
acne conglobata 544
perifolliculitis capitis abscedens et suffodiens
(dissecting cellulitis of the scalp) 544
deep folliculitis
folliculitis barbae, decalvans 544
scarring alopecias . . . . . .
pseudopelade of Brocq 483
follicular degeneration syndrome 482
folliculitis decalvans 487
tufted folliculitis 487
central centrifugal scarring alopecia 482
postmenopausal frontal fibrosing
alopecia 488

B. Pathology Involving Sweat Glands 99

The sebaceous glands, eccrine glands, and apocrine glands may be involved in inflammatory processes (hidradenitis).

1. Scant Inflammation 99

Sweat glands are abnormal in color or size and number but there is little or no inflammation.

argyria 327
syringosquamous metaplasia 322
eccrine nevus 883
eccrine angiomatous hamartoma 883
coma blister 273

2. Lymphocytes Predominant 99

There is a predominantly lymphocytic infiltrate in and around the sweat glands.

lupus erythematosus 279
syringolymphoid hyperplasia with
alopecia 490
lichen striatus 193
morphea/scleroderma 295
syringotropic mycosis fungoides
(cutaneous T-cell lymphoma) 939
Fox-Fordyce disease (apocrine miliaria) 492

a. With Plasma Cells 99

There is a predominantly lymphocytic infiltrate in and around the sweat glands. Plasma cells are also present as a minority population.

lupus erythematosus 279
secondary syphilis 581
cheilitis glandularis 380
morphea/scleroderma

b. With Eosinophils 99

There is an inflammatory infiltrate with eosinophils in and around the sweat glands.

arthropod assault reactions 634

c. With Neutrophils 99

There is an inflammatory infiltrate with neutrophils in and around the sweat glands.

insect-bite reactions 634
neutrophilic eccrine hidradenitis 314, 491
palmoplantar hidradenitis 491
secondary syphilis 581

C. Pathology Involving Nerves 99

Specific inflammatory involvement of nerves is uncommon in dermatopathology.

1. Lymphocytic Infiltrates 99

Neurotropic spread of neoplasms, especially neurotropic melanoma, may be associated with a dense lymphocytic infiltrate that may tend to obscure a subtle infiltrate of neoplastic spindle cells. Certain infections may also be associated with inflammation of nerves.

neurotropic melanoma 755
leprosy 558

2. Mixed Inflammatory Infiltrates 99

There is a mixed inflammatory infiltrate involving nerves.

leprosy 558
erythema chronicum migrans 586

3. Neoplastic Infiltrates 99

Many neoplasms may occasionally involve nerves. The involvement by carcinomas (basal cell, squamous cell, metastatic) is commonly in the perineural space, whereas involvement by neurotropic melanoma tends to occupy the endoneurium and to be associated with a dense lymphocytic infiltrate that may tend to obscure a subtle infiltrate of neoplastic spindle cells.

neurotropic melanoma 755
neurotropic tumors 1144

D. Pathology of the Nails 100

Several inflammatory dermatoses more often seen elsewhere in the skin may present incidentally or exclusively in the nails. The reaction patterns may vary from those seen elsewhere because of the unique responses of the nail unit to injury.

1. Lymphocytic Infiltrates 100

spongiotic dermatitis 503
lichen planus 185

2. Lymphocytes with Neutrophils 100

psoriasis 174, 504
tinea unguium, onychomycosis 504, 595

3. Bullous Diseases 100

Darier's disease 506
pemphigus 506
erythema multiforme 506
toxic epidermal necrolysis 506
epidermolysis bullosa 506

4. Parasitic Infestations 100

scabies 508, 626

VIII. DISORDERS OF THE SUBCUTIS

The reactions in the subcutis are mostly inflammatory, although tumors (proliferations) of the subcutis do occur (lipoma). Pathologic conditions arising in the dermis may infiltrate the subcutis.

A. Subcutaneous Vasculitis and Vasculopathy (Septal or Lobular) 100

True vasculitis is defined by the presence of necrosis and inflammation in vessel walls. Other forms of vasculopathy include thrombosis and thrombophlebitis, fibrointimal hyperplasia, and neoplastic infiltration of vessel walls.

1. Neutrophilic 100

Neutrophils and disrupted nuclei are present in the wall of the vessel, with associated eosinophilic "fibrinoid" necrosis.

leukocytoclastic vasculitis 215
subcutaneous polyarteritis nodosa 209
superficial migratory thrombophlebitis 515
erythema nodosum leprosum 564

2. Lymphocytic 100

The concept of "lymphocytic vasculitis" is controversial. Many disorders characterized by lymphocytes within the walls of vessels are best classified as lymphocytic infiltrates. The term "vasculitis" may be appropriate when there is vessel wall damage, as in nodular vasculitis, even in the absence of neutrophils and "fibrinoid."

nodular vasculitis 519
perniosis 526
angiocentric lymphomas 913
superficial migratory thrombophlebitis 209

3. Granulomatous 100

The inflammatory infiltrate in the vessel walls is composed of mixed cells including more or less epithelioid histiocytes and giant cells. Other cell types, including lymphocytes and plasma cells, and sometimes neutrophils and eosinophils, also are commonly present.

erythema induratum/nodular vasculitis
(inconspicuous vasculitis) 519
erythema nodosum leprosum
(type 2 leprosy reaction) 564
Wegener granulomatosis 214
Churg-Strauss vasculitis 113
Crohn's disease 415

B. Septal Panniculitis without Vasculitis 100

1. Septal Panniculitis, Lymphocytes, and Mixed Infiltrates 100

The inflammation predominantly involves the subcutaneous septa, although there may be "spillover" into the fat lobules. The infiltrate is mainly lymphocytic, although other cells can be found, including plasma cells and acute inflammatory cells.

erythema nodosum and variants 511
Crohn's disease 415
morphea 295, 531

2. Septal Panniculitis, Granulomatous 100

Subcutaneous granulomas may present as ill-defined collections of epithelioid histiocytes, as well-formed epithelioid-cell granulomas, and as palisading granulomas in which histiocytes are radially arranges around areas of necrosis or necrobiosis.

palisaded granulomas
subcutaneous granuloma annulare 361
rheumatoid nodules 367
necrobiosis lipoidica 363
sarcoidosis 370
lichen scrofulosorum 554
Crohn's disease 514
subcutaneous infections
syphilis 579
tuberculosis 550

3. Septal Panniculitis, Sclerotic 100

Sclerosis of the panniculitis may begin as a septal process and extend into the lobules.

scleroderma, morphea 516
eosinophilic fasciitis 186
ischemic liposclerosis 510
toxins 510

C. Lobular Panniculitis without Vasculitis 101

The inflammation is mainly confined to the lobules, although there may be some septal involvement.

1. Lobular Panniculitis, Lymphocytes Predominant 101

Lymphocytes are the primary infiltrating cells.

lupus panniculitis 521
nodular vasculitis/erythema induratum,
inapparent vasculitis 519
poststeroid panniculitis 530
subcutaneous lymphoma-leukemia 911

2. Lobular Panniculitis, Lymphocytes, and Plasma Cells 101

Lymphocytes and plasma cells are the primary infiltrating cells.

lupus profundus 521
morphea profunda 535

3. Lobular Panniculitis, Neutrophilic 101

Lymphocytes and neutrophils are the primary infiltrating cells.

infection (cellulitis) 527
ruptured follicles and cysts 803
pancreatic fat necrosis 531
necrotizing panniculitis 516
Weber-Christian disease 523

4. Lobular Panniculitis, Eosinophils Prominent 101

Lymphocytes and eosinophils are the primary infiltrating cells.

eosinophilic fasciitis 303
eosinophilic panniculitis 515
arthropod bites 634
parasites 621

5. Lobular Panniculitis, Histiocytes Prominent 101

Lymphocytes and histiocytes are the primary infiltrating cells.

cytophagic histiocytic panniculitis 532
Rosai-Dorfman disease 534

6. Lobular Panniculitis, Mixed with Foam Cells 101

Lymphocytes, plasma cells, and a variety of infiltrating cells can be seen, including giant cells and foamy histiocytes.

α-1-antitrypsin deficiency panniculitis 516
Weber-Christian disease 523
traumatic fat necrosis 530
cold panniculitis 526
injection granuloma 525
factitious panniculitis 525
necrobiotic xanthogranuloma with
paraproteinemia 683

7. Lobular Panniculitis, Granulomatous 101

Lymphocytes and histiocytes are the primary infiltrating cells.

erythema induratum/nodular vasculitis
(if vasculitis is inapparent) 519
palisaded granulomas

subcutaneous granuloma annulare/
pseudorheumatoid nodule 361
rheumatoid nodules 367
subcutaneous sarcoidosis 370
tuberculosis 550

8. Lobular Panniculitis, Crystal Deposits, and Calcifications 101

Crystalline deposits derived from free fatty acids or other precipitated salts are present in the fat lobules.

sclerema neonatorum 529
subcutaneous fat necrosis of the newborn 529
gout 438
oxalosis 510
calcifying panniculitis 530

9. Lobular Panniculitis, Necrosis Prominent 101

There is fat necrosis with a resulting infiltrate that is mixed.

pancreatic panniculitis 528
erythema induratum, inapparent vasculitis 519
necrobiotic xanthogranuloma with
paraproteinemia 683
infarct 230
abscess 555

10. Lobular Panniculitis, Embryonic Fat Pattern 101

Due to atrophy or to failure of normal morphogenesis, immature small fat cells are present in the lobules.

lipoatrophy 526
lipodystrophy 526

11. Lobular Panniculitis, Miscellaneous 101

Lymphocytes, plasma cells, and a variety of infiltrating cells can be seen, including giant cells and histiocytes.

lipomembranous panniculitis 531
lipogranulomatosis of Rothmann-Makai 524
granulomatous panniculitis in
light-chain disease 524
early stages of pyoderma gangrenosum 517
necrobiotic xanthogranuloma

D. Mixed Lobular and Septal Panniculitis 102

Neoplastic infiltrates and inflammation due to trauma or infection do not respect anatomic compartments of the subcutis.

1. With Hemorrhage or Sclerosis 102

Inflammation due to trauma is likely to be associated with hemorrhage, neutrophilic inflammation, and sclerosis in late lesions.

traumatic panniculitis 525
cold panniculitis 526
injections, including factitial panniculitis 525
blunt trauma: sclerosing lipogranuloma 514
lipomembranous panniculitis/
lipodermatosclerosis 531
lupus panniculitis/profundus 521

2. With Many Neutrophils 102

Neutrophilic inflammation diffusely involves the subcutis.

necrotizing fasciitis (bacterial infection) 541
abscesses 555
North American blastomycosis 603
pyoderma gangrenosum (involves dermis also) 411
ecthyma gangrenosum 547
α-1-antitrypsin deficiency 516
infection (cellulitis) 527, 541
dissecting cellulitis of the scalp (perifolliculitis
abscedens et suffodiens) 544
hidradenitis suppurativa 544
ruptured follicles and cysts 801
Weber-Christian disease 523
miscellaneous necrotizing panniculitis 516
e.g., nodular vasculitis, pyoderma gangrenosum,
inflammatory reaction near ulcers or abscesses
of all causes, bacterial or fungal infection, etc.

3. With Many Lymphocytes 102

Lymphocytic infiltrates diffusely involve the subcutis.

lupus panniculitis (also with plasma
cells and sclerosis) 280, 522
chronic lymphocytic leukemia 925
subcutaneous T-cell lymphoma 948
histiocytic cytophagic panniculitis (early lesion) . . .948

4. With Cytophagic Histiocytes 102

Histiocytes with phagocytized erythrocytes diffusely infiltrate the subcutis.

α-1-antitrypsin deficiency (late lesion) 516
histiocytic cytophagic panniculitis (late lesion) 948
Rosai-Dorfman disease 678

5. With Granulomas 102

There is granulomatous inflammation diffusely involving the subcutis.

gummatous tertiary syphilis 583
erythema nodosum leprosum 564
chronic erythema nodosum 511
mycobacterial panniculitis 549
subcutaneous sarcoidosis 370

E. Subcutaneous Abscesses 102

A collection of neutrophils in the subcutis, usually surrounded by granulation tissue and fibrosis.

1. With Neutrophils 102

The center of the abscess contains pus, which is viscous because of the presence of DNA fragments derived from neutrophils and dead organisms.

acute or chronic bacterial
abscesses 567
deep fungal infections 604
phaeohyphomycotic cyst 602
North American blastomycosis 603
chromoblastomycosis 607
cutaneous alternariosis 603
paracoccidioidomycosis 605
coccidioidomycosis 608
sporotrichosis 612
protothecosis 615
mycobacterial panniculitis 549

CHAPTER 6

Bernett L. Johnson, Jr.
Albert C. Yan

Congenital Diseases (Genodermatoses)

ICHTHYOSIS

A classification of ichthyosis includes four major and three minor forms. In addition, there are a number of syndromes that are associated with ichthyosis.

Ichthyosis Vulgaris

Ichthyosis vulgaris is a common disorder caused by mutations in filaggrin and inherited in an autosomal dominant fashion. It develops a few months after birth. The skin shows scales that are large and adherent on the extensor surfaces of the extremities, resembling fish scales, and are small elsewhere. The flexural creases are spared. Keratosis pilaris is often present, and the palms and soles may show hyperkeratosis.

An acquired, noninherited form of the disease may appear in patients with lymphoma, particularly Hodgkin's disease (1), but this form has been reported also in association with carcinoma (2) and sarcoidosis. The expression of profilaggrin is reduced in this disorder. Profilaggrin mRNA in keratinocytes cultured from subjects with ichthyosis vulgaris is unstable and has a shorter half-life compared with that in normal cells. Therefore, a stabilizing factor may be absent or functionally inactive (3).

Histopathology. The characteristic finding is the association of a moderate degree of hyperkeratosis with a thin or absent granular layer (Fig. 6-1). The hyperkeratosis often extends into the hair follicles, resulting in large keratotic follicular plugs. The dermis is normal.

Histogenesis. Labeling with tritiated thymidine shows a normal rate of epidermal proliferation (4). The hyperkeratosis is regarded as a retention keratosis resulting from increased adhesiveness of the stratum corneum. The reason for this, as seen by electron microscopy, is a delay in the dissolution of the desmosomal disks in the horny layer. Keratohyaline granules are regularly seen on electron microscopy, in contrast to light microscopy. The stratum granulosum, however, consists of only a single layer, and the keratohyaline granules appear small and crumbly or spongy, which is evidence of defective synthesis. The reason for the inadequate formation of keratohyaline granules lies in a defect in the synthesis of filaggrin, a histidine-rich protein (4). Defective profilaggrin expression in ichthyosis vulgaris may be a result of selectively impaired posttranscriptional control (5). In noninherited ichthyosis vulgaris associated with neoplasia, the keratohyaline granules have been described as being small but showing a normal structure, indicating a reduced but not an abnormal synthesis (6).

Differential Diagnosis. Although the noninflamed but dry skin of patients with atopic dermatitis clinically resembles ichthyosis vulgaris, on histologic examination it does not show the features of ichthyosis vulgaris but rather increased epidermal thickness, patchy parakeratosis, and slight hypergranulosis in places, as seen in chronic dermatitis (6).

X-Linked Ichthyosis

X-linked ichthyosis is recessively inherited, with about 90% caused by gene deletion. It is only rarely present at birth. Although female heterozygotes are frequently affected, males have a more severe form of the disorder. The thickness of the adherent scales increases during childhood (7). In contrast to ichthyosis vulgaris, the flexural creases may be involved.

Histopathology. In hyperkeratosis, the granular layer is normal or slightly thickened but not thinned as in dominant ichthyosis vulgaris. The epidermis may be slightly thickened (6).

Histogenesis. X-linked ichthyosis, like ichthyosis vulgaris, shows a normal rate of epidermal proliferation. The disorder is a retention hyperkeratosis characterized by delayed dissolution of the desmosomal disks in the horny layer. In contrast to that of ichthyosis vulgaris, the synthesis of keratohyaline granules in X-linked ichthyosis is not defective, and the rate of synthesis is slightly increased (8). The cause of the retention hyperkeratosis in X-linked ichthyosis is the virtual absence of steroid sulfatase activity. This was first recognized in skin fibroblasts (9) but was found subsequently also in the entire epidermis and in leukocytes (10). X-linked ichthyosis is caused by an extensive deletion of the steroid sulfatase gene (11). Steroid sulfatase normally acts on cholesteryl sulfate, a product of the Odland bodies that is discharged with them from the granular cells into the intercellular space and provides cell cohesion in the lower stratum corneum. Failure of steroid sulfatase to remove cholesteryl sulfate results in persistent cell cohesion even in the upper stratum corneum and interferes with the normal process of desquamation (12).

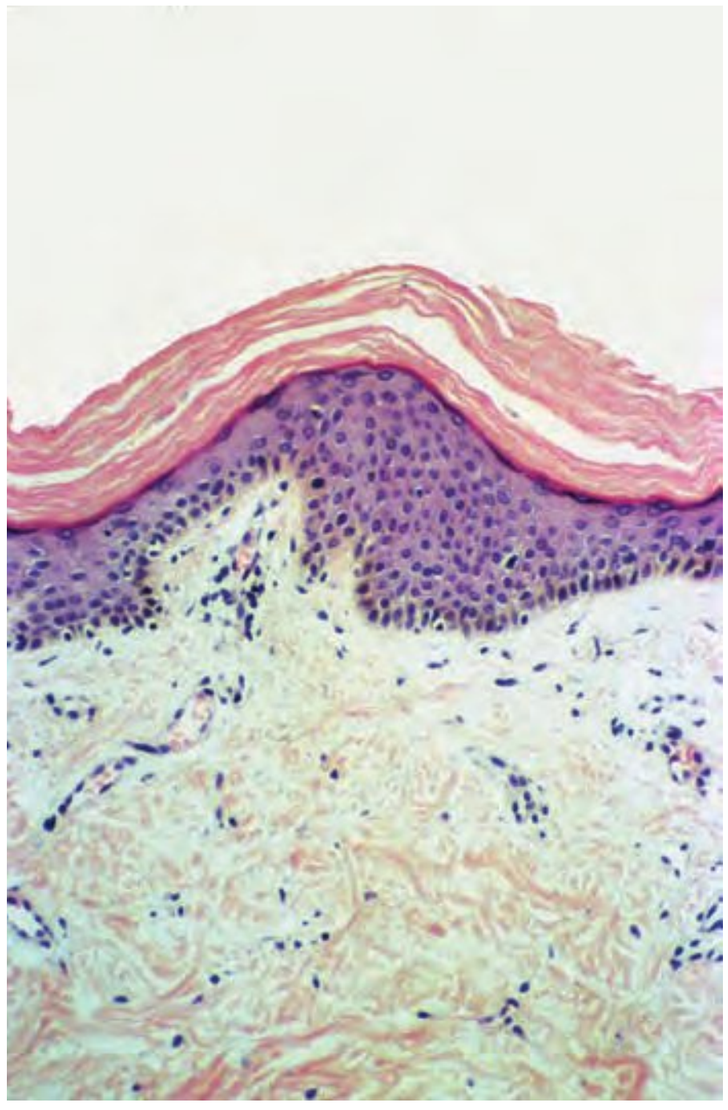


FIGURE 6-1. Ichthyosis vulgaris. Hyperkeratosis with a diminished and focally absent granular cell layer (original magnification ×100).



FIGURE 6-2. Epidermolytic hyperkeratosis. Generalized erythema, scaling, and a re-epithlialized right axilla (previously denuded).

Epidermolytic Hyperkeratosis

Epidermolytic hyperkeratosis, an autosomal dominantly inherited disease also known as *bullous congenital ichthyosiform erythroderma*, shows generalized erythema from the time of birth (Fig. 6-2). Within a few days after birth, there is thick, brown, verrucous scaling (Fig. 6-3). The flexural surfaces of the extremities show marked involvement, often consisting of furrowed hyperkeratosis. Vesicles and bullae and erosions are usually encountered only during the first few years.

Histopathology: A characteristic histologic picture is seen in the epidermis (Fig. 6-4) and is referred to either as *epidermolytic hyperkeratosis* (7) or as *granular degeneration* (13). It is present in bullous as well as in nonbullous areas. There are variously sized clear spaces around the nuclei in the upper stratum spinosum and in the stratum granulosum. Peripheral to the clear spaces, the cells show indistinct boundaries formed by lightly staining material or by keratohyaline granules. A markedly thickened granular layer containing an increased



FIGURE 6-3. Epidermolytic hyperkeratosis. Erythema and thick "scales" in older child.

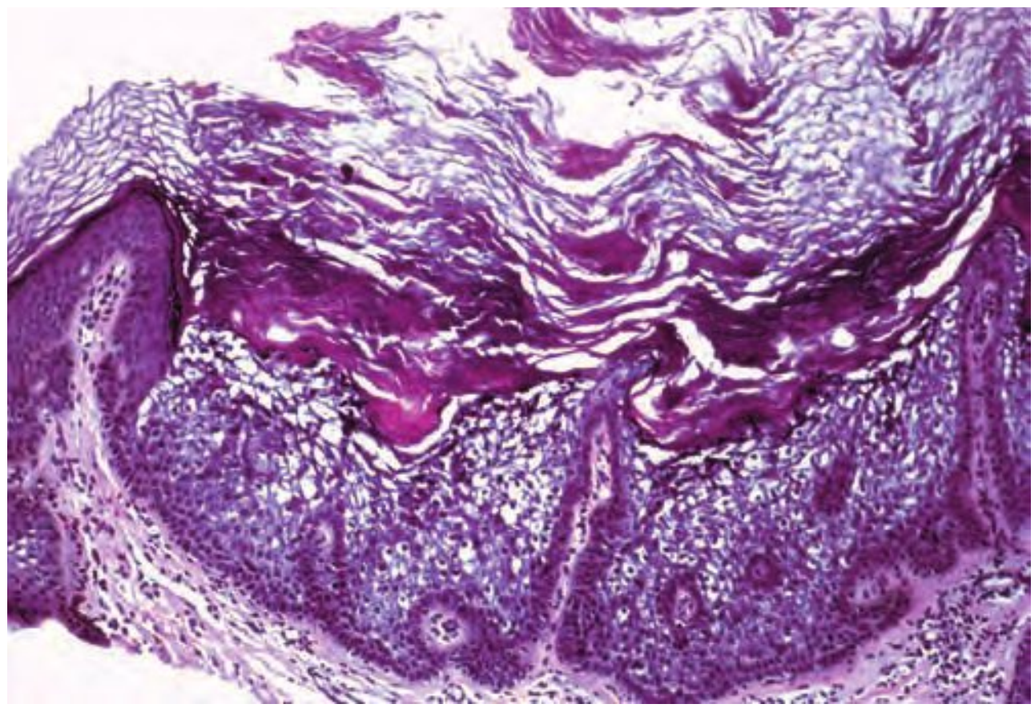


FIGURE 6-4. Epidermolytic hyperkeratosis. There is vacuolization of the upper and mid-spinus layer. There is hyperkeratosis with large keratohyaline granules in the vacuolated expanded granular cell layer (original magnification ×100).

number of irregularly shaped keratohyaline granules and compact hyperkeratosis is observed (14). When bullae form, they arise intraepidermally through separation of edematous cells from one another (15). The upper dermis shows a moderately severe, chronic inflammatory infiltrate. Mitotic figures are five times more numerous than in normal epidermis (7).

Pathogenesis. Defects in keratin genes (KRT1 and KRT10) (16) are now known to be associated with this disorder. Mutations have been found in the carboxy terminal of the rod domain of keratin 1 and the aminoterminal of the rod domain of keratin 10 (17). The essential electron microscopic features are excessive production of tonofilaments and excessive and premature formation of keratohyaline granules; thus, at the periphery of the cells, numerous keratohyaline granules are embedded in thick shells of irregularly clumped tonofilaments (18,19). The desmosomes appear normal, but the association of tonofilaments and desmosomes is disturbed, so many desmosomes are attached to only one keratinocyte instead of connecting two neighboring keratinocytes. Because of this disturbance in desmosomal attachment, blister formation takes place and real acantholysis occurs (16). Labeling with tritiated thymidine reveals greatly increased proliferative activity in the epidermis (7). It can be concluded that keratinization is both excessive and abnormal.

Differential Diagnosis. Although the histologic picture of epidermolytic hyperkeratosis is diagnostic for the type of ichthyosis called *epidermolytic hyperkeratosis*, it is not specific for it. Hyperkeratosis is found also in several other seemingly unrelated conditions (20,21): epidermolytic keratosis palmaris et plantaris, solitary epidermolytic acanthoma, disseminated epidermolytic acanthoma, and linear epidermal nevus, usually of the systematized type. This latter entity was thought to be an entirely different condition than epidermolytic hyperkeratosis but with similar histologic findings. However, it is now known that epidermal nevi of the epidermolytic hyperkeratotic type are a mosaic genetic disorder of suprabasal keratin (i.e., point mutations of 10k alleles of epidermal cells in keratinocytes from lesional skin) that can be transmitted to offspring producing generalized epidermolytic hyperkeratosis (21). Epidermolytic hyperkeratosis can be an incidental finding in a variety of conditions (22,23).

Autosomal Recessive Ichthyosis

In many instances, it is possible to subdivide recessive ichthyosis into two types. A less severe type, *congenital ichthyosiform erythroderma*, shows fine white scales with fairly pronounced erythroderma and has a tendency to improve at the time of puberty. The more severe type, *lamellar ichthyosis*, shows large, platelike scales and severe ectropion but only slight erythroderma. In both forms, the flexural surfaces and the palms and soles are involved (10,24). Several pathogenetic mechanisms have been identified for this condition, including transglutaminase acylation defects (25), defects in lamellar body secretion (26), and abnormalities in the processing of LOX gene products (27). The condition results from deleterious mutations in the transglutaminase 1 (TGM1) gene. However, the disease is genetically heterogeneous due to some families who were found to be unlinked to TGM1 and 2q33-3J (28). In some of these instances, mutations in ABCA12 have been identified. In rare instances, autosomal recessive ichthyosis is associated with storage of neutral lipid in multiple tissues, the Chanarin-Dorfman syndrome (29). It is easily recognized by the presence of lipid vacuoles in leukocytes.

Histopathology. The histologic findings in both congenital ichthyosiform erythroderma and lamellar ichthyosis are nonspecific. As a rule, however, congenital ichthyosiform erythroderma shows only mild thickening of the stratum corneum with foci of parakeratosis, whereas lamellar ichthyosis has a markedly thickened stratum corneum without areas of parakeratosis (30).

In the Chanarin-Dorfman syndrome, lipid stains reveal prominent neutral lipid droplets in some of the epidermal cells (29).

CHILD Syndrome

CHILD syndrome is a rare but clinically striking dermatosis that shows from birth unilateral ichthyosiform erythroderma and ipsilateral underdevelopment of the limbs (Fig. 6-5). It is known under the acronym **C**ongenital **H**emidysplasia with **I**chthyosiform erythrodermal and **L**imb **D**efects (31). Because nearly all published cases have been female, it is likely that the disease is the result of an X-linked dominant gene defect that is lethal in the hemizygote male fetus. Peroxisomal abnormalities have been found in fibroblasts from involved skin in these children (32). More recently, this disorder has been shown to result from mutations in genes encoding enzymes involved in sequential steps in the conversion of lanosterol to cholesterol (33).

Histopathology. On a thickened epidermis, a pronounced hyperkeratosis with prominent parakeratotic foci is observed (34).



FIGURE 6-5. CHILD syndrome. Note unilateral erythema, scaling, and underdevelopment of limbs.

Harlequin Ichthyosis

Harlequin ichthyosis is a rare condition that is frequently but not invariably fatal. It is probably of autosomal recessive inheritance, as in one family, five siblings have the disease. At birth, the child is encased in a thick, horny cuirass with deep fissures. Marked ectropion and eclabium are present. Fetal skin biopsy is the only available method for prenatal diagnosis.

Histopathology. There is usually a massive hyperkeratosis, the stratum corneum being 20 to 30 times thicker than the stratum malpighii (35). The appearance of the stratum granulosum is variable; it may be normal, or it may be flattened to absent. A stain for fat has shown small droplets of neutral fat distributed uniformly throughout the cornified cells. Some cases have shown papillomatosis in addition to the massive hyperkeratosis or areas of parakeratosis.

Pathogenesis. An abnormality in lamellar body formation and secretion (36) exists as a result of deleterious mutations in ABCA12, which leads to an inadequate delivery of desmosomal proteases to the stratum corneum (37), a failure to degrade corneodesmosomes and, therefore, massive hyperkeratosis (38).

Erythrokeratodermia Variabilis

A rare, dominantly inherited disorder, erythrokeratodermia variabilis starts in infancy rather than at birth. It has two morphologic components. First, areas of erythema expand centrifugally and coalesce into circinate figures. These lesions fluctuate, sometimes rapidly, in their configuration and extent and thus are "variable." Second, persistent hyperkeratotic plaques develop both within the areas of erythema and in areas of apparently normal skin (39). In rare cases, referred to as *progressive symmetric erythrokeratodermia*, only persistent erythematous hyperkeratotic plaques are present, and they are limited to the extremities (40).

Histopathology. The changes are nonspecific. In the hyperkeratotic plaques, they consist of hyperkeratosis with moderate papillomatosis and acanthosis. The granular layer appears normal, being two to three cell layers thick (39).

Pathogenesis. Labeling with tritiated thymidine shows a normal rate of proliferation. It is likely that the hyperkeratosis is due to decreased shedding of horny cells and is of the retention type (39). Mutations in the genes gjb3 and gjb4, which affect connexins 31 and 30.3, have been described (41).

Ichthyosis Linearis Circumflexa

Ichthyosis linearis circumflexa, a recessive disorder that is present at birth or starts shortly thereafter, manifests as extensive migratory polycyclic lesions of erythema and scaling (42). At their periphery, some of the areas show a distinctive "double-edged" scale. The presence of extensive erythema causes a resemblance to psoriasis. The dermatosis persists through life. In more than half of the reported cases, hair anomalies have been present in the scalp, usually trichorrhexis invaginata, as part of Netherton's syndrome (43).

Histopathology. The areas of erythema and scaling show nonspecific changes with some resemblance to psoriasis, such as elongation of the rete ridges and hyperkeratosis, as well as parakeratosis (44).

The double-edged scale frequently shows in the upper stratum malpighii intracellular edema and irregular spongiosis, resulting in multilocular vesicles or vesiculopustules within the horny layer (45). In other cases, focal accumulations of PAS-positive, diastase-resistant, homogeneous material representing exuded serum protein are seen within a parakeratotic stratum corneum (46). The presence of such exudative changes, however, is not specific or characteristic for ichthyosis linearis circumflexa, as has been claimed (47).

Pathogenesis. Electron microscopic examination has shown the presence of multilocular vesicles that are filled with an amorphous substance compatible with serum protein (48).

Syndromes Associated with Ichthyosis

There is an expanding list of syndromes that combine ichthyosis with neuroectodermal and mesodermal defects (49). Some of the syndromes described in the literature may be chance associations (50). Among the well-established syndromes are the *Sjögren-Larsson syndrome*, which is characterized by lamellar ichthyosis in association with mental retardation and spastic paresis (51)—skin fibroblasts and leukocytes from these patients are deficient in activity of the enzyme fatty alcohol and NAD oxidoreductase (52) and are due to a gene defect in FALDH (53); *Rud's syndrome*, showing generalized ichthyosis with hypogonadism, mental deficiency, and epilepsy (54); and *Conradi-Hunermann syndrome*, an X-linked form of chondrodysplasia punctata in which ichthyosis with a whorled pattern is associated with skeletal and ocular abnormalities (55), with a gene defect in emopamil binding protein affecting delta 8, delta 7 sterol isomerase (56). Some forms are associated with peroxisome abnormalities (57). *Netherton's syndrome* consists of a combination of either ichthyosis linearis circumflexa or, less commonly, lamellar ichthyosis, a predisposition to atopic dermatitis, with trichorrhexis invaginata; *IBIDS syndrome*, which is icthyosis associated with brittle hair, impaired intelligence, decreased fertility, and short stature (52); and *PIBIDS syndrome*, showing photosensitivity and IBIDS. Patients with these syndromes have sulfur-deficient, sparse hair. Also included are *KID syndrome*, keratitis associated with ichthyosis and deafness (58); *neutral lipid storage disease*, ichthyosis with cataracts, deafness, ataxia, and lipid droplets in many circulating cells (59); and *multiple sulfatase deficiencies*, a combination of ichthyosis, neurodegeneration, organomegaly, and skeletal dysplasia (includes steroid sulfatase deficiency). The only syndrome showing specific histologic changes in the skin is *Refsum's syndrome*.

Refsum's Syndrome

An autosomal recessive disorder, Refsum's syndrome is characterized by generalized ichthyosis, cerebellar ataxia, progressive paresis of the extremities, and retinitis pigmentosa.

Histopathology. The skin shows hyperkeratosis, hypergranulosis, and acanthosis. In the basal and suprabasal cells of the epidermis are variably sized vacuoles that on staining for lipids are seen to contain lipid accumulations (60).

Pathogenesis. The primary metabolic defect in Refsum's syndrome is an accumulation of phytanic acid, which results from a deficiency of alpha-phytanic acid alpha-hydroxylase (61). Refsum's disease is caused by mutations in the phytanol-CoA hydroxylase gene (62).

KERATOSIS PALMARIS ET PLANTARIS

Three major autosomal dominant forms and two autosomal recessive forms of keratosis palmaris et plantaris exist. Evidence is accruing that indicates abnormalities in intracellular structural proteins (e.g., loricrin, keratins), desmosomal proteins, gap junction components (e.g., connexins), and enzymes (e.g., cathepsins) lead to the varying palmoplantar keratodermas. Gene defects causing many types of hereditary palmoplantar keratodermas have been discovered (63). The three dominantly inherited forms include the following:

1. *Keratosis palmaris et plantaris of Unna-Thost*, showing either diffuse or localized, occasionally linear hyperkeratosis of the palms and soles (Fig. 6-6). A division into two types—a circumscribed type with limitation to the palms and soles and an extending type with gradual progression to the dorsa of the hands and feet, the ankles and wrists, and the elbows and knees—is not tenable, because both types may occur in the same family (64).
2. *Epidermolytic keratosis palmaris et plantaris*, although clinically indistinguishable from the Unna-Thost type, histologically shows epidermolytic hyperkeratosis. This form appears to be quite common (65). This variant has been associated with mutations in keratin type 9 localized within the keratin gene cluster on chromosome 17q 12-q21 and keratin type 1 on chromosome 12q13 (66).
3. *Keratosis palmoplantaris punctata* (or *papulosa*) has multiple keratotic plugs.

The two recessively inherited forms include the following:

1. *Keratosis palmaris et plantaris of the Meleda type*, showing diffuse involvement of the palms and soles and a marked tendency toward progression to the dorsa of the hands and feet, the ankles and wrists, and the elbows and knees (67).
2. The *Papillon-Lefèvre syndrome* shows the clinical characteristics of the Meleda type in association with periodontosis resulting in the loss first of the deciduous teeth and later of the permanent teeth (68). Abnormalities in cathepsin C localized to chromosome 11q14.1 has been found as well as keratins 6b,9,16,17 on 12q13 and 17q12-q21 and connexin 30 on 13q12 (69).

In addition, keratosis palmaris et plantaris occurs in three syndromes: (a) pachyonychia congenita, (b) hidrotic ectodermal dysplasia, and (c) the Richner-Hanhart syndrome associated with tyrosinemia (tyrosine tyrosinase on 16q22,1-q22.3) (69).



FIGURE 6-6. Keratosis palmeris et plantaris of Unna-Thost. Thickened palms and soles of the father, whose child has similar findings.

Histopathology. In keratosis palmaris et plantaris of the Unna-Thost type and the Meleda type, as well as in the Papillon-Lefèvre syndrome, the histologic picture is nonspecific, consisting of considerable hyperkeratosis, hypergranulosis, acanthosis, and a sparse inflammatory infiltrate of lymphocytes in the upper dermis (67,68).

In epidermolytic keratosis palmaris et plantaris, the histologic picture is identical with that seen in epidermolytic hyperkeratosis. Many cells in the middle and upper stratum malpighii appear vacuolated, and scattered cavities are present as a result of ruptured cell walls. Keratohyaline granules are numerous and large (70–72).

In keratosis palmoplantaris punctata, there is massive hyperkeratosis over a sharply limited area, with depression of the underlying malpighian layer below the general level of the epidermis. There is an increase in the thickness of the granular layer. The dermis is free of inflammation (73). In two cases reported as punctate keratoderma, a cornoid lamella was seen in the center of the hyperkeratotic plug; these cases represent punctate porokeratosis with the lesions limited to the palms and soles, rather than keratosis palmoplantaris punctata (74,75).

ACROKERATOELASTOIDOSIS

Acrokeratoelastoidosis is a rare, autosomal dominantly inherited condition in which firm, shiny papules are seen at the periphery of the palms and soles with extension to the dorsa of the fingers and the sides of the feet (76,77) (Fig. 6-7).

Histopathology. The essential histologic feature in the papules consists of diminution and fragmentation of the elastic fibers, especially in the deeper portions of the dermis (76,77). Some of the fragmented elastic fibers appear thickened and tortuous (78).

Histogenesis. On electron microscopic examination, the elastic fibers in the reticular dermis appear disaggregated, with fragmentation of the microfibrils (77,79).

Differential Diagnosis. In *focal acral hyperkeratosis,* the lesions have the same clinical appearance as in acrokeratoelastoidosis.



FIGURE 6-7. Acrokeratoelastoidosis. Firm papules at side of foot.

There may or may not be a familial predisposition, but the elastic tissue stains fail to reveal any abnormalities (80,81). In *degenerative collagenous plaques of the hands,* the lesions develop late in life; there is no involvement of the feet and no familial predisposition. These histologic changes consist of basophilic degeneration of the elastic tissue (82,83).

PACHYONYCHIA CONGENITA

A disorder with autosomal dominant inheritance, pachyonychia congenita is characterized by the following triad: (a) subungual hyperkeratosis with accumulation of hard, keratinous material beneath the distal portion of the nails (Fig. 6-8), lifting the nails from the nail bed; (b) keratosis palmaris et plantaris with thick callosities, especially on the soles, that are tender and often associated with blister formation; and (c) thick white areas on the oral mucosa (Fig. 6-9) that resemble those seen in white sponge nevus and possess no tendency toward malignant degeneration (84). Follicular hyperkeratosis may occur, mainly on the elbows and knees. Several clinical variants have been described. Type I shows prominent palmoplantar hyperkeratosis and extensive follicular hyperkeratosis that also involves the trunk. Type II (most common) manifests scalloped tongue and oral leukokeratosis. Type III develops corneal thickenings and cataracts. Type IV (Jackson-Lawler variant) develops cysts of the head, neck, and chest at puberty. They may also manifest hidradenitis suppurativa and milia. A late onset type may also exist.

Histopathology. The nail bed shows marked hyperkeratosis. As in a normal nail bed, there is no granular layer (84). The blisters that may be seen beneath and around the plantar callosities arise in the upper layers of the stratum malpighii through increasing intracellular edema and vacuolization. Unlike friction blisters, they show no areas of necrosis (85). The oral lesions show thickening of the oral epithelium with extensive intracellular vacuolization, exactly as seen in white sponge nevus, and without evidence of dyskeratosis (86).



FIGURE 6-8. Pachyonychia congenita. Thickened nails in infant with this syndrome.

Pathogenesis. A defect in keratin synthesis in types I and II is suggested by mutations of K6b, K9, K16, and K17 mapped to chromosome 12q13 or 17q12-q21 (87,88).

DYSKERATOSIS CONGENITA

Dyskeratosis congenita usually is inherited as an X-linked recessive disorder, most likely location Xq28, occurring only in males; but in some instances, it is transmitted in an autosomal dominant fashion, in which case females also may be affected (89). It is characterized by the following triad: (a) dystrophy of the nails, with failure of the nails to form a nail plate; (b) white thickening (leukokeratosis) of the oral and occasionally also of the anal mucosa; and (c) extensive areas of netlike pigmentation of the skin suggestive of poikiloderma atrophicans vasculare but with less atrophy and telangiectasia. In the X-linked form, testicular atrophy is also common. Carcinoma may develop in areas of buccal and anal leukokeratosis. In many cases, a Fanconi



FIGURE 6-9. Pachyonychia congenita. Note whitened mucosa at back of tongue.

type of anemia develops that may begin with leukopenia and thrombocytopenia but ends in severe pancytopenia (90).

Histopathology. In dyskeratosis congenita, the areas of netlike pigmentation show melanophages in the upper dermis as their only constant feature (91). In contrast to poikiloderma atrophicans vasculare, atrophy of the epidermis, vacuolization of basal cells, and inflammatory infiltration of the upper dermis are either absent (92) or are mild and thus not diagnostic (91). Oral biopsies may show squamous cell carcinoma *in situ* or invasive squamous cell carcinoma.

Pathogenesis. The gene responsible for X-linked dyskeratosis congenita (DKC1) encodes a protein called *dyskerin*, which is essential for ribosome biogenesis and telomerase RNP assembly. X-linked and autosomal dyskeratosis congenita have reduced telomere lengths but normal telomerase activity (93,94).



FIGURE 6-10. Porokeratosis. Linear hyperkeratosis along the feet and legs.

POROKERATOSIS

Porokeratosis has a wide variety of manifestations, but with the exception of the punctate type, it is characterized by a distinct peripheral keratotic ridge that corresponds histologically to the cornoid lamella (Fig. 6-10). Porokeratosis is inherited in an autosomal dominant pattern. Five different forms can be distinguished (95).

The *plaque type*, as originally described by Mibelli, shows a single or a few lesions several centimeters in diameter. Rarely, there are numerous lesions (96). The border often consists of a raised wall, having on its top a furrow filled with keratotic material. The lesions have a tendency toward peripheral extension.

Disseminated superficial actinic porokeratosis, the most common type, shows lesions that often are most pronounced in sun-exposed areas and may be exacerbated by exposure to the sun (97). However, the term *actinic* cannot be applied to all cases. In some instances, the lesions are distributed mainly in areas not exposed to the sun (98), and in some cases, immunosuppression has been the eliciting factor (99). The extensor surfaces of the extremities are the most common site of involvement. The lesions in disseminated superficial porokeratosis are small and are surrounded only by a narrow, slightly raised, hyperkeratotic ridge without a distinct furrow (97).

Linear porokeratosis may involve only a segment of the body or may have a generalized distribution. The lesions clinically resemble those of linear verrucous epidermal nevus (100,101).

Porokeratosis plantaris, palmaris, et disseminata is characterized by the appearance in adolescence or early adult life of many lesions on the palms and soles and subsequently by the involvement of other areas of the body with large numbers of small superficial lesions (102–104).

Punctate porokeratosis, limited to the palms and soles, shows numerous punctate, 1- to 2-mm seedlike keratotic plugs without tendency to centrifugal enlargement. They may be moderately tender to pressure (105).

Development of a squamous cell carcinoma or of Bowen's disease within lesions of porokeratosis has been repeatedly reported in patients with solitary lesions (106) and in persons with disseminated lesions (102) or linear lesions (107). In one reported instance with many lesions and multiple squamous cell carcinomas, visceral metastases resulted in death (96).

Histopathology. It is essential that the specimen for biopsy be taken from the peripheral, raised, hyperkeratotic ridge. On histologic examination, the ridge then shows a keratin-filled invagination of the epidermis. In the plaque type of porokeratosis, the invagination extends deeply downward at an angle, the apex of which points away from the central portion of the lesion. In the center of this keratin-filled invagination rises a parakeratotic column, the so-called cornoid lamella, representing the most characteristic feature of porokeratosis of Mibelli (108) (Fig. 6-11). Within the parakeratotic column, the horny cells appear homogeneous and possess pyknotic nuclei. In the epidermis beneath the parakeratotic column, the keratinocytes are irregularly arranged and have pyknotic nuclei with perinuclear edema. In the upper stratum malpighii, some cells possess an eosinophilic cytoplasm as a result of premature keratinization (109). Usually, no granular layer is found at the site at which the parakeratotic column arises, but elsewhere, the keratin-filled invagination of the epidermis has a well-developed granular layer.

The histologic changes in the other forms of porokeratosis are similar to those seen in the plaque type but less pronounced, the central invagination being rather shallow, especially in disseminated superficial actinic porokeratosis. The shallow parakeratotic invagination then stands out by showing homogeneous cells rather than the basket weave pattern seen in the surrounding orthokeratotic stratum corneum (Fig. 6-12).

Because the peripheral raised ridge in porokeratosis slowly moves centrifugally, it stands to reason that the invagination is not bound to a definite structure, such as the sweat pore, as originally assumed by Mibelli. Although the invagination occasionally may be seen within a sweat pore or a pilosebaceous



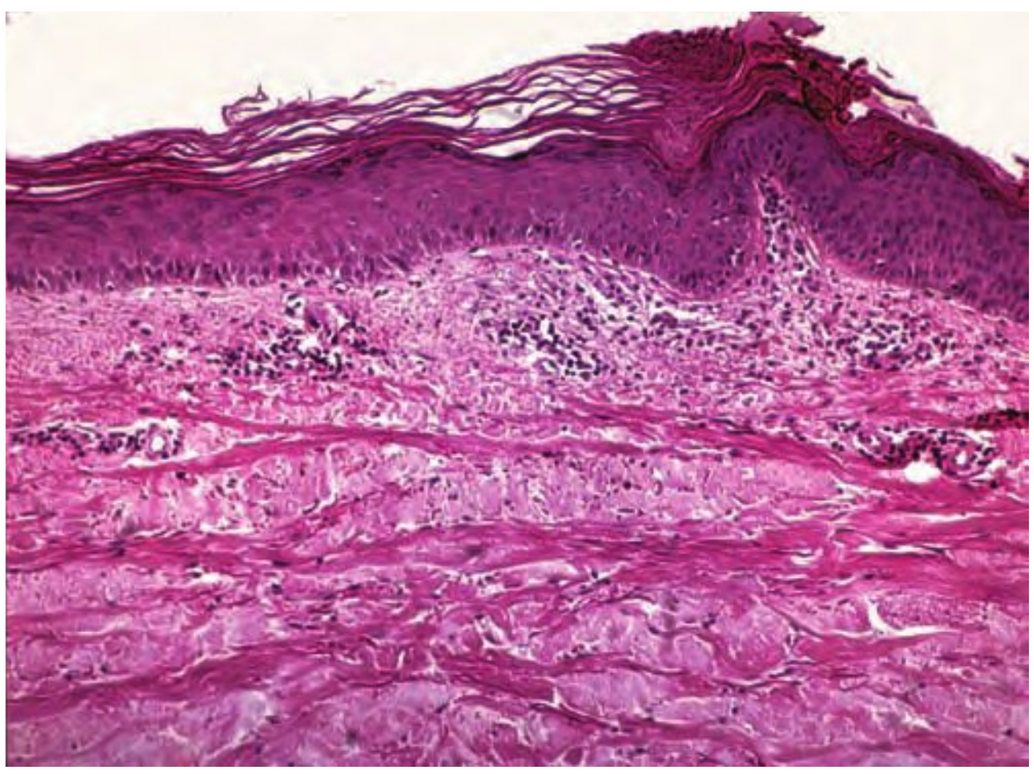
FIGURE 6-11. Porokeratosis of Mibelli. Stacked parakeratosis in an area of delled epidermis. The underlying granular cell layer is diminished to absent (original magnification ×200).

follicle, it is found most commonly in the epidermis independent of these cutaneous appendages (110). Overexpression of the P53 tumor suppressor protein has been found in porokeratosis (111). The epidermis overlying the central portion of a lesion of porokeratosis may be either flattened or normal in thickness or, rarely, acanthotic. A nonspecific perivascular infiltrate of chronic inflammatory cells is present in the dermis.

Pathogenesis. The presence of a clone of abnormal epidermal cells located at the base of the parakeratotic column explains the lesions of porokeratosis. As a result of a gradual centrifugal movement of this clone, the furrow is slanted, its apex pointing away from the center of the lesion (110).

Electron microscopic examination reveals that in the epidermis beneath the parakeratotic column, many keratinocytes show signs of degeneration. They show a pyknotic nucleus, large perinuclear vacuoles that are separated from one another by cytoplasmic strands, and condensation of tonofilaments at their periphery (112). At the base of the parakeratotic column, dyskeratotic cells composed of nuclear remnants and aggregated tonofilaments are seen (113). The parakeratotic column is composed chiefly of cells with a pyknotic nucleus and a cytoplasm possessing high electron density because of the presence of many partially degraded organelles. In addition, a few dyskeratotic cells are present (114).

Differential Diagnosis. Even though cornoid lamellation is a typical finding for porokeratosis, it is found in a variety of other conditions (115), especially in verruca vulgaris and solar



A



B

FIGURE 6-12. Disseminated actinic porokeratosis. A: A parakeratotic column arises that is quite superficially located, overlying an effaced epidermis. A lymphocytic infiltrate is seen in the dermis (original magnification ×45). B: Numerous pink-brown plaques on the leg, with a characteristic raised peripheral rim. (Photograph by William K. Witmer.)

keratosis. A histologic distinction of punctate porokeratosis from plantar or palmar warts may be impossible, and clinical data such as age of onset, inheritance, and number and size of lesions may be needed. For discussion of porokeratotic eccrine duct nevus, see the section on nevus comedonicus.

XERODERMA PIGMENTOSUM

In xeroderma pigmentosum, an autosomal recessive disorder, excessive solar damage to the skin develops at an early age. Consequently, the lesions occur chiefly in areas of the skin that habitually are exposed to sunlight. Three stages are recognized. In the first stage, which usually starts when the child is 1 or 2 years old, slight diffuse erythema is associated with scaling and small areas of hyperpigmentation resembling freckles. In the second stage, atrophy of the skin, mottled pigmentation, and telangiectases give the skin an appearance similar to that of a chronic radiodermatitis. Solar keratoses arise in areas of scaling. In the third stage, which usually starts in adolescence but sometimes much earlier in the patient's life, various types of malignant tumors of the skin appear, often causing death. They include squamous cell carcinoma, basal cell carcinoma, and, rarely, fibrosarcoma. In about 3% of patients with xeroderma pigmentosum, malignant melanomas arise. In some patients, they show no tendency to metastasize; however in others, they metastasize rapidly (116). Multiple malignant melanomas have been observed (117). The eyes also are affected, showing conjunctivitis and often keratitis with corneal opacities.

A very rare form of xeroderma pigmentosum is the *De Sanctis-Cacchione syndrome*, which in addition to severe skin lesions shows neurologic manifestations, especially microcephaly, retarded growth, and cerebellar ataxia (118).

Histopathology. In the first stage, the histopathologic appearance is not specific, but the diagnosis is suggested by a combination of changes that normally are not seen in the skin of young persons. They are hyperkeratosis; thinning of the stratum malpighii, with atrophy of some of the rete ridges and elongation of others; a chronic inflammatory infiltrate in the upper dermis; and irregular accumulations of melanin in the basal cell layer, with or without an increase in the number of melanocytes.

In the second stage, the hyperkeratosis and irregular hyperpigmentation already present in the first stage are more pronounced. The epidermis shows atrophy in some areas and acanthosis in others. There may be disorder in the arrangement of the epidermal nuclei, and in some areas the epidermis may show atypical downward growth, so the histologic picture in such areas is identical with that of solar keratosis. The upper dermis shows basophilic degeneration of the collagen and solar elastosis, as also is seen in solar degeneration.

In the third, or tumor, stage, histologic evidence of the various malignant tumors mentioned earlier is found.

Pathogenesis. In patients with xeroderma pigmentosum (with the exception of those who have the so-called XP variant; see below), cells of the skin in tissue culture show a decrease in their ability to repair the damage induced by sunlight to their deoxyribonucleic acid (DNA). This repair is brought about by *excision repair*, a system whereby damaged single-strand regions of DNA are excised and replaced with new sequences of bases (119). The reason for the inadequate excision repair is that the DNA–endonuclease that initiates the excision process is deficient. *In vitro* testing of skin fibroblasts from different patients with xeroderma pigmentosum shows considerable variation in the excision defect, with the extent of repair replication varying between 0% and 90% of normal. Affected siblings are usually similar to each other in degree of repair replication. However, no correlation exists between the level of repair replication and the severity of clinical symptoms (120).

There are at least five patients known in whom excision repair is normal but the cells are defective in a DNA repair mode referred to as *postreplication repair*. This represents the so-called XP variant form. In cells of this variant form, the rate of conversion from low– to high–molecular weight DNA is defective (121). Mutated genes in this condition include XP(A-G) and h RAD 30 with affected protein function complementation group A-G and DAN polymerase (122).

In pigmented areas, electron microscopic examination of the epidermis has revealed marked pleomorphism and a definite increase in the number of melanosomes. In some cases, very large melanosomes, referred to as *giant melanosomes*, are present in both melanocytes and keratinocytes (123). Even epidermis that is protected from light and shows no clinical abnormalities exhibits significant cellular alterations.

ECTODERMAL DYSPLASIA

The ectodermal dysplasias share abnormalities of the hair, nails, teeth, and sweat glands. Additionally, other abnormalities including mental retardation are described. Over 170 different clinical conditions have been reported as ectodermal dysplasias, many of which have clinical overlap. For the purpose of simplification, *hidrotic* and *anhidrotic* (now called *hypohidrotic*) forms will be discussed (124).

The *hidrotic* form, which has an autosomal dominant inheritance, is primarily a disorder of keratinization that is characterized by hypotrichosis, dystrophic nails, and palmoplantar hyperkeratosis. It is sometimes associated with dental hypoplasia (125). The degree of alopecia varies from slight to total (126). A mutated gene gap junction protein beta-b (GJB6) on chrosome 13q12, which encodes connexin 30, has been described (127).

The *anhidrotic* (hypohidrotic) form is an X-linked recessive disorder occurring in its full expression only in males. Mutations in the genes for ectodysplasin, its receptor, or mediating proteins (EDA or dL or EDARADD, respectively) cause these forms of ectodysplasia (128) and are localized to Xq12-q13.1. Females, as heterozygotes, may be mildly affected, with reduced sweating and faulty dentition. Males affected with anhidrotic ectodermal dysplasia show the tetrad of anhidrosis or hypohidrosis—hypotrichosis, dental hypoplasia, and a characteristic facies (129)

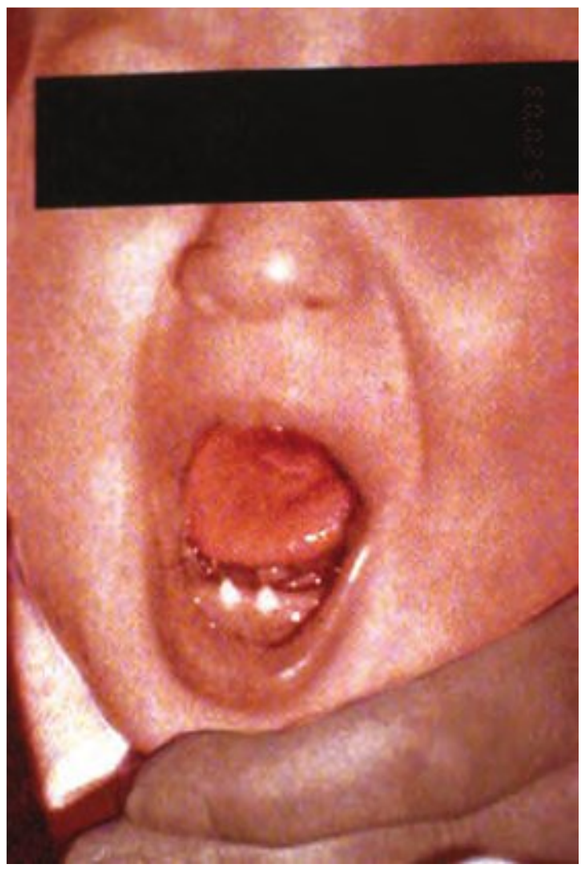


FIGURE 6-13. Hypohidrotic ectodermal dysplasia. Characteristic pegged teeth.

(Fig. 6-13). Frequently, there is also dystrophy of the nails (129). The greatly reduced or absent function of the eccrine glands results in intolerance to heat. The face shows prominent frontal bosses and a depressed nasal bridge (Fig. 6-14). In addition, the mucous glands of the mouth and respiratory tract may be absent (130). The lack of mammary glands and nipples has been noted (131).

Histopathology. Both the hidrotic and the anhidrotic forms show hypoplasia of the hair and the sebaceous glands, with a decrease in their number, size, and degree of maturation (125,131).

In the anhidrotic form, there is, in addition, either a total absence or severe hypoplasia of the eccrine glands. In the case of hypoplasia, eccrine glands are present in only a few areas, especially the axillae and palms, but even in these areas, they are sparse and poorly developed. The secretory cells may be small and flat, so that they resemble endothelial rather than epithelial cells, and the excretory ducts may be composed of a single instead of a double layer of epithelial cells (132). The apocrine glands of the axillae are present in some patients with the anhidrotic form; in others, these glands are hypoplastic and cannot be distinguished from hypoplastic eccrine glands; in still others, both eccrine and apocrine glands are absent.



FIGURE 6-14. Hypohidrotic ectodermal dysplasia. In addition to frontal bossing and a flat nasal bridge, this infant demonstrates hyperpigmentation of the eyelids and surrounding skin as well as patulous lips.

FOCAL DERMAL HYPOPLASIA SYNDROME

The focal dermal hypoplasia syndrome, or Goltz syndrome, is probably due to an X-linked dominant gene that is lethal in homozygous males. Mutations in PORCN, which are involved in the Wnt signaling pathway, have been identified as causal in Goltz syndrome (133). Therefore, the syndrome occurs largely in females. Its occasional occurrence in males had been considered to be the result of a new mutation, but recent evidence reveals that all affected males may be mosaic for mutations in PORCN. The mode of inheritance thus is similar to that of incontinentia pigmenti (IP).

The cutaneous manifestations of the focal dermal hyperplasia syndrome include widely distributed linear areas of hypoplasia of the skin resembling striae distensae; soft, yellow nodules, often in linear arrangement; and large ulcers due to congenital absence of skin that gradually heal with atrophy. It is important to remember that there are varied presentations of this syndrome (134). Frequent additional abnormalities include lack of a digit, which may be associated with syndactyly and results in the very characteristic "lobster-claw deformity"; colobomata of the eyes, or microphthalmia, or agenesis of an eye (135); and hypoplasia of hair, nails, or teeth (136). The presence of fine, parallel, vertical striations in the metaphysis of long bones on radiography, referred to as osteopathia striata, is a reliable diagnostic marker of Goltz's syndrome (137).

Histopathology. The linear areas of hypoplasia of the skin show a marked diminution in the thickness of the dermis, with the collagen being present as thin fibers not united into bundles. The soft, yellow nodules represent accumulations of fat that largely replace the dermis; thus, the subcutaneous fat extends upward to the epidermis in some areas (136,138) (Fig. 6-15). Thin fibers of collagen and even some bundles of collagen resembling those of normal dermis may be located between the subepidermal adipose tissue and the subcutaneous fat (137).

Pathogenesis. Electron microscopic examination shows, in addition to collagen fibrils 70 nm or more in diameter, many fine filamentous structures measuring 5 to 70 nm in diameter. There are two types of fat cells, one unilocular and the other multilocular, the latter representing young lipocytes (139).

Differential Diagnosis. Fat cells are seen in the dermis and also in the nevus lipomatosus of Hoffmann and Zurhelle, but the extreme attenuation of the collagen that occurs in some areas of

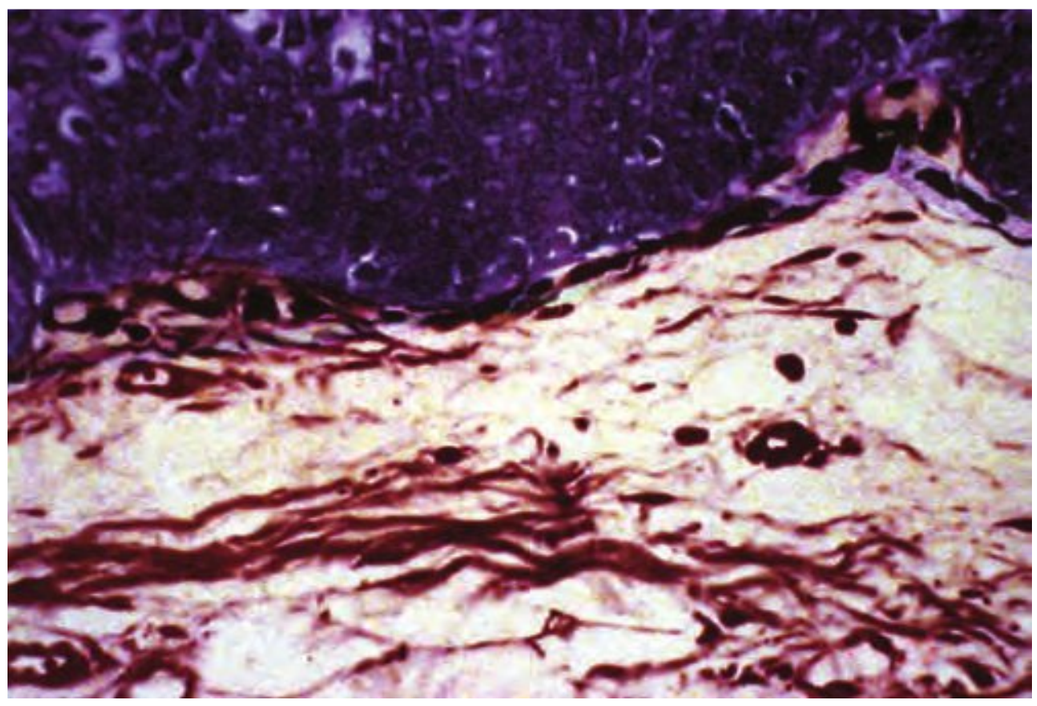


FIGURE 6-15. Focal dermal hypoplasia. Adipose tissue is present very near the epidermis, separated from it by only a few collagen fibers (original magnification ×200).

the skin in patients with focal dermal hypoplasia syndrome is not seen in nevus lipomatosus. Several females with deletions of the distal short arm of X(Xp22.3–p22.2) have recently been described who have lapping features of this syndrome.

APLASIA CUTIS CONGENITA

Aplasia cutis congenita consists of a localized absence of skin at the time of birth (Fig. 6-16) and may be membranous or nonmembranous. Most commonly, one observes a single ulcer or several ulcers on the scalp that measure only 1 to 3 cm in diameter and heal uneventfully. In some instances, intrauterine healing has occurred. Occasionally, large defects of the skin are present; but even then, as a rule, healing takes place within several months (140,141). The condition includes a diverse group of disorders in which localized absence of skin occurs alone or in association with a wide variety of abnormalities (142).



FIGURE 6-16. Aplasia cutis congenita. Two areas of congenitally absent skin (scarred and hairless).

Histopathology. Ulcers extend through the entire thickness of the dermis, exposing the subcutaneous fat (143). Healed areas show, besides a flattened epidermis, fibrosis in the dermis and complete absence of adnexal structures (140).

Differential Diagnosis. Aplasia cutis should not be confused with congenital absence of the skin, where only epidermis is absent. This is a variant of *epidermolysis bullosa (EB) (Bart's syndrome)* (144).

POIKILODERMA CONGENITALE (ROTHMUND-THOMSON SYNDROME)

Poikiloderma congenitale is inherited in an autosomal recessive pattern due to mutations in the DNA helicase gene RECQLA on gene map locus 8q24.3 (145). It begins a few months after birth with erythema on the face (Fig. 6-17) and subsequently extends to the dorsa of the hands and feet and occasionally also to the arms, legs, and buttocks. Later on, slight atrophy develops with telangiectases and mottled hyper- and hypopigmentation, so the appearance is that of poikiloderma atrophicans vasculare (Fig. 6-18). Exposure to light aggravates the lesions. Most patients show dwarfism and hypogonadism. In about 40% of patients, cataracts develop between the ages of 4 and 7 years (146). Recent evidence suggests that children with this syndrome have a reduced DNA repair capacity (147).

Histopathology. During the early phase occurring in infancy and early childhood, there is hydropic degeneration of the basal layer leading to "pigment incontinence" with presence of melanophages in the upper dermis (131). A mild chronic inflammatory infiltrate is intermingled with the melanophages and may show a bandlike arrangement close to the flattened



FIGURE 6-17. Poikiloderma congenitale. An older child with pokiloderma, atrophy, and hyperpigmentation.



FIGURE 6-18. Poikiloderma congenitale. Older child with poikilodermatous changes of the cheek and ear.



FIGURE 6-20. Bloom's syndrome. Erythema of the shoulders with photodistributed skin changes on the back.

epidermis (146) (Fig. 6-19). The histologic changes thus may be identical with those seen in the early stage of poikiloderma atrophicans vasculare. In later childhood and adult life, the epidermis is flattened, and dilated capillaries as well as melanophages are present in the upper dermis, but there is no longer any inflammatory infiltrate.

BLOOM'S SYNDROME (CONGENITAL TELANGIECTATIC ERYTHEMA)

Bloom's syndrome, with autosomal recessive inheritance due to mutations in the gene encoding DNA helicase RecQ protein-like 2 on gene map locus 15q26.1 (148), resembles poikiloderma congenitale by showing (a) telangiectatic erythema of the face starting in infancy and often extending to the forearms and hands, (b) sensitivity to sunlight, (c) café au lait macules in over 50% of patients (149), and (d) growth retardation (Fig. 6-20). It differs from poikiloderma congenitale by (a) the lack of netlike hyper- and hypopigmentation (150); (b) the absence of hypogonadism (testicular atrophy and sterility are common in male patients) and cataracts; (c) the occasional presence of immunoglobulin deficiencies, especially of IgA and IgM (151,152); (d) a high incidence of nonspecific chromosomal breakage (152) and a great increase in the frequency of another type of chromosome instability, sister chromatid exchanges (153); and (e) an increased risk for malignant disease, especially leukemia, lymphoma, and carcinoma of the alimentary tract (154).

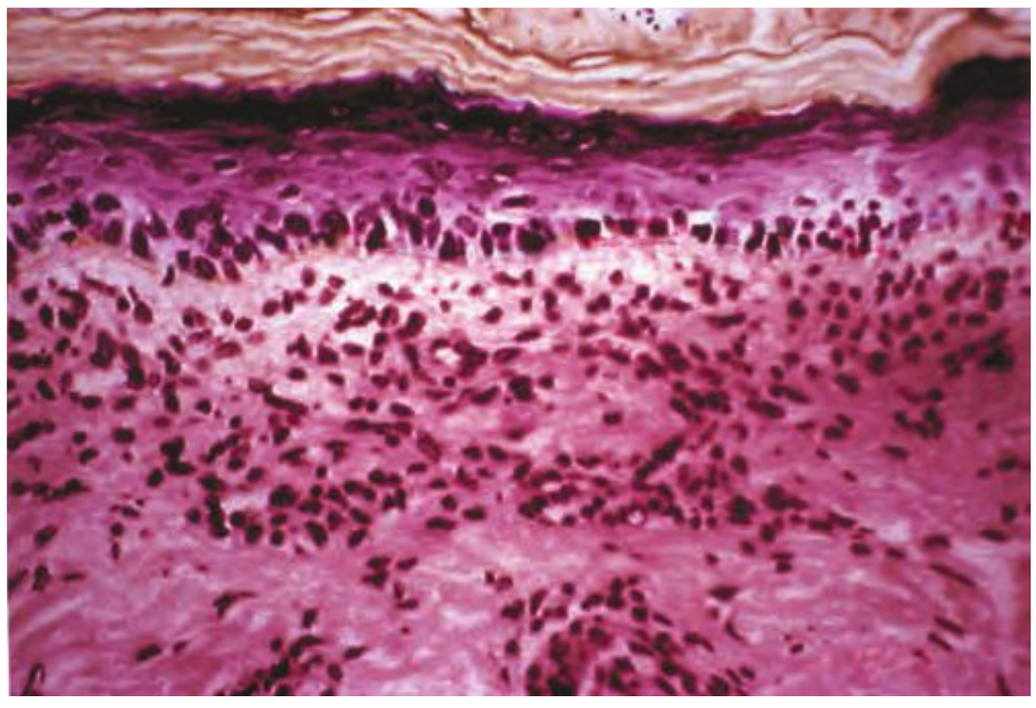


FIGURE 6-19. Poikiloderma congenitale (Rothman-Thompson), early. This section from a young child shows flattening of the epidermis, hydropic degeneration of the basal layer, and a bandlike inflammatory infiltrate in the upper dermis (original magnification ×200).

Histopathology. The epidermis is flattened and may show hydropic degeneration of the basal cell layer (153). There is dilatation of the capillaries in the upper dermis, which may be associated with a perivascular mononuclear infiltrate (149,153); however, there may be absence of any infiltrate (150).

Pathogenesis. Bloom's syndrome shows impairment of both cellular and humoral immunity, although this is not as pronounced as in *ataxia-telangiectasia* (see later). Evidence of impaired cellular immunity is the occasional absence of delayed hypersensitivity reactions (152) and the tendency toward development of malignant disease. Evidence of impaired humoral immunity is the occasional presence of immunoglobulin deficiencies. However, in contrast to ataxia-telangiectasia, susceptibility to infections is not pronounced.

Differential Diagnosis. Pigmentary incontinence is not pronounced in Bloom's syndrome, as it is in poikiloderma congenitale. The presence of hydropic degeneration of the basal cell layer and of a perivascular infiltrate may cause difficulties in differentiation from lupus erythematosus. However, no linear deposits of immunoglobulin are seen at the dermal–epidermal junction in Bloom's syndrome (153).

ATAXIA-TELANGIECTASIA

Ataxia-telangiectasia is transmitted in an autosomal recessive mode. The ataxia is evident already in infancy, whereas the telangiectases do not appear until childhood. They usually appear first on the bulbar conjuntivae, with subsequent extension to the cheeks, ears, and neck and often also to other areas, such as the buttocks and extremities. A marked susceptibility to infections, particularly sinopulmonary infections, exists. Death from chronic respiratory infection or lymphoma-leukemia is common in the second or third decade of life (155).

Histopathology. The upper dermis shows numerous markedly dilated vessels that belong to the subpapillary venous plexus (156).

Pathogenesis. All patients have severe defects in both humoral and cellular immunity. In approximately 75% of patients, there is an absence or extreme deficiency of the serum IgA; in about 80%, there is a great IgE deficiency (157). Autopsies have established maldevelopment of the thymus as an integral part of ataxia-telangiectasia (158). Increased number of T cells with gamma/delta chains in the T-cell receptors rather than alpha/beta chains may produce defects in immunity (159). Chromosomal breakage is common, but there is no increased rate of sister chromatid exchanges (156). Mutations in the ATM gene, which affects protein kinase, have been mapped to gene locus 11q22.3 (160).

PROGERIA OF THE ADULT (WERNER'S SYNDROME)

Werner's syndrome, which has an autosomal recessive mode of inheritance, does not manifest itself until the second or third decade of life. The subcutaneous fat and the musculature of the extremities undergo atrophy, so the patient exhibits thin arms and legs. The skin of the extremities gradually becomes taut, and ulcers may develop on the legs. As signs of premature senility, patients show graying of the hair, cataracts, and atherosclerosis in early adult life. Diabetes of the late-onset type (161) and hypogonadism due to interstitial fibrosis of the testes (162) are common. Death usually occurs in the fifth decade of life because of atherosclerosis.

Histopathology. On the arms and legs, where the skin is taut, the epidermis is thin and devoid of rete ridges, and the dermis shows fibrosis with or without hyalinization of the collagen. The pilosebaceous structures degenerate. The subcutaneous fatty tissue is largely replaced by newly synthesized, hyalinized collagen that merges with the collagen of the overlying dermis (163).

Pathogenesis. Poor growth and decreased life span of cultured skin fibroblasts have been found (164). The cause is due to mutation in the RECQL2 gene, which encodes a homolog of the *Escherichia coli* RecQ DNA helicase on gene map locus 8p12-11.2 (148).

Differential Diagnosis. Differentiation from a late lesion of scleroderma may be difficult, because fibrosis and hyalinization of the collagen are seen also in scleroderma (161). In its late stage, scleroderma may also show no inflammatory infiltrate, so that differentiation has to be made on the basis of the patient's history and clinical manifestations.

EPIDERMOLYSIS BULLOSA

On the basis of clinical, histologic, and electron microscopic findings, three groups of EB are recognized: epidermal, junctional, and dermal (Table 6-1).

In all types of EB, the blisters form as a result of minor trauma. Because of the great differences in prognoses, identification of the type of EB is often very important. In families with the potential of having an infant born with one of the frequently or potentially fatal forms of EB, such as *EB letalis*

TABLE 6-1 Comparison of the Clinical Features and Prognosis in Epidermolysis Bullosa

Type	Epidermolysis Bullosa	Distribution	Inheritance	Oral	Scarring	Prognosis
Epidermal	EB simplex	Generalized	Dominant	+	−	Good
	EB Cockayne	Feet, hands	Dominant	−	−	Good
	EB Dowling–Meara (Herpetiform)	Generalized	Dominant	+	Atrophy	Improves by school age
Junctional	EB letalis	Generalized	Recessive	+	−	Usually fatal
	EB benign	Generalized	Recessive	±	Atrophy	Good
Dermal	EB dystr-dom	Extremities	Dominant	±	+	Good
	EB dystr-rec	Generalized	Recessive	++	+++	Poor
	EB dystr-rec	Localized	Recessive	+	+	Good
	EB dystr-inversa	Mainly trunk	Recessive	+	+, late	Good
	EB acquisita	Generalized	—	+	+	Good

EB, epidermolysis bullosa; dystr-dom, dystrophica-dominant; dystr-rec, dystrophica-recessive; dystr-inversa, dystrophica-inversa.



FIGURE 6-21. Junctional epidermolysis bullosa. Erosions of the face, arm, and trunk.



FIGURE 6-23. Epidermal epidermolysis bullosa. Herpetiform blistering on the leg.

(Fig. 6-21) or generalized *EB dystrophica-recessive* (Fig. 6-22), a prenatal biopsy at 18 to 20 weeks of gestation is recommended. On electron microscopy, EB letalis shows abnormalities of the hemidesmosomes while generalized EB dystrophica-recessive shows absence of anchoring fibrils.

There is more variability in the clinical course in some forms of EB than was previously appreciated (165). For example, within the epidermal type of EB, which usually has a good prognosis, some cases of *EB herpetiformis*, which is known also as the *Dowling-Meara variant*, may show generalized blistering that at times is associated with mortality during early infancy (166) (Fig. 6-23). Also, the junctional form of EB can result in scarring as *cicatricial junctional EB* (167). Occasionally, dermal EB may be transient and heal within a few months (168,169). It is likely that the majority of cases published as Bart's syndrome, which was originally described as congenital absence of the skin (170), belong in this group (171,172).



FIGURE 6-22. Recessive dystrophic epidermolysis bullosa. Child with mitten deformity of hands as well as generalized blisters and scarring.

Histopathology. If a fresh blister is available, a specimen for biopsy may be taken from its edge. However, it is advisable to carry out a biopsy also on an induced blister because it will show a blister free of secondary changes. In an existing blister, the location of the blister may have changed as the result of regeneration of keratinocytes at the base of the blister or degeneration of the keratinocytes over the blister. The mode of artificially producing a blister depends on the degree of vulnerability of the skin. However, in most instances, gentle friction with a cotton swab or a pencil eraser is used. The preferred type of biopsy is either a shave or an ellipse. The use of a punch is not recommended because the applied torsion will frequently cause total separation and even loss of the epidermis (173).

Even though electron microscopic examination (discussed later) is informative, the light microscopic features seen in the various forms of EB are of diagnostic value.

In *epidermal EB*, which includes EB simplex, EB of feet and hands of Weber and Cockayne (174), and EB herpetiformis (Dowling-Meara) (175,176), the primary separation in experimentally induced blisters always occurs within the basal cell layer. Spontaneously arising blisters may be found subepidermally as the result of complete disintegration of the basal cell layer; in bullae of more than 1 day's duration, the cleavage may be found intraepidermally or subcorneally as a result of epidermal regeneration (174). In sections stained with the PAS technique, the PAS–positive basement membrane zone is located on the dermal side of the blister (177).

In *junctional EB*, the trauma of having a specimen taken for biopsy generally is sufficient to induce separation. This separation is located between the epidermis and the dermis, with

the PAS–positive basement membrane zone usually remaining with the dermis (178). In some cases of EB letalis, autopsy has revealed extensive subepithelial separation also in the gastrointestinal, respiratory, and urinary tracts (178,179). There are no morphologic or enzymatic abnormalities to distinguish the atrophic benign form of junctional EB from EB letalis (180).

In *EB dystrophica-dominant* and *EB dystrophica-recessive*, light microscopy shows dermal–epidermal separation. A PAS stain is of little help in ascertaining the exact level of cleavage because the PAS–positive basement membrane zone often appears hazy (178). If recognizable, it is seen in contact with the detached epidermis or appears split. In EB dystrophica-dominant, scarring is mild. However, in generalized EB dystrophica-recessive, extensive erosions may occur, resulting in ulcerations and severe scarring. Severe oral involvement can lead to esophageal stenoses (181). In especially severe cases, death may occur. The ulcers and scars of the skin, mouth, and esophagus may give rise to squamous cell carcinomas, which tend to metastasize (182).

EB acquisita is not a genodermatosis but an autoimmune disorder (see also chapter 9).

Pathogenesis. If possible, all specimens of artificially induced blisters should be subjected to electron microscopic examination and immunofluorescence mapping (178). The latter procedure consists of exposing cryostat sections to specific antisera against type IV collagen (localized in the lamina densa or basal lamina), against laminin (localized in the lower portion of the lamina lucida), and against bullous pemphigoid antigen (localized in the upper portion of the lamina lucida in the vicinity of the hemidesmosomes). For the latter test, bullous pemphigoid antibodies contained in many bullous pemphigoid sera are used.

In the epidermal types of EB, electron microscopic examination shows that cleavage is the result of degenerative cytolytic changes occurring in the lower portion of the basal cells between the dermal–epidermal junction and the nucleus (EM 4). Immunofluorescence mapping shows that all three antigens (type IV collagen, laminin, bullous pemphigoid antigen) are located beneath the cleavage. Studies in several families with the Dowling-Meara form of EB have revealed point mutations of keratin genes for KRT5 and KRT14 on chromosome 12 and 17, respectively (183). Different mutations in the KRT5 gene can lead to the Koebner type of EBS or the Weber-Cockayne type.

In the junctional types of EB, electron microscopic examination often shows the hemidesmosomes to be abnormal, especially in EB letalis. They may be reduced in size or number and may lack their subbasal cell-dense plaque (184). However, there are exceptions. In one fatal case of EB letalis, the hemidesmosomes were structurally and numerically normal. Also, one patient with nonlethal junctional EB showed similar abnormalities of the hemidesmosomes, as seen in the majority of patients in the lethal group (185). It is possible that the abnormalities of the hemidesmosomes are a secondary phenomenon and that the basic cause of the junctional types of EB is a biochemical disorder of a lamina lucida constituent. In favor of this theory is the fact that normal skin shows separation at the dermal–epidermal junction when cultured with blister fluid of patients with EB letalis (186). Immunofluorescence mapping shows type IV collagen and laminin on the floor of the blister; bullous pemphigoid antigen is present mainly on the blister roof but also in a more spotty distribution and to a much lesser extent on the blister floor (178). Mutations have been found in any of three polypeptides of laminin-5: alpha-3 (LAMA3), BETA-3 (LAMB3), and GAMMA-2 (LAMC2). The gene is responsible for encoding a portion of laminin 5. This mutation may have significance in reducing adhesion between the epidermis and dermis (187). A newly found mutation of the gene encoding $beta_4$ integrin has been found in the subset of EB letalis with pyloric atresia (186).

The dermal types of EB, on electron microscopy, show abnormalities in regard to their anchoring fibrils. Generalized recessive dystrophic EB shows absence of the anchoring fibrils even in nonlesional unscarred skin. On the other hand, in both dominant dystrophic EB and in localized recessive dystrophic EB, structurally normal anchoring fibrils are present but in significantly reduced number (188). The complete absence of anchoring fibrils in generalized recessive dystrophic EB could be established through the lack of a reaction with monoclonal antibodies to anchoring fibrils (189). Because type VII collagen is a major structural component of the anchoring fibrils, immunofluorescence staining with polyclonal antibodies to type VII collagen reveals complete absence of staining, even in the unaffected skin of patients with severe dystrophic recessive EB (190). Similarly, there was no reaction with periodic acid-thiosemicarbazide-silver proteinate, which stains anchoring fibrils selectively (191). Mutations in the gene encoding type VII collagen (COL 7A1) located at chromosome band 3p21 have been reported to cause these abnormal findings in the dystrophic forms of EB (192,193). Immunofluorescence mapping shows all three basement membrane zone constituents—bullous pemphigoid antigen, laminin, and type IV collagen—on top of the cleavage (178).

Epidermolysis Bullosa Acquisita

EB acquisita starts in childhood or adult life (196) with blisters at sites of trauma resulting in atrophic scars that in some cases are not pronounced (Figs. 6-24 and 6-25). Milia may not appear until the disorder has been present for many years. Oral lesions are seen occasionally. A significant proportion of patients with EB acquisita have circulating IgG antibodies (194).

Histopathology. The bullae are located beneath the epidermis and thus are indistinguishable in their location from those seen in bullous pemphigoid. The prevalence of eosinophils in the infiltrate of bullous pemphigoid often helps in distinguishing the two diseases. However, because the findings by light microscopic immunofluorescence are identical in the two diseases, patients with EB acquisita have been misdiagnosed frequently as having bullous pemphigoid before the recognition of the

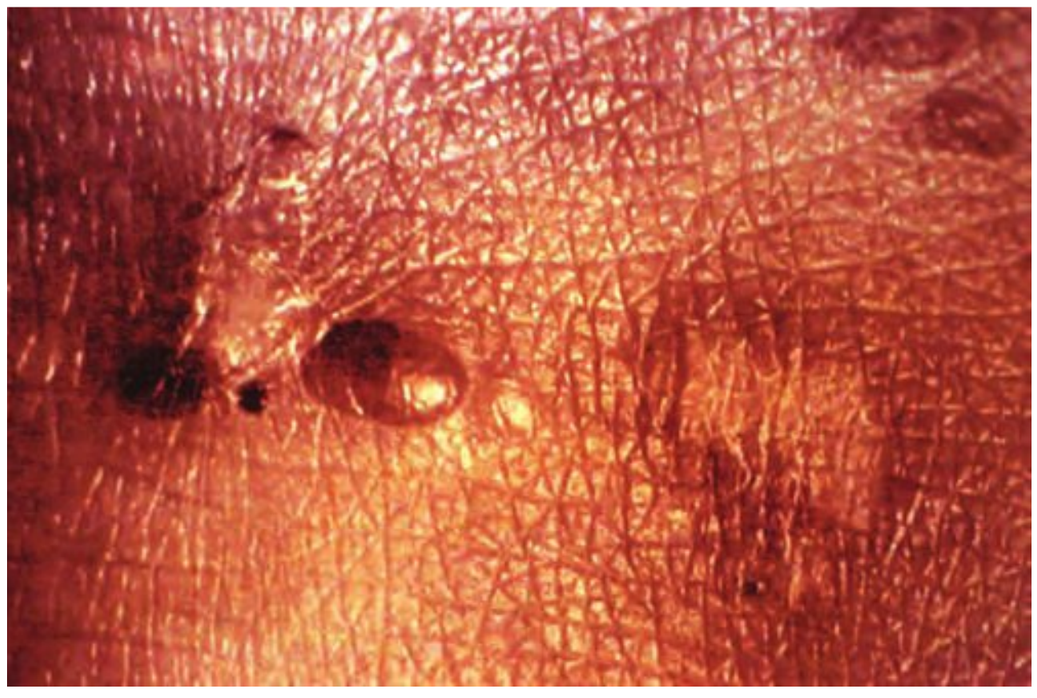


FIGURE 6-24. Epidermolysis bullosa acquisita. A blister surrounded by two scars.

different location of the respective antibodies on immunoelectron microscopy. "Salt-split" skin combined with immunofluoresence has proven to be an aid in distinguishing EB acquisita from bullous pemphigoid. Early studies demonstrated EB acquisita antibodies on the dermal side (floor) of the salt-split skin and bullous pemphigoid antibodies on the epidermal side (roof) (195,196). Later studies have found bullous pemphigoid as well as EB acquisita antibodies on the floor of the salt split (197). Despite these latter studies, this technique still has value in differentiating these two conditions.

Histogenesis. Since EB acquisita on direct immunofluorescence shows subepidermal deposits of IgG and C3 and on indirect immunofluorescence often shows circulating antibodies against IgG, a misdiagnosis of bullous pemphigoid has been made in some cases (198), or in the case of pronounced scarring, a misdiagnosis of cicatricial pemphigoid (199). Immunoelectron microscopy, however, has shown a different location of the IgG deposits in these two disease groups: in bullous pemphigoid and cicatricial pemphigoid, they are located in the lamina lucida (200); in EB acquisita, they are found in the upper dermis just beneath or contiguous to the lamina densa (194). Similarly, whereas type IV collagen and laminin are located at the floor of the blister in bullous pemphigoid, they are seen on the roof of the blister in EB acquisita. Because antibody to human type IV collagen functions also in formalin-fixed, paraffin-embedded tissue sections, standard immunoperoxidase methods have revealed type IV collagen to be associated with the blister roof in EB acquisita and with the blister base in bullous pemphigoid and cicatricial pemphigoid (201).



FIGURE 6-25. Epidermolysis bullosa acquisita. Blistering and scarring on backs of hands.

FAMILIAL BENIGN PEMPHIGUS (HAILEY-HAILEY DISEASE)

Familial benign pemphigus is inherited as an autosomal dominant trait, with a family history obtainable in about two thirds of patients. Genetic studies have localized the key mutations to the ATP2C1 gene on chromosome 3q (202), specifically 3q21-q24, the area responsible for ATP-dependent calcium transport (203). It is characterized by a localized, recurrent eruption of small vesicles on an erythematous base. By peripheral extension, the lesions may assume a circinate configuration. The sites of predilection are the intertriginous areas, especially the axillae and the groin. Only very few instances of mucosal lesions have been reported, of the mouth (204,205), the labia majora (205), and the esophagus (206).

Histopathology. Although, as in *Darier's disease,* early lesions may show small suprabasal separations, so-called lacunae, fully developed lesions show large separations, that is, vesicles and even bullae, in a predominantly suprabasal position (Fig. 6-26). Villi, which are elongated papillae lined by a single layer of basal cells, protrude upward into the bulla, and in some cases,

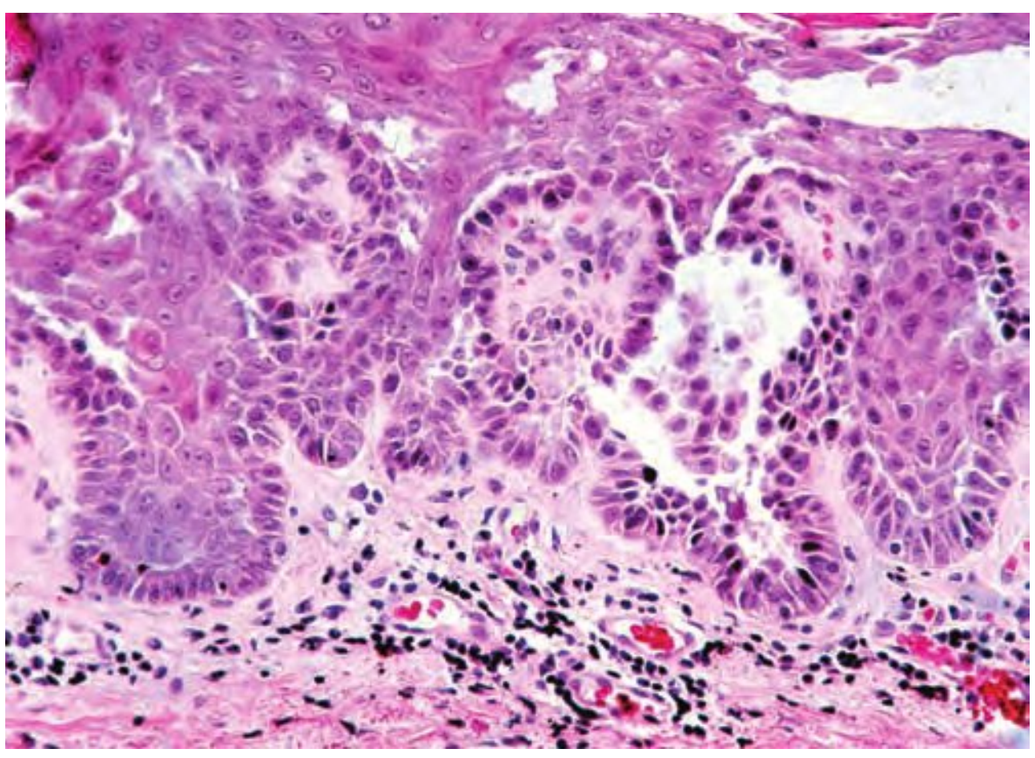


FIGURE 6-26. Familial benign pemphigus (Hailey-Hailey). The bulla is largely in a suprabasal position. The extensive loss of intercellular bridges with partial coherence of cells gives the detached epidermis the appearance of a dilapidated brick wall. On the right side within the granular layer, a corps rond can be seen (original magnification ×40).

narrow strands of epidermal cells proliferate downward into the dermis. Many cells of the detached stratum malpighii show loss of their intercellular bridges; thus, acantholysis affects large portions of the epidermis. Individual cells and groups of cells usually are seen in large numbers in the bulla cavity. Despite the extensive loss of intercellular bridges, the cells of the detached epidermis in many places show only slight separation from one another, because a few intact intercellular bridges still hold them loosely together. This quite typical feature gives the detached epidermis the appearance of a dilapidated brick wall.

Many of the cells of the stratum malpighii that have lost all or most of their intercellular bridges show a fairly normal cytoplasm and a normal nucleus in which mitotic activity has even been observed (207,208). Some of the acantholytic cells, however, have a homogenized cytoplasm, suggesting premature partial keratinization. In some instances, such acantholytic cells with premature keratinization resemble the grains of Darier's disease. Occasionally, a few corps ronds are present in the granular layer (207–209) (Fig. 6-26).

Differential Diagnosis. Histologically, familial benign pemphigus shares certain features with both Darier's disease and pemphigus vulgaris. In all three diseases, one finds predominantly suprabasal separation of the epidermis caused by acantholysis and resulting in lacunae or bullae and villi formation.

Differentiation of familial benign pemphigus from Darier's disease as a rule is not very difficult, because in Darier's disease, (a) the suprabasal separations usually are smaller, thus appearing as lacunae rather than as bullae; (b) acantholysis is less pronounced, being limited to the lower epidermis, especially the suprabasal region; and (c) dyskeratosis consisting of the formation of corps ronds and grains is much more evident.

Pemphigus vulgaris often resembles familial benign pemphigus to a striking degree, and in some specimens, histologic differentiation of these two diseases may be impossible. As a rule, however, there is less extensive acantholysis in pemphigus vulgaris, limited largely to the suprabasal region, so the detached epidermis appears normal and lacks the appearance of a dilapidated brick wall, and more severe degeneration of the acantholytic cells within and near the bulla cavity. The presence of eosinophils in the bulla points toward a diagnosis of pemphigus vulgaris, but their absence does not rule it out. In case of doubt, immunofluorescence will decide the issue.

There used to be much discussion as to whether familial benign pemphigus represents a vesicular variant of Darier's disease. Two points in favor of the basic unity of the two diseases were stressed: the alleged simultaneous presence of both diseases in the same patient and the occurrence of corps ronds in both diseases. However, it has become apparent that patients described as having both diseases were either cases of Darier's disease with vesicular lesions (210) or cases of familial benign pemphigus with the presence of corps ronds (211,212). Evidence against a relationship is also shown by the fact that in affected families, always only one of the two diseases occurs and the genetic basis of the two diseases has been elucidated and are clearly different though related—the ATP2C1 gene on chromosome 3q is mutated in Hailey-Hailey (202), while Darier's disease is due to a mutation in the the ATP2A2 gene on chromosome 12 (206).

KERATOSIS FOLLICULARIS (DARIER'S DISEASE)

Darier's disease is usually transmitted in an autosomal dominant pattern. It has been found to be due to mutations in the ATP2A2 gene on chromosome T2, which encodes the sarcoplasmic/endoplasmic reticulum calcium pumping ATPase SERCA2 (206). The gene is 12q23-24.1. In typical cases, there is a more or less extensive, persistent, slowly progressive eruption consisting of hyperkeratotic or crusted papules often showing a follicular distribution. By coalescence verrucous, crusted areas may form. The so-called seborrheic areas are the sites of predilection. The oral mucosa is involved occasionally (213). In some cases of Darier's disease, keratotic papules that resemble those seen in *acrokeratosis verruciformis of Hopf* are found on the dorsa of the hands and feet (214).

Special clinical variants of keratosis follicularis are a hypertrophic type, a vesiculobullous type, and a linear or zosteriform type. In the hypertrophic type, widespread, markedly thickened, and hyperkeratotic lesions are seen, especially in the intertriginous areas (215). In the vesiculobullous type, vesicles and small bullae are seen in addition to papules (216,217). In the linear or zosteriform type, usually limited to one side, there are either localized or widespread lesions that may be present at birth (218) but in most cases have arisen in infancy, childhood, or adult life (219). The question has been raised as to whether this type of lesion represents a linear epidermal nevus with acantholytic dyskeratosis rather than Darier's disease (218), and the designation *acantholytic dyskeratotic epidermal nevus* has been suggested (219). It is quite likely that some of the cases with scattered papular lesions of limited extent arising in adult life and diagnosed as acute, eruptive Darier's disease (220) or acute adult-onset Darier-like dermatosis in reality represented transient acantholytic dermatosis. A recent review on the clinical aspects of this condition has been written (221).

Histopathology. The characteristic changes in Darier's disease include the following: (a) a peculiar form of dyskeratosis resulting in the formation of corps ronds and grains; (b) suprabasal acantholysis leading to the formation of suprabasal clefts or lacunae; and (c) irregular upward proliferation into the lacunae of papillae lined with a single layer of basal cells, so-called villi (Fig. 6-27). There are also papillomatosis, acanthosis, and hyperkeratosis. The dermis shows a chronic inflammatory infiltrate. In some cases, there is downward proliferation of epidermal cells into the dermis.

The corps ronds occur in the upper stratum malpighii, particularly in the granular and horny layers; grains are found in the horny layer and as acantholytic cells within the lacunae. Corps ronds possess a central homogeneous, basophilic,

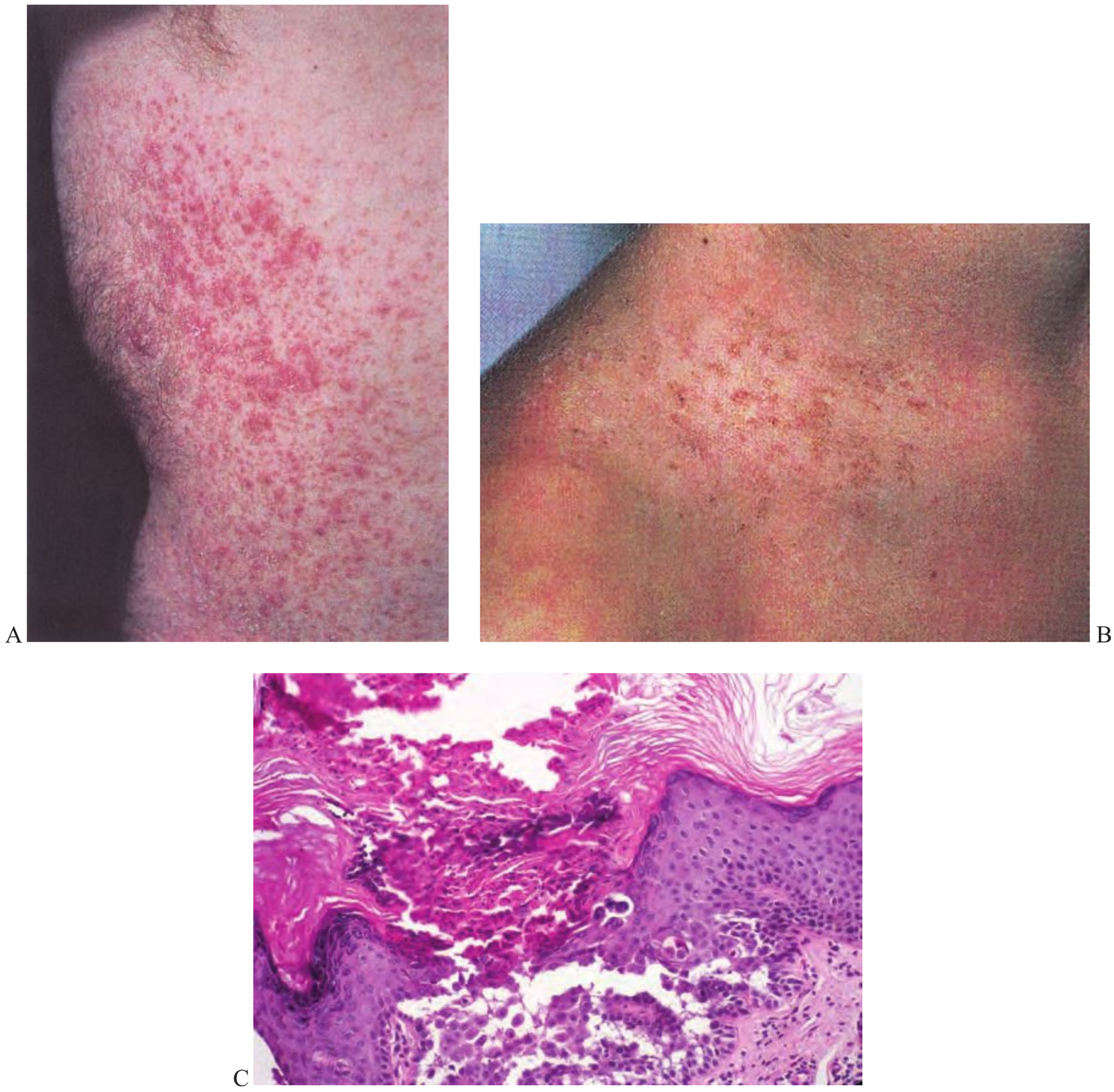


FIGURE 6-27. A: Darier's disease. Multiple tiny hyperkeratotic papules that coalesce into plaques present on the trunk. B: Crusted papules in a follicular distribution at the base of the neck and upper chest. C: Darier's disease, low magnification. Hyperkeratosis and papillomatosis are evident. Numerous lacunae are present. On the left are elongated papillae lined by a single layer of cells, so-called villi. Corps ronds are present in the granular layer, and grains are seen in the horny layer. The lacunae contain desquamated cells (original magnification ×100).

pyknotic nucleus that is surrounded by a clear halo. By virtue of size and the conspicuous halo, corps ronds stand out clearly (Fig. 6-28). Peripheral to the halo lies basophilic dyskeratotic material as a shell (222). The nonstaining halo in some instances is partially replaced by homogeneous, eosinophilic dyskeratotic material (223). Compared with the corps ronds, the grains are much less conspicuous. They resemble parakeratotic cells but are somewhat larger. The nuclei of grains are elongated and often grain shaped and are surrounded by homogeneous dyskeratotic material that usually stains basophilic but may stain eosinophilic. The lacunae represent small, slitlike intraepidermal vesicles most commonly located directly above the basal layer. They contain acantholytic cells and show premature partial keratinization. Because of shrinkage, some of them are elongated, and these then appear identical with the grains in the horny layer. The villi projecting into the lacunae may be quite tortuous, so on histologic examination, some of them appear in cross section as rounded dermal structures lined by a solitary row of basal cells (see Fig. 6-27).

Hyperkeratosis and papillomatosis may cause the formation of keratotic plugs, which often fill the pilosebaceous follicles but are found also outside of follicles. That Darier's disease is not exclusively a follicular disorder is also proved by the fact

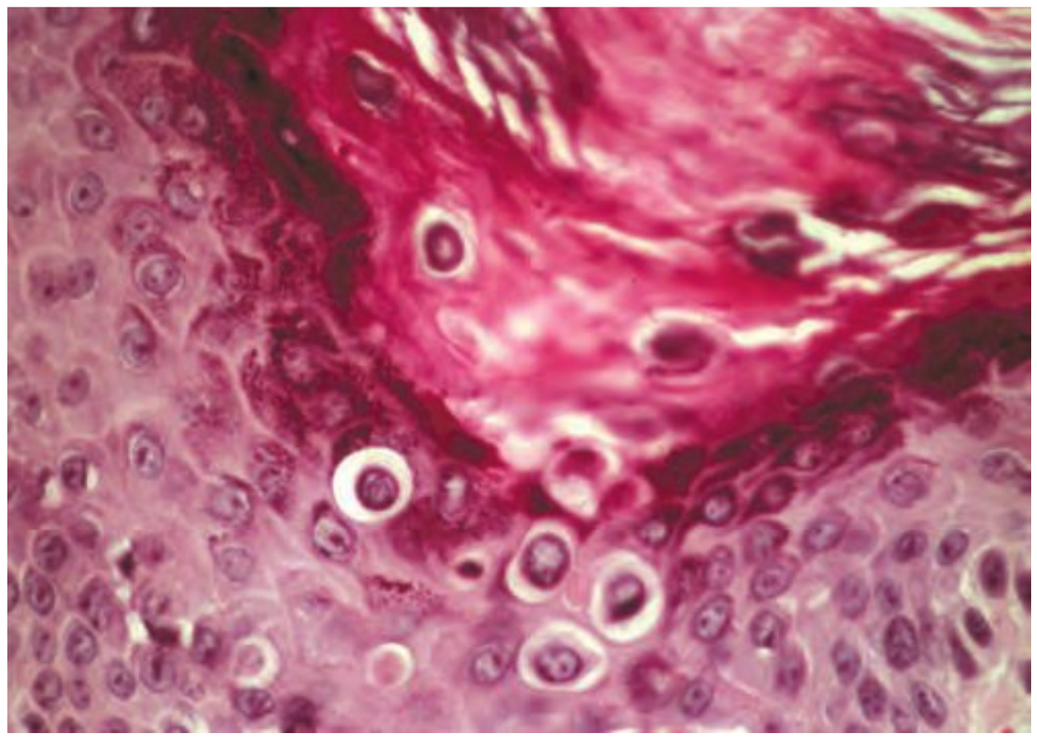


FIGURE 6-28. Darier's disease. Hyperkeratosis corps ronds are in the thickened stratum corneum and epidermis. Suprabasalar acantholysis is present (original magnification ×400).

that areas devoid of follicles, such as palms, soles, and the oral mucosa, may be affected.

In hypertrophic lesions of Darier's disease, considerable acanthosis may occasionally be observed, either as proliferations of basal cells or as pseudocarcinomatous hyperplasia. Proliferations of basal cells consist of long, narrow cords composed of two rows of basal cells separated by a narrow lacunar space (224).

The vesiculobullous lesions, which occur in rare instances, differ from lacunae merely in size; they contain numerous shrunken cells with the appearance of grains (216,217).

The keratotic papules that may occur on the dorsa of the hands and feet and that clinically resemble those seen in acrokeratosis verruciformis of Hopf in most instances, on serial sectioning, show mild dyskeratotic changes and often suprabasal clefts as well (214). They are a manifestation of Darier's disease and not of acrokeratosis verruciformis.

The lesions on the oral mucosa are analogous in appearance to those observed on the skin and thus show lacunae and dyskeratosis, although definite well-formed corps ronds generally are absent (225).

The occasional reports of patients having both Darier's disease and familial benign pemphigus or a transition from one of these two diseases to the other are discussed in the differential diagnosis of familial benign pemphigus.

Pathogenesis. Whereas histologically a distinction between Darier's disease and familial benign pemphigus is generally possible, with dyskeratosis being the predominating factor in Darier's disease and acantholysis in familial benign pemphigus, this distinction is not as clearly evident in electron microscopic examination. The reason for this is that for electron microscopy, only a small specimen can be processed, which in either of the two diseases shows predominantly acantholysis in some instances and dyskeratosis in others and only rarely shows both. In both diseases, however, acantholysis precedes dyskeratosis.

Acantholysis has been thought by some authors to be due to the loss of the intercellular contact layer within desmosomes, both in Darier's disease (226,227) and in familial benign pemphigus (228). The two halves of the desmosomes then pull apart, after which the tonofilaments become detached from them. Another group of authors believes that there is some basic defect in the tonofilament—desmosome complex in Darier's disease (223,229) and in familial benign pemphigus (230)—resulting in separating of tonofilaments from the attachment plaques of desmosomes and subsequently leading to the disappearance of desmosomes and thus to acantholysis. It is likely that both processes take place simultaneously in both Darier's disease (222) and familial benign pemphigus (231).

The cause for the acantholysis in Darier's disease and familial benign pemphigus is not yet definitely known. Faulty synthesis of the intercellular substance has long been suspected. It seems likely that mutations underlying Darier's disease and Hailey-Hailey disease would affect structural components but both disorders mapped to chromosome regions devoid of any known candidate gene. Furthur studies have suggested that intercellular communication is crucial for epidermal differentiation. This was corroborated when mutations found in ATP2A2 caused Darier's disease and disclosed a role for the SERCA2 pump in the calcium signaling pathway that regulates cell to cell adhesion and differentiation of the epidermis (232).

In association with the loss of desmosomes, excessive amounts of tonofilaments form within the keratinocytes around the nucleus as thick, electron-dense bundles. A defect of the tonofilaments would best explain the dyskeratotic features of both Darier's disease and familial benign pemphigus. In Darier's disease, in which the dyskeratosis is much more pronounced than in familial benign pemphigus, thick bundles of tonofilaments, often in association with large keratohyaline granules, form large aggregates of homogenized dyskeratotic material. The corps ronds, on electron microscopic examination, are characterized by extensive cytoplasmic vacuolization (233). They show in their center an irregularly shaped nucleus surrounded by a halo of autolyzed electron-lucid cytoplasm and at their periphery a shell of tonofilaments (EM 16) (222,226). On electron microscopic examination, the grains are seen to consist of nuclear remnants surrounded by dyskeratotic bundles of tonofilaments.

In familial benign pemphigus, too, after loss of the desmosomes, excessive amounts of tonofilaments form within the keratinocytes and aggregate around the nucleus as thick, electron-dense bundles, often in a whorling configuration; however, even though dyskeratosis is present, it is less pronounced than in Darier's disease, and most of the keratinocytes keratinize normally, with only very few becoming grains or corps ronds as the result of dyskeratotic degeneration.

On intralesional injection of tritiated thymidine, one group (234) observed labeling of many acantholytic keratinocytes in familial benign pemphigus but not in Darier's disease, suggesting that in familial benign pemphigus, the epidermal cells participated in the renewal of the epidermis but

did not do so in Darier's disease, probably because these cells were undergoing keratinization. However, another group (235) could not confirm this observation.

Differential Diagnosis. Although acantholytic dyskeratosis in association with corps ronds is highly characteristic of Darier's disease, it occurs also in several other conditions (229): in warty dyskeratoma, a solitary lesion with a deep central invagination; in transient or persistent acantholytic dermatosis, in which the lesions consist of discrete papules; in focal acantholytic dyskeratoma, manifesting itself as a solitary papule; and as an incidental small focus in a variety of unrelated lesions. Occasionally, a few corps ronds are seen also in familial benign pemphigus (see preceding text).

ACROKERATOSIS VERRUCIFORMIS OF HOPF

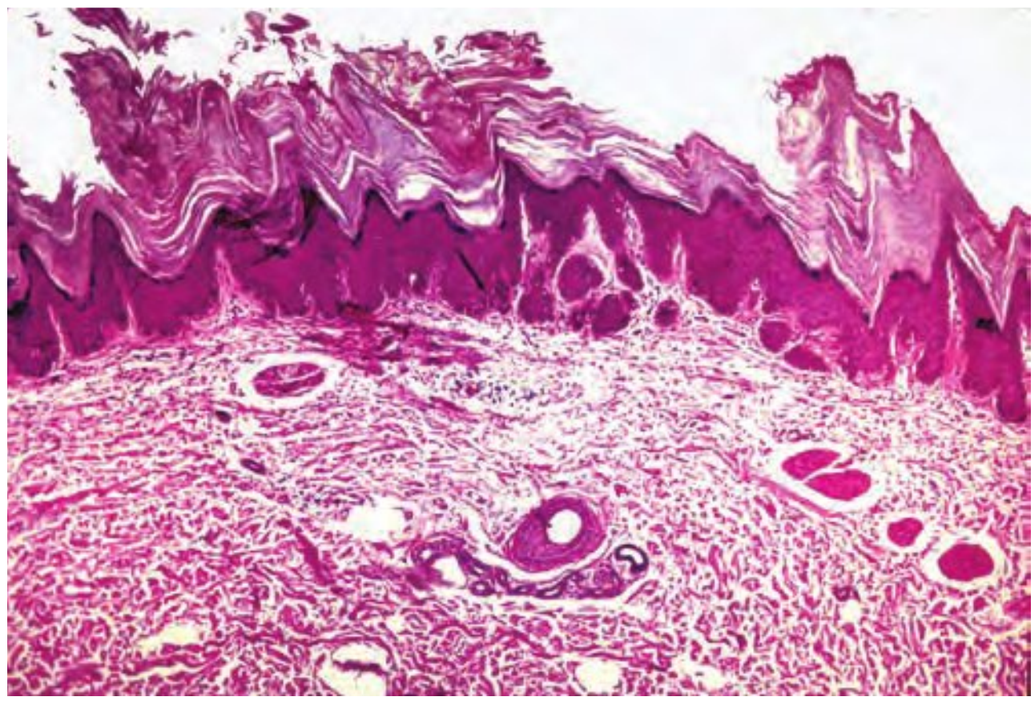
In acrokeratosis verruciformis, an autosomal dominant disorder, numerous flat, hyperkeratotic, occasionally verrucous papules are present on the distal part of the extremities, predominantly on the dorsa of the hands (Fig. 6-29A) and feet (236).

Histopathology. The papules show considerable hyperkeratosis, an increase in thickness of the granular layer, and acanthosis. In addition, there is slight papillomatosis, which is frequently but not always associated with circumscribed elevations of the epidermis resembling church spires (237,238) (Fig. 6-29B). The rete ridges are slightly elongated and extend to a uniform level.

Histogenesis. A possible relationship between acrokeratosis verruciformis and Darier's disease has been repeatedly discussed. On the one hand, there is no question that acrokeratosis verruciformis usually occurs as an independent entity, often in several family members (239) and occasionally even in many family members (240) but also as a solitary incidence (238). On the other hand, a relationship to Darier's disease is suggested by several observations: (a) patients with Darier's disease not infrequently show lesions that are indistinguishable from acrokeratosis verruciformis both clinically and histologically (237,241); (b) some of the lesions of presumed acrokeratosis verruciformis occurring in patients with Darier's disease show dyskeratosis and lacunae as seen in Darier's disease, whereas others do not; and (c) patients with apparent histologic lesions of acrokeratosis verruciformis may later develop histologic lesions of Darier's disease. Admittedly, there can be considerable clinical resemblance between the acral lesions of both diseases, but if multiple specimens for biopsy are taken and serial sections carried out, clear histologic evidence of Darier's disease is obtained only in those patients who have Darier's disease (249). It seems that there is only one instance in which both diseases were seen in different members of the same family (242), and this may well have been coincidence. Rather than taking the view that the two diseases result from a single dominant defect with variable expressivity (242), it is best to regard acrokeratosis verruciformis as an independent entity.



A



B

FIGURE 6-29. A: Acrokeratosis verruciformis of Hopf. B: A well-circumscribed lesion shows hyperkeratosis and papillomatosis. The latter is associated with elevations of the epidermis resembling church spires (original magnification ×100).

Differential Diagnosis. Although elevations of the epidermis with the configuration of church spires are quite typical of acrokeratosis verruciformis, they may be absent and are not specific for that disease. Particularly, they are present in the hyperkeratotic type of seborrheic keratosis. Even though seborrheic keratoses usually are larger than the lesions of acrokeratosis verruciformis, clinical data may be necessary for the differentiation of these two conditions. Also, acrokeratosis verruciformis may resemble verrucae clinically, but it differs from verruca plana by the absence of vacuolization in the cells of the upper epidermis and from verruca vulgaris by the absence of parakeratosis.

PSEUDOXANTHOMA ELASTICUM

In this disorder, genetically abnormal elastic fibers with a tendency toward calcification occur in the skin and frequently also in the retina and within the walls of arteries, particularly the gastric mucosal arteries, coronary arteries, and large peripheral

arteries. The inheritance is usually autosomal recessive but is occasionally autosomal dominant. It seems that two recessive and two dominant forms exist. Struk predicted that allelic heterogeneity with different variants of a single disease gene residing on 16p13.1 accounts for both recessive and dominant forms of pseudoxanthoma elasticum, and subsequent work by Ringpfeil and Struk have documented that mutations in the ABC-C6 gene are responsible for cases of pseudoxanthoma elasticum (243,244). The classic disorder in this classification is recessive type 1. In the dominant type 1, the cutaneous and internal manifestations are more severe than in recessive type 1, whereas in dominant type 2 they are less severe. The very rare recessive type 2 shows only cutaneous involvement, which, however, is extensive (245). The accuracy of the Pope classification has been disputed, leading to a new classification (246).

The cutaneous lesions usually appear first in the second or third decade of life and are generally progressive in extent and severity. They consist of soft, yellowish, coalescing papules, and the affected skin appears loose and wrinkled. The sides of the neck, the axillae, and the groin are the most common sites of lesions (Fig. 6-30). In the eyes, so-called angioid streaks of the fundi may cause progressive impairment of vision. Involvement of the arteries of the gastric mucosa may lead to gastric hemorrhage; involvement of coronary arteries may result in attacks of angina pectoris, although myocardial infarction is rare; and involvement of the large peripheral arteries may cause intermittent claudication (247). Radiologic examination in such cases reveals extensive calcification of the affected peripheral arteries (248).

In rare instances, the coexistence of pseudoxanthoma elasticum with elastosis perforans serpiginosa has been reported, with perforation and transepidermal elimination present only in the lesions of elastosis perforans serpiginosa (249). Calcific elastosis, which has been referred to also as *perforating pseudoxanthoma elasticum* or *localized acquired pseudoxanthoma elasticum*, is not related to pseudoxanthoma elasticum. The absence of skin lesions should not be used to exclude pseudoxanthoma elasticum in patients with an inherited predisposition and suspicious manifestations, such as angioid streaks or gastric bleeding. In these patients, biopsies of scars or of flexural skin may show the characteristic changes of pseudoxanthoma elasticum in the deep dermis (246).



FIGURE 6-30. Pseudoxanthoma elasticum. Yellow coalescing papules at the side of neck.

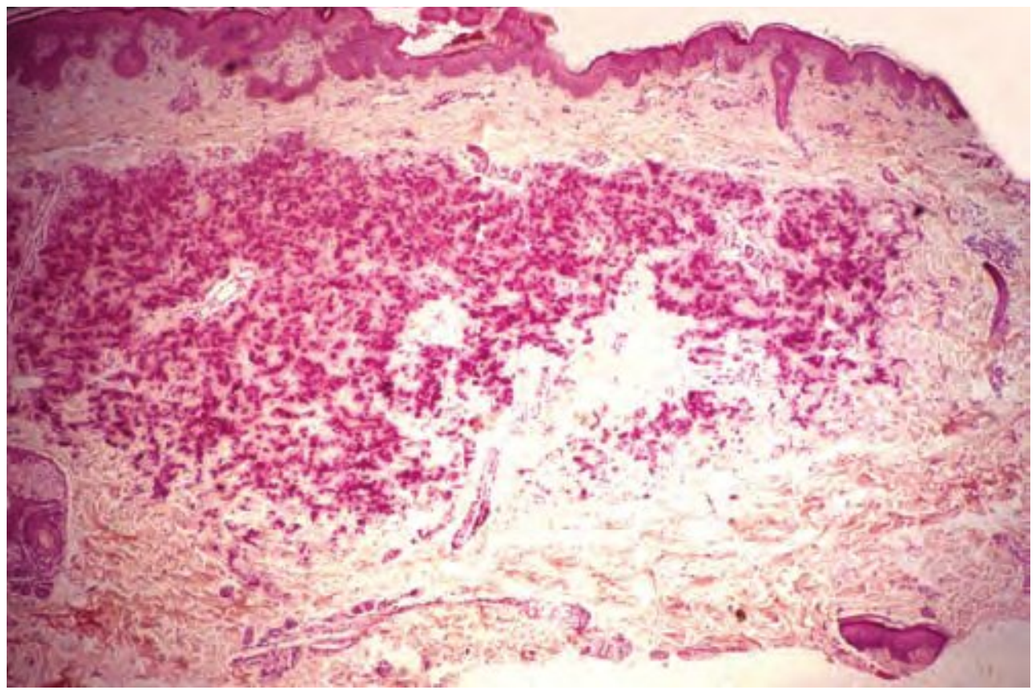


FIGURE 6-31. Pseudoxanthoma elasticum. Low magnification, H&E stained tissue showing calcified altered elastic fibers in the midreticular dermis (original magnification ×100).

Histopathology. Histologic examination of the involved skin reveals considerable accumulations of swollen and irregularly clumped fibers staining like elastic fibers in the middle and lower thirds of the dermis; that is, they stain deeply black with orcein or Verhoeff's stain (Figs. 6-31 and 6-32). Although normally elastic fibers do not stain with routine stains such as hematoxylin-eosin, the altered elastic fibers in pseudoxanthoma elasticum stain faintly basophilic because of their calcium imbibition. Staining for calcium with the von Kossa method also shows these fibers well.

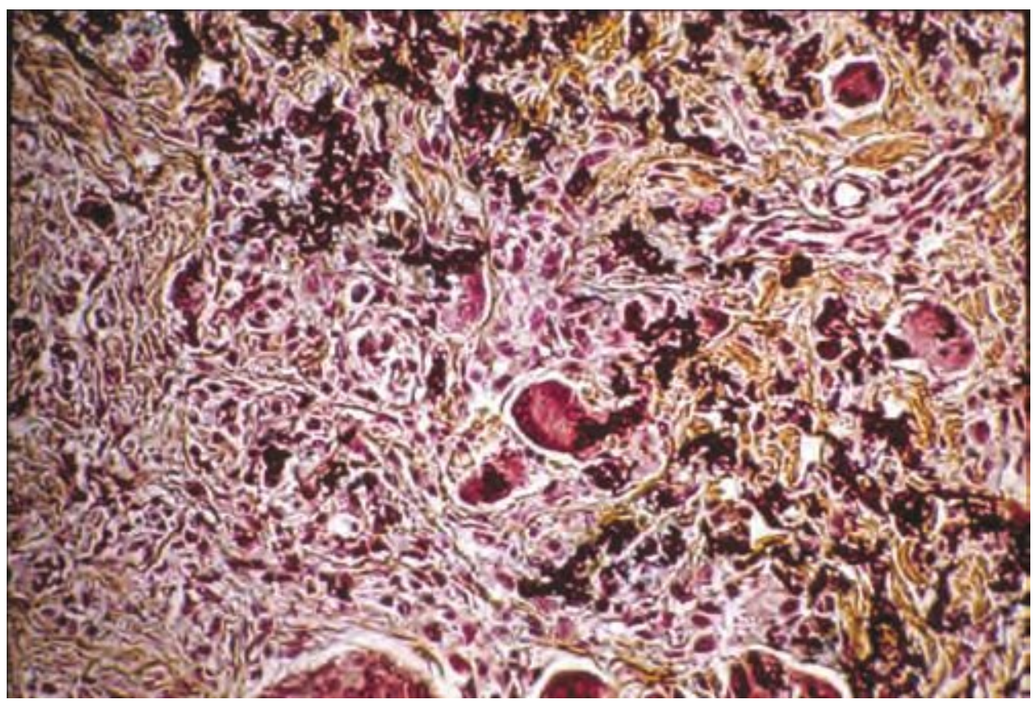


FIGURE 6-32. Pseudoxanthoma elasticum, high magnification, elastic tissue stain. The elastic fibers show marked degeneration (original magnification ×100).

In the vicinity of the altered elastic fibers, there may be accumulations of a slightly basophilic mucoid material, which stains strongly positive with the colloidal iron reaction or with Alcian blue (250). The number of collagen bundles is reduced in such areas, and numerous reticulum fibers are seen on impregnation with silver (251). In some cases with pronounced elastic tissue calcification, a macrophage and giant cell reaction may be present (252).

The angioid streaks occur in Bruch's membrane, which is located between the retina and the choroid and possesses numerous elastic fibers in its outer portion, the lamina elastica. Calcification of these fibers causes fissures to form in the lamina elastica. These fissures result in repeated hemorrhages and exudates, which in turn cause degenerative changes in the retina consisting of scar formation and pigment shifting (252,253).

Gastric bleeding is the result of calcification of elastic fibers in the thin-walled arteries located immediately beneath the gastric mucosa. The internal elastic lamina is particularly affected. In muscular arteries, such as the coronary arteries and the large peripheral arteries, calcification begins in the internal and external elastic laminae, leading to their fragmentation, and subsequently extends to the media and intima (247). Calcification of the elastic fibers in the endocardium is a common occurrence but is clinically silent (254).

Histogenesis. Electron microscopic examination shows that the calcification occurs in normal-appearing elastic fibers (251,254–257). In some patients, especially in young persons, only some of the elastic fibers in the lower dermis are calcified, and the calcification is variable in degree. However, in adult patients, most elastic fibers show considerable calcification and, as a result, degeneration. Early calcification of elastic fibers consists either of diffuse granular deposits throughout the elastic fiber or of dense aggregates that may be located in the center or near the margin of the fiber (EM 5). With progression of the calcification, the elastic fibers ultimately become fully calcified, showing marked swelling and bizarre distortions. In addition, heavy calcium deposits may be seen in the ground substance adjacent to elastic fibers and free in the ground substance. The presence of calcified material outside of elastic fibers can be explained by the disintegration of completely calcified elastic fibers (257).

Besides varying numbers of normal collagen fibrils, irregularly twisted collagen fibrils and granulofilamentous aggregates are present. It appears unlikely that the process of calcification begins in the granulofilamentous material, as maintained by some authors who regard this material as an abnormal precursor of elastic fibers (256,258). It is probable that this misinterpretation has resulted from the examination of advanced lesions containing disintegrated calcified elastic fibers within the granulofilamentous material (254). In favor of a primary location of the calcification within elastic fibers is the important observation that in decalcified sections of endocardial lesions, the internal structure of the calcified segments of elastic fibers is very similar to that of the adjacent noncalcified segments.

Differential Diagnosis. Solar elastosis, like pseudoxanthoma elasticum, shows abnormal elastic tissue. However, in solar elastosis, this material is located in the upper third of the dermis and is present as dense masses rather than as individual altered fibers. Furthermore, these dense masses always show negative staining for calcium. If associated with a perforation, calcific elastosis is easily distinguished from pseudoxanthoma elasticum. In the absence of a perforation, the two are indistinguishable, and clinical data are necessary for differentiation.

CONNECTIVE TISSUE NEVUS

The connective tissue nevus represents a hamartoma in which the amount of collagen is increased, but the amount of elastic tissue may be increased, normal, or decreased. The lesions consist of slightly elevated, slightly indurated nodules that may be grouped together in one or several plaques or may be widely disseminated (Fig. 6-33). A connective tissue nevus can occur without alterations in other organs and without being genetically determined (259); occur without alterations in other organs, being inherited as an autosomal dominant trait (260); or occur with osteopoikilosis, being inherited in an autosomal dominant pattern (261). The shagreen patches of tuberous sclerosis do not strictly belong in the category of connective tissue nevi, since they always consist only of excessive amounts of collagen and thus are "collagen nevi" rather than connective tissue nevi (262).

Connective tissue nevi associated with osteopoikilosis are also referred to as *Buschke-Ollendorff syndrome,* because these authors first recognized the frequent simultaneous occurrence of these two types of lesions. The skin lesions in this syndrome consist of firm, pale papules and plaques in asymmetric distribution with a tendency to grouping (261,263). Individual members of affected families may have skin lesions without bone lesions and vice versa. The bone lesions of osteopoikilosis are asymptomatic and on x-ray examination consist of round or oval densities 2 to 10 mm in diameter in the long bones and in the bones of the hands, feet, and pelvis.

Histopathology. A clear separation of collagenoma and elastoma is not always possible, because in many instances both



FIGURE 6-33. Connective tissue nevus. Grouped slightly raised nodules producing an irregular surface on the lower posterior chest.

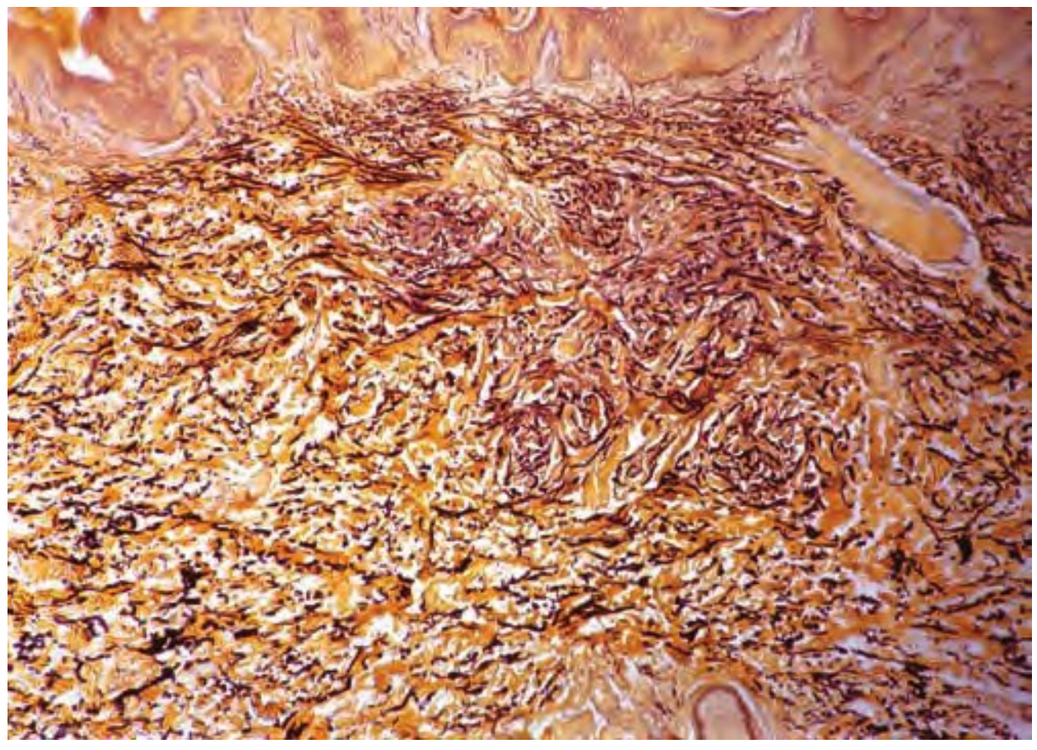


FIGURE 6-34. Connective tissue nevus. The elastic fibers are markedly increased in number and size without showing signs of degeneration (original magnification ×100).

collagenous and elastic fibers are increased, as indicated by the fact that most lesions of connective tissue nevus feel firm to the touch. The increase in the amount of collagen may be difficult to ascertain if the collagen bundles are normal in appearance. In some lesions of collagenoma (260) and lesions of the connective tissue nevus–osteopoikilosis syndrome (263), the collagen bundles are thickened and homogenized.

Most cases of the connective tissue nevus–osteopoikilosis syndrome clearly show a marked increase in the amount of elastic fibers, which are present as broad, interfacing bands, without showing signs of degeneration (264,265) (Fig. 6-34).

Pathogenesis. On electron microscopic examination, connective tissue nevi show a variable picture. In some cases, the elastic fibers appear thick and are surrounded by a thready material (259). In the Buschke-Ollendorff syndrome (266), the elastic fibers lack their microfibrillar component, so only electron-lucent elastin is present (267).

Differential Diagnosis. Pseudoxanthoma elasticum is the major differential disease. The connective tissue nevus does not show elastic tissue fragmentation and calcification as does pseudoxanthoma elasticum.

LINEAR MELORHEOSTOTIC SCLERODERMA

Melorheostosis is characterized by linear hyperostosis of an extremity. It may be associated with thickening and hypertrichosis of the overlying skin. Although not familial, its start in infancy suggests a congenital disorder (268).

Histopathology. The skin shows thickening of the dermis caused by the extension of normal-appearing collagen and elastic tissue in strands and lobules into the subcutaneous fat (269).

Pathogenesis. Hyperplasia of the skin is related to the underlying cortical hyperostosis. The normal appearance of the thickened dermis indicates that the process does not represent localized scleroderma (269).

WINCHESTER SYNDROME

A rare autosomal recessive disorder described only in the offspring of consanguinous parents, Winchester syndrome is characterized by dwarfism, small-joint destruction, corneal opacities, thickening and hypertrichosis of the skin, and hypertrophic lips and gingivae and is related to mutations in the matrix metalloproteinase 2 gene (270,271). The condition is related to nodulosis-arthropathy-osteolysis (NAO) syndrome, which is allelic with Winchester syndrome.

Histopathology. In the early stage, the skin shows proliferation of fibroblasts in the lower portions of the dermis with extension into the subcutaneous tissue. At a later stage, the collagen appears homogenized and contains only few fibroblasts. Some areas may show an increase in both the number of fibroblasts and the density of the collagen bundles (272).

Pathogenesis. Abnormal functioning of the fibroblasts is the likely cause for all manifestations. Electron microscopic examination has shown dilated and vacuolated mitochondria in the fibroblasts (271).

EHLERS-DANLOS SYNDROME

Ehlers-Danlos (E-D) syndrome (EDS) has been divided into more than 10 types on the basis of clinical, genetic, and biochemical information (273). The common clinical features are hyperextensibility of the skin; fragility of the skin with impaired wound healing, resulting in the formation of atrophic scars; and hypermobility of the joints, which may lead to dislocations (Fig. 6-35). Occasionally, raisin-like pseudotumors that are raised and soft and have a wrinkled



FIGURE 6-35. Ehlers-Danlos syndrome. Hyperelasticity of the skin.

surface are observed at sites of traumatic hematomas. In some cases, firm, spheroid subcutaneous nodules form at sites of traumatic fat necrosis.

E-D types I, II, and III, the most common forms of this syndrome, are inherited in an autosomal dominant pattern and are distinguished by the extent and severity of the symptoms, type I being the gravis type, type II the mitis form, and type III the benign hypermobile type. No biochemical defect has been detected. Absence of the inferior labial frenulum and the lingual frenulum has recently been described in EDS II and EDS III (274). EDS I and II are allelic with mutations in pro-alpha-1 (V) collagen chains (COL5A1) causing both types (275). Type II EDS can also be caused by a missense mutation in the COL5A2 gene (276). Mutations in more than one gene can lead to type III phenotype (277).

E-D type IV, the arterial form, is inherited as an autosomal dominant or recessive trait. The skin of persons with this disorder is thin and fragile. Ecchymoses are very common. Patients rarely live beyond the second decade of life because of ruptures of large arteries or of the gastrointestinal tract (278). This tendency toward rupture is explained by the fact that there is a deficiency of type III collagen (COL3A1 gene) in the skin and in other tissues. Even though cultured fibroblasts are capable of normal synthesis of collagen type III, they show poor secretion of it into the medium (279).

E-D type V has an X-linked recessive inheritance pattern and clinical features similar to those of type I. The fibroblasts produce only 15% to 30% of the normal amount of lysyl oxidase. This deficiency results in deficient intramolecular cross-linking in the collagen molecule (282). An abnormality in the expression of COL5A1 may be the issue here (280).

E-D type VI, the ocular type, with autosomal recessive inheritance, is characterized by severe scoliosis and intraocular bleeding. There is a deficiency in lysyl hydroxylase in this form of the disorder. The gene for this enzyme maps to 1p36.3. p36.2 (277).

E-D type VII, the arthrochalasis type, also with autosomal dominant or recessive inheritance, shows marked looseness of joints resulting in multiple joint dislocations. The skin and tendons of patients with this form of E-D contain collagen polypeptides with a length intermediate between pro-alpha (procollagen) chains and alpha (collagen) chains. This is due to a structural mutation in the pro-alpha 2 chain that prevents the normal enzymatic removal of the aminopropeptide from it (281). A mutation at one of at least two loci COL1A1 and COL1A2 can produce this autosomal dominant phenotype (280). The autosomal recessive subtype may be due to mutations in the ADMTS2 gene (282).

E-D type VIII, the periodontal type, inherited as an autosomal dominant trait, is characterized by severe periodontitis and moderate skin fragility. Its biochemical defect is thought to be due to decreased production of type III collagen.

E-D type IX, the occipital horn syndrome (X-linked cutis laxa), with X-linked recessive inheritance, shows moderate skin extensibility, joint hypermobility, bladder diverticula, herniae, and rhizomelic limb shortening. The defect is due to abnormal copper metabolism caused by a mutation in the Cu^{++} transporting ATPase alpha peptide and a decrease in lysyl oxidase. This disorder may be allelic with Menkes' syndrome (283).

E-D type X, the fibronectin type, with autosomal recessive inheritance, shows stria, moderate skin extensibility, joint hypermobility, and a platelet aggregation defect caused by dysfunction of the plasma fibronectin (284) gene map locus 2q34.

Histopathology. Except for areas of the skin that have been altered secondarily by trauma, most patients with types I to III show no abnormalities either in the thickness of the skin or in the appearance of the collagen or of the elastic fibers. Only an exceptional patient shows thin collagen fibers that are not united to collagen bundles. In these cases, the skin may also be reduced in thickness and show a relative increase in amount of elastic fibers. These changes are more pronounced in the type I (gravis) than in the types II and III and are more evident when a large excision biopsy is carried out rather than a punch biopsy. They are often seen best in the collagen bundles of the connective tissue septae of the hypodermis, with the collagen bundles appearing thin and rare (285).

E-D type IV shows the most pronounced degree of dermal thinning of all types, usually to half or three quarters of normal thickness. There is a relative abundance of elastic fibers that appear shortened and fragmented. This probably is secondary to changes in collagen fiber morphology (286).

The raisin-like pseudotumors that arise at the site of hematomas show fibrosis and numerous capillaries; they may also show accumulations of foreign body giant cells (287). The spheroid subcutaneous nodules consist of partially necrotic adipose tissue that may contain areas of dystrophic calcification and that is surrounded by a thick layer of dense collagen (288).

Histogenesis. The enzyme deficiencies observed in the various types of the EDS suggest a disturbance in collagen biosynthesis. In several electron microscopic studies, no abnormalities were observed in the normal skin of patients with EDS (289,290); however, other studies have reported abnormalities. In a study comparing healing experimental wounds in a patient with EDS with those in normal persons, the fibroblasts of the patient with EDS showed a paucity of rough-surfaced endoplasmic reticulum, and the bundles of collagen appeared small and sparse (291). Similar abnormalities were observed also in the normal-appearing skin of five patients with various types of EDS. The fibroblasts were smaller than in the skin of normal control persons, the endoplasmic reticulum was underdeveloped, and ribosome content was diminished. In addition, some collagen fibrils possessed an irregular outline, and lateral aggregation of the fibrils into bundles was reduced (291,292). Scanning electron microscopic examination in various types of EDS has revealed thinner collagen bundles than normal and, within the bundles, gross disorganization of the collagen fibers (290). Scanning electron microscopy has shown that the hyperextensibility in EDS is due to defective "wicker work" of the collagen fiber bundles.

CUTIS LAXA (ELASTOLYSIS)

Cutis laxa, also called *dermatochalasis* and *generalized elastolysis*, is characterized by loose, pendulous skin resulting in a prematurely aged appearance (Fig. 6-36). There are two types: congenital occipital horn syndrome (see page 156, type IX EDS) and acquired. In the congenital type, the usual mode of inheritance is autosomal recessive (293), although autosomal dominant transmission due to a mutation in the elastin gene has been described in a few relatively mild cases (294). The occipital horn syndrome is X-linked (293). The acquired type has no genetic background (295).

In both the congenital and acquired types, internal organs are frequently involved. There may be pulmonary emphysema causing death in infancy in some of the congenital cases (293,296) or later in life in some of the acquired cases (295). The congenital form may show wormian bones of the lambdiodal suture and osteoporosis. The deficiency in lysyl oxidase is due to a mutation on the encoding gene located on chromosome 5q (297). In addition, there may be diverticula in the gastrointestinal tract or in the bladder. Also, rectal prolapse and inguinal, umbilical, and hiatal hernias have been observed (293). About half of the cases of acquired cutis laxa are preceded or accompanied by a cutaneous eruption showing urticaria (298), erythematous plaques (299), or a vesicular eruption (300). The occipital horn syndrome is discussed in the section on EDS and should be categorized as a disorder of copper metabolism.

Histopathology. In cases without an inflammatory infiltrate, the changes are limited to the elastic fibers and depend on the stage and the severity of the disease. In the early stage, the elastic fibers are diminished either throughout the dermis or largely in the upper dermis or the lower dermis (301). Those elastic fibers that are present may be considerably thickened in their midportion and may taper to a point at either end. Their borders may be indistinct, and they may stain unevenly, showing a granular appearance (Fig. 6-37). Ultimately, no intact elastic fibers may be identifiable. Instead, fine, dustlike orceinophilic granules may be scattered in the dermis.



FIGURE 6-36. Cutis laxa. Child with pendulous skin.

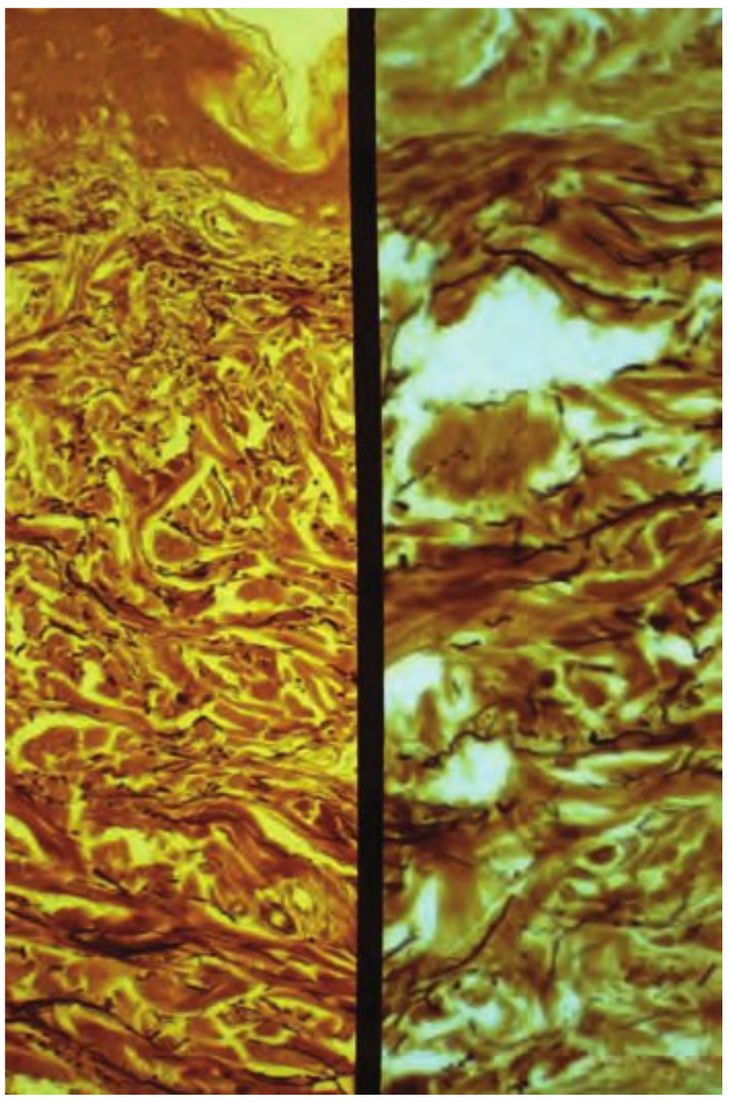


FIGURE 6-37. Cutis laxa, elastic tissue stain. The degenerated elastic fibers stain unevenly, resulting in a granular appearance and indistinct border. (Split views 100×/4,000×.)

In cases in which an inflammatory infiltrate is present, it may consist of a nonspecific chronic inflammatory infiltrate of lymphocytes and histiocytes. However, it may also contain neutrophils. If vesicles are present, they are subepidermal in location and may show papillary microabscesses composed of neutrophils and eosinophils suggestive of dermatitis herpetiformis.

In patients with involvement of internal organs, the lungs and gastrointestinal tract show the same granular changes in the elastic fibers as seen in the skin.

Histogenesis. Electron microscopic examination shows degenerative changes in the elastic fibers that vary somewhat from case to case. In some instances, the elastic fibers show normal microfibrils but a deficiency of the amorphous, electron-lucent elastin (296,302); in other instances, the elastin is preserved and the microfibrils are absent. In most electron microscopic examinations, the most significant finding is the presence of electron-dense amorphous or granular aggregates in the vicinity of the elastic fibers (303). The presence of this electron-dense material outside of elastic fibers suggests that instead of a primary elastolysis, as generally assumed, a defect in the synthesis of elastic fibers causes the disease (296,299).

Another controversy concerns the role of the cutaneous eruption that precedes or accompanies many of the reported cases of acquired cutis laxa. The traditional view has been that the inflammatory infiltrate is in some way responsible for the damage to the elastic fibers (304). However, in one reported case, sequential biopsies seemed to indicate that the changes in the elastic fibers induced the inflammatory infiltrate, and the

possibility therefore exists that the inflammatory infiltrate is a consequence of changes in the fibers.

PACHYDERMOPERIOSTOSIS

An idiopathic and an acquired form of pachydermoperiostosis exist, the latter being secondary to carcinoma of the lung. The idiopathic form is transmitted as an autosomal dominant trait, with males being more severely affected than females (305). The manifestations include (a) clubbing of the digits, with periosteal proliferation of the bones of the hands and feet; (b) hyperplasia of the soft parts of the forearms and legs, with periosteal proliferation of the corresponding bones; and (c) thickening and furrowing of the skin of the face and scalp (cutis verticis gyrata). In abortive forms, there may be only clubbing of the fingers with periosteal proliferation of the bones of the hands and forearms (306).

Histopathology. The skin of the face shows thickening of the dermis, with thick fibrous bands extending into the subcutaneous tissue (307). In addition to an increase in the amount and size of the collagen bundles in the dermis, there is an increase in the number of fibroblasts and in the amount of ground substance. The latter stains with colloidal iron, and because it is composed largely of hyaluronic acid, it stains with Alcian blue at pH 2.5 but not at pH 0.45.

URTICARIA PIGMENTOSA (MASTOCYTOSIS)

Urticaria pigmentosa, although occasionally showing an autosomal dominant mode of transmission (308,309) with a possible relationship to mutations in the KIT gene (310), in most instances occurs without a family history. It can be divided into four forms: (a) urticaria pigmentosa arising in infancy or early childhood without significant systemic lesions (311), (b) urticaria pigmentosa arising in adolescence or adult life without significant systemic lesions (312), (c) systemic mast cell disease, and (d) mast cell leukemia.

In the first form, the cutaneous lesions often improve or even clear at puberty (313). Systemic lesions are absent as a rule and if present usually are few in number. Progression into systemic mast cell disease is very rare (see later). In the second form, urticaria pigmentosa arising in adolescence or adult life, systemic lesions are often present but as a rule are rather static in their course (314,315). However, spontaneous regression has never been documented in adults, in contrast to children (316). In only a few patients is there progression to the third form, systemic mast cell disease, which shows extensive and progressive involvement of internal organs (see section on systemic lesions). The fourth form, mast cell leukemia, is very rare. It is characterized by the presence of cytologically malignant mast cells in many organs of the body, especially in the bone marrow and the peripheral blood, and is a rapidly fatal disease (327). Usually, there are no skin lesions (317).

Patients with extensive mast cell infiltration of the skin or the internal organs commonly have attacks of flushing, palpitation, or diarrhea as a result of degranulation of mast cells and the release of histamine.

Five types of cutaneous lesions are seen in urticaria pigmentosa (313). Two types can occur in both the infantile and the adult forms. First is the maculopapular type, the most common type, consisting usually of dozens or even hundreds of brown lesions that urticate on stroking (Fig. 6-38A); the second type exhibits multiple brown nodules or plaques and on stroking shows urtication and occasionally blister formation (Fig. 6-38B). The third type, seen almost exclusively in infants, is characterized by a usually solitary, large cutaneous nodule, which on stroking often shows not only urtication but also large bullae. In rare instances, solitary nodules have been described as arising in adults without giving rise to bullae (318). The fourth type, the diffuse erythrodermic type, always starts in early infancy and shows generalized brownish red, soft infiltration of the skin, with urtication on stroking. Multiple blisters may form during the first 2 years of life on stroking and also spontaneously. If bullae are a predominant clinical feature, the term *bullous mastocytosis* has been applied (319,320). Although visceral lesions are common in the diffuse erythrodermic type,



A



B

FIGURE 6-38. A: Urticaria pigmentosa. Multiple papular lesions of urticaria pigmentosa. B: Blister formation.

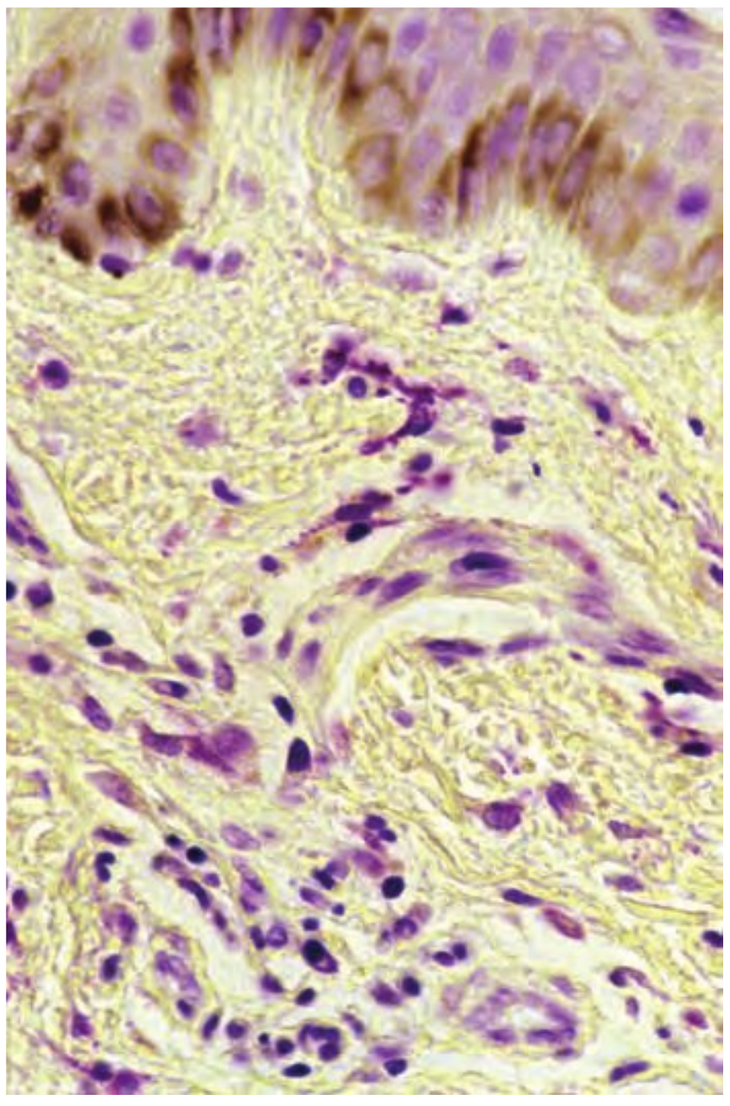


FIGURE 6-39. Urticaria pigmentosa, maculopapular (adult type). Scattered mast cells are seen, some cuboidal in shape. The greatest numbers are about dermal vessels. The epidermis is hyperpigmented (original magnification ×100).

they usually improve and only very rarely progress to fatal systemic mast cell disease. On rare occasions, death occurs in early infancy, apparently as a result of histamine shock with no or with only insignificant mast cell infiltration of visceral organs (321). The fifth type of lesion, telangiectasia macularis eruptiva perstans, which usually occurs in adults, consists of an extensive eruption of brownish red macules showing fine telangiectasias, with little or no urtication on stroking (322).

Histopathology. In all five types of lesions, the histologic picture shows an infiltrate composed chiefly of mast cells, which are characterized by the presence of metachromatic granules in their cytoplasm. These granules are not visible with routine stains but can be seen well after staining with a Giemsa stain or with toluidine blue. Also, the method using naphthol AS-D chloroacetate esterase, often called *Leder's method,* makes mast cell granules appear red and thus quite conspicuous (323).

In the maculopapular type and in telangiectasia macularis eruptiva perstans, the mast cells are limited to the upper third of the dermis and are generally located around capillaries. In some mast cells, the nuclei may be round or oval, but in most mast cells, they are spindle shaped (Fig. 6-39). Because the mast cells may be present only in small numbers, and because in sections stained with hematoxylin-eosin their nuclei resemble those of fibroblasts or pericytes, the diagnosis may be missed unless special staining is employed (324).

In cases with multiple nodules or plaques or with a solitary large nodule, the mast cells lie closely packed in tumor-like aggregates (Figs. 6-40 and 6-41). The infiltrate may extend

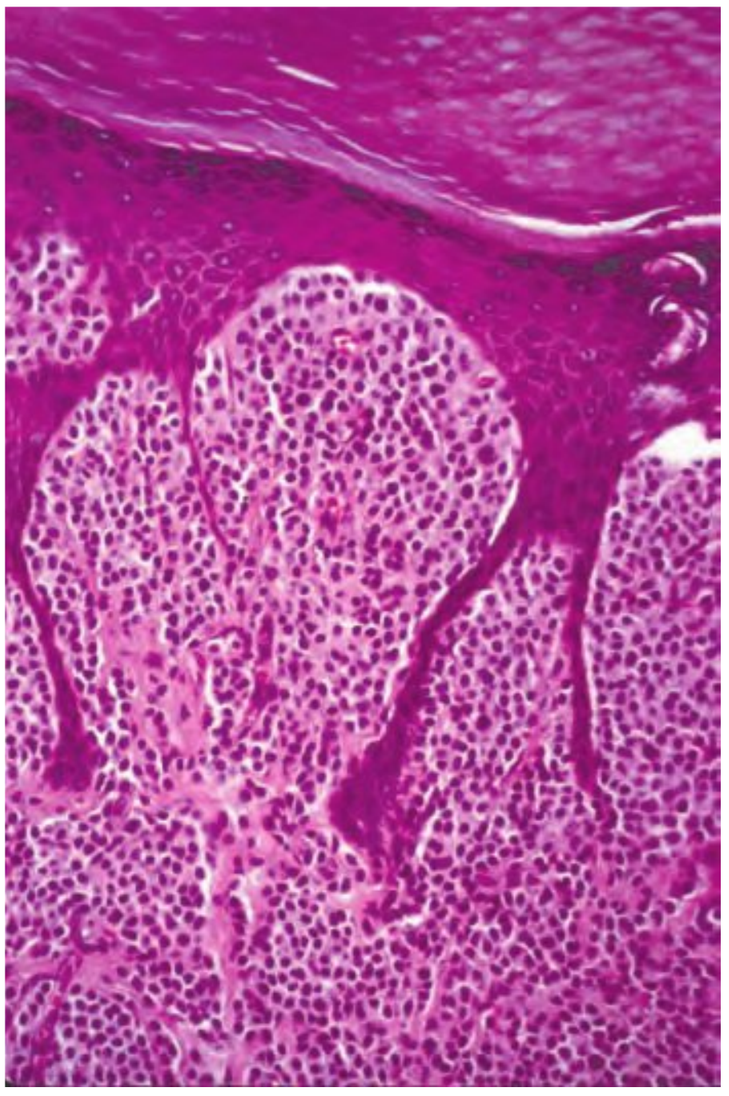


FIGURE 6-40. Urticaria pigmentosa, nodular type. Mast cells fill the expanded papillary dermis (H&E stain, original magnification ×100).

through the entire dermis and even into the subcutaneous fat (325). Whenever the mast cells lie in dense aggregates, their nuclei are cuboidal rather than spindle shaped, and they show ample eosinophilic cytoplasm and a well-defined cell border. Because of the shape of their nuclei and ample cytoplasm, they have a rather distinctive appearance, so the diagnosis usually can be made even before special staining has been carried out.

In the diffuse, erythrodermic type, a dense, bandlike infiltrate of mast cells with a rather uniform appearance showing round to oval nuclei and a distinctly outlined cytoplasm is observed in the upper dermis (326).

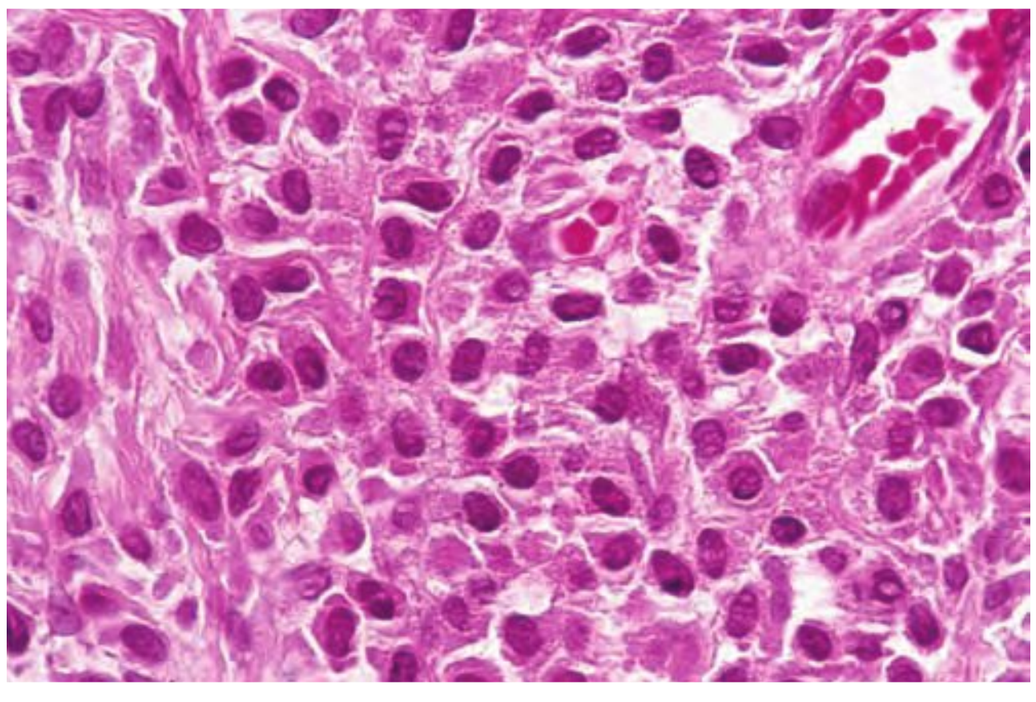


FIGURE 6-41. Urticaria pigmentosa, nodular type. Cuboidal mast cells that fill and expand the papillary dermis. These cells closely resemble nevus cells. Special stains will differentiate (original magnification ×400).

Eosinophils may be present in small numbers in all types of urticaria pigmentosa with the exception of telangiectasia macularis eruptiva perstans, in which eosinophils are generally absent because of the small numbers of mast cells within the lesions. If a biopsy is taken shortly after the lesion has been stroked, an increased number of eosinophils and extracellular mast cell granules are observed, which is an indication that granules have been released by the cells (327).

The bullae that may occur in infants with multiple or solitary nodules or with the diffuse erythrodermic type arise subepidermally (328). Because of regeneration of the epidermis at the base of the bulla, older bullae may be located intraepidermally. The bullous cavity often contains mast cells as well as eosinophils (329). The pigmentation of lesions of urticaria pigmentosa is due to the presence of increased amounts of melanin in the basal cell layer and occasionally also of melanophages in the upper dermis.

Systemic Lesions

It is important to distinguish between asymptomatic systemic involvement of limited degree and true systemic mast cell disease, in which the lesions are symptomatic, widespread, and progressive.

Asymptomatic systemic involvement of a limited degree may occur in urticaria pigmentosa of children, but it is not common. It occurs most commonly in the erythrodermic and nodular types and consists of bone and bone marrow involvement or of hepatosplenomegaly. In urticaria pigmentosa of adults, systemic lesions are more common. For instance, in routinely carried out bone marrow biopsies, as many as 75% of adult patients show mast cell infiltration of bone marrow in contrast to only 18% of children; radiologic survey of the skeleton has revealed bone changes in 44% of adult patients with urticaria pigmentosa but in only 5% of children (330). On radiologic examination, bones with mast cell infiltration may show areas of increased lucency intermingled with areas of increased density owing to the fact that mast cell aggregates in the bone marrow can cause focal bone resorption as well as reactive bone formation (331).

In true systemic mast cell disease, massive infiltration of the bones may cause collapse of several vertebrae or a fracture of long bones (332). Myelofibrosis may occur, resulting in anemia, leukopenia, and thrombocytopenia (313). Pancytopenia may cause death. Systemic mastocytosis, besides involving the bone marrow and bones, generally involves various groups of lymph nodes and the liver and spleen, resulting in hepatosplenomegaly. In some cases, the gastrointestinal tract, lungs, and meninges are also infiltrated with mast cells (326). Mature mast cells may be found in the peripheral blood.

Histogenesis. As seen by both light microscopy and electron microscopy, the mast cells of urticaria pigmentosa do not differ from normal mast cells either in structure or in mode of degranulation (333,334). Because mast cells contain histamine and release it during degranulation, chemical analysis of cutaneous lesions of urticaria pigmentosa reveals a considerably higher level of histamine than is found in normal skin (335).

The increased melanin pigmentation in lesions of urticaria pigmentosa is the result of stimulation of epidermal melanocytes by mast cells. It is not caused by any substance present within the mast cells. In one case of nodular urticaria pigmentosa, however, some mast cells showed dual granulation containing both mast cell granules and melanosomes as well as granules representing intergrades between mast cell granules and melanosomes (336).

Differential Diagnosis. Even if numerous mast cells are present, an absolutely reliable diagnosis of urticaria pigmentosa requires the demonstration of mast cell granules with the Giemsa stain, Leder's method, or toluidine blue stain. On routine staining, the mast cells in macular lesions may resemble fibroblasts or pericytes, but those in nodular or erythrodermic lesions may resemble the histiocytes that are seen in Letterer-Siwe disease or in eosinophilic granuloma. Differentiation of urticaria pigmentosa from these two diseases on routine staining can be particularly difficult because in all three diseases, the infiltrate may contain eosinophils. In contrast with Letterer-Siwe disease, the cells of urticaria pigmentosa have no tendency to invade the epidermis. Occasionally, the cuboidal mast cells in nodular urticaria pigmentosa resemble nevus cells, but they show no tendency to lie in nests and show no junction activity.

The macular type of urticaria pigmentosa, especially telangiectasia maculosa eruptiva perstans, occasionally may be difficult to diagnose even with the Giemsa stain because the number of mast cells may be so small that it does not differ significantly from the number normally present (330). Some inflammatory dermatoses, such as atopic dermatitis, lichen simplex chronicus, and lichen planus, may contain a high percentage of mast cells in their inflammatory cell infiltrates (337). However, in urticaria pigmentosa, the infiltrate consists exclusively of mast cells, except for a slight admixture of eosinophils as a result of the degranulation of some of the mast cells.

INCONTINENTIA PIGMENTI

Incontinentia pigmenti (IP) is an X-linked dominantly inherited disorder. Females with the abnormal gene on only one of their two X chromosomes are heterozygous for this condition and are not severely affected, but males with the abnormal gene on their single X chromosome are hemizygous for this condition and hence are so severely affected that they typically die *in utero*. This explains the predominance of female patients with this disorder (338). To date, over 40 male patients with IP have been reported (339). Male patients may survive either through hypomorphic mutations, as in cases of genetic mosaicism, or through the presence of a compensatory X chromosome, as in cases of 47,XXY or Klinefelter syndrome (340,341). The familial form of this disorder, IP2 (or classical incontinentia pigmentosa), is localized to the Xq28 region (342). It is due to a mutation in the IKK-gamma gene as part of the NEMO complex.

The disorder has four stages. The first stage, consisting of erythema and bullae arranged in lines, either is present at birth or starts shortly thereafter. The extremities are predominantly affected. There is also marked blood eosinophilia. In the second stage, which occurs after about 2 months, the vesicular lesions gradually are superseded by linear, verrucous lesions that persist for several months. As the verrucous lesions subside, widely disseminated areas of irregular, spattered, or whorled pigmentation develop. This pigmentation, representing the third stage, is most pronounced on the trunk (Fig. 6-42A). It diminishes gradually after several years and may even clear completely. The fourth stage is seen in adult females. Subtle, faint, hypochromic or atrophic lesions in a linear pattern are most apparent on the lower extremities.

In about 80% of the cases, IP is associated with various congenital abnormalities, particularly of the central nervous system, eyes, and teeth. Partial alopecia at the vertex is also often seen (343).

Histopathology. The vesicles seen during the first stage arise within the epidermis and are associated with spongiosis. They are of the type seen in dermatitis (344). However, they differ from the vesicles of dermatitis by the numerous eosinophils within them and around them in the epidermis (eosinophilic spongiosis) (Fig. 6-42B and C). The epidermis between the vesicles often shows single dyskeratotic cells and whorls of squamous cells with central keratinization. Like the epidermis, the dermis shows an infiltrate containing many eosinophils and some mononuclear cells.

The alterations in the second stage consist of acanthosis, irregular papillomatosis, and hyperkeratosis. Intraepidermal keratinization, consisting of whorls of keratinocytes and of scattered dyskeratotic cells, is often more pronounced than in the first stage. The basal cells show vacuolization and a decrease in their melanin content. The dermis shows a mild, chronic inflammatory infiltrate intermingled with melano-phages. This infiltrate extends into the epidermis in many places.

The areas of pigmentation seen in the third stage show extensive deposits of melanin within melanophages located in the upper dermis. Usually, this dermal hyperpigmentation is found in association with a diminution of pigment in the basal layer, the cells of which show vacuolization and degeneration (345). In some cases, however, the cells of the basal layer contain abundant amounts of melanin (346,347).

A different pattern has recently been described on the skin of the legs of an infant in whom the vesiculation had produced superficial scarring and depigmentation. The light-colored skin lacked melanocytes and appendages as the result of scarring, and the darker skin showed a normal degree of pigmentation without incontinence of pigment (348).

Pathogenesis. The fact that the first two stages of IP are seen predominantly on the extremities and the third stage mainly on the trunk has led to the assumption by some authors that

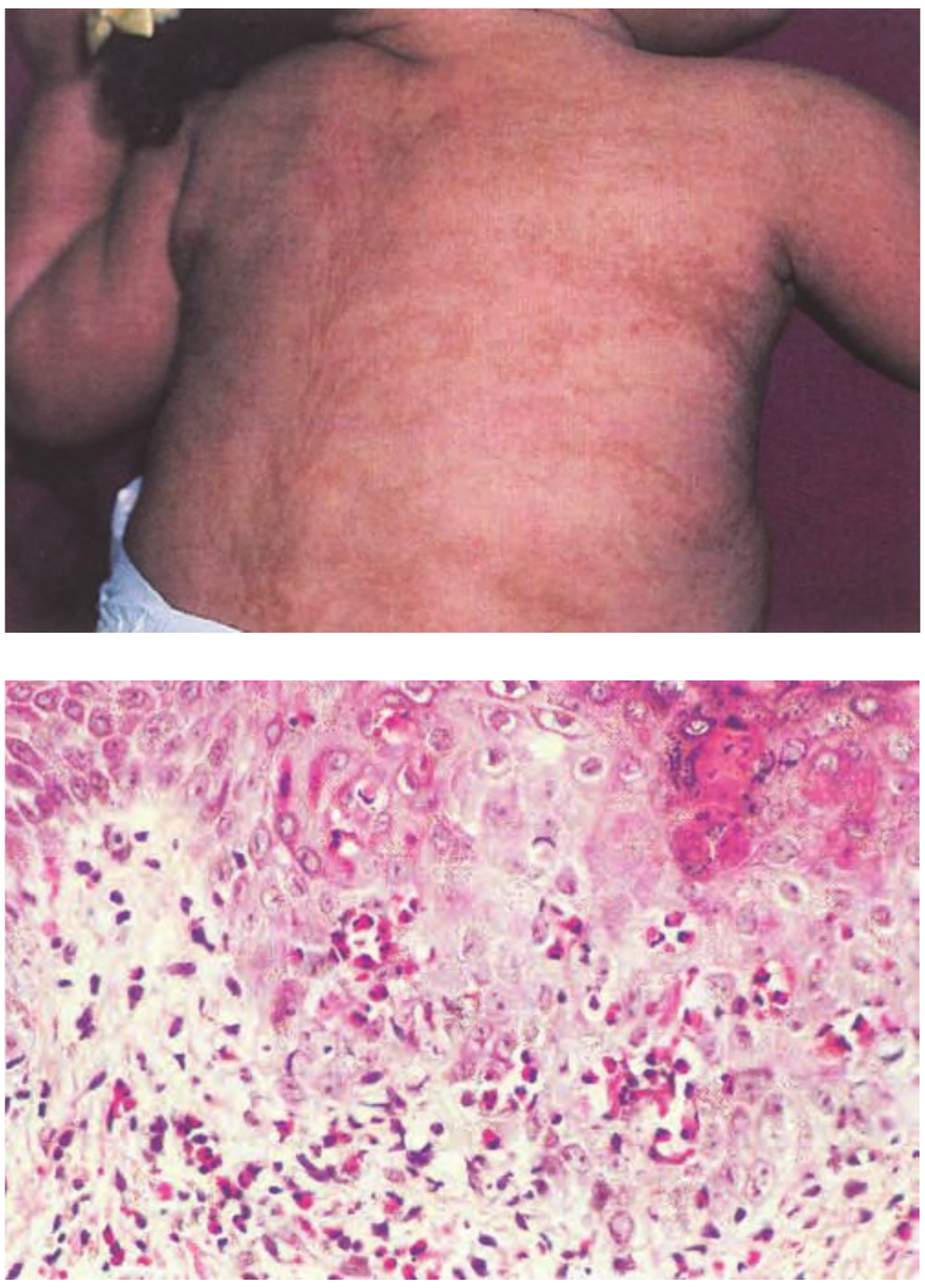


FIGURE 6-42. A: Incontinentia pigmenti. Streaking and whorling pigmentation on the trunk. B: The transition stage between vesicular and acanthotic. Many eosinophils are seen in the dermis and in the focally acanthotic and spongiotic epidermis. C: High magnification of Fig. 6-42B, showing eosinophilic spongiosis and acanthosis.

the pigmentary changes of the third stage occur independently of the bullous and verrucous lesions of the first two stages and represent some sort of nevoid anomaly. However, electron microscopic studies have revealed common features, albeit to varying extents, in all three stages of IP and thus suggest that the three stages are related to each other (349–351). Even in the first stage, many keratinocytes and melanocytes show degenerative changes resulting in the migration of macrophages to the epidermis, where they phagocytize dyskeratotic keratinocytes and melanosomes. Subsequently, the macrophages return to the dermis (EM 6). The macrophages seen in the dermis in the second and third stages contain many melanosome complexes and thus are easily recognizable as melanophages even by light microscopy, whereas the macrophages in the first stage contain only few melanosome complexes and therefore can be identified as melanophages only in the electron microscope (349). The phagocytosis of melanin by dermal macrophages in the first stage of the disease (350) and the presence of dyskeratotic keratinocytes in the epidermis during all three stages of the disease have been confirmed.

The presence of eosinophils in epidermal and dermal infiltrates can be explained by the presence in the early vesicular stage of basophils, which release eosinophil chemotactic factor of anaphylaxis (352). Eosinophil chemotactic activity has been demonstrated in patients with IP in the blister fluid (353) and in eluates of crusted scales overlying the lesions (354).

HYPOMELANOSIS OF ITO

Hypomelanosis of Ito was originally called *incontinentia pigmenti achromians*, but because the disorder shows no pigmentary incontinence, this term has been largely abandoned. However, it is now felt that hypomelanosis of Ito is not an entity but a symptom of many different states of mosaicism and is due to an X/autosome translocation involving Xp11 (355).

The hypomelanosis seen in this disorder may be present at birth. However, it usually develops during the first year of life. In some instances, the loss of pigment does not begin until childhood. There is a tendency for the pigmentary loss to become more pronounced at first but to be followed by partial repigmentation in adult life. The pattern and distribution of the hypopigmentation in hypomelanosis of Ito is similar to the pattern of hyperpigmentation seen in IP (Fig. 6-43). Although first reported in Japanese patients, hypomelanosis of Ito has since been observed in many races.

Congenital abnormalities are found in 50% of the cases (355). Most common are mental retardation and seizure disorders, but there also may be abnormalities of the eyes, hair, teeth, or the musculoskeletal system (356). Abnormal chromosomal constitutions are common (357).

Histopathology. In the hypopigmented areas, a Fontana-Masson stain shows a decrease in the amount of melanin granules in the basal cell layer, with a complete absence of melanin in some areas (358). With the dopa reaction, the hypopigmented areas are seen to contain fewer and smaller melanocytes than normal, with sparse, short dendrites (359).



FIGURE 6-43. Hypomelanosis of Ito. Streaking hypopigmentation on trunk.

Pathogenesis. The electron microscopic findings show a significant decrease in the number of melanosomes within melanocytes and keratinocytes (356,359). In addition, some melanocytes show degenerative changes and an absence of melanosomes (360).

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CHAPTER 7

Narciss Mobini
Sonia Toussaint
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Noninfectious Erythematous, Papular, and Squamous Diseases

URTICARIA

Urticaria is characterized by the presence of abrupt-onset transient and recurrent wheals, which are raised erythematous and edematous areas of skin that are often pruritic. When large wheals occur and the edema extends to the subcutaneous or submucosal tissues, the process is referred to as angioedema (1). Recently, a large survey of nearly 1,000 patients revealed that angioedema can occur without urticarial flares (2). Acute episodes of urticaria generally last only several hours. When episodes of urticaria last up to 24 hours and recur over a period of at least 6 to 8 weeks, the condition is considered chronic urticaria. When urticaria and angioedema occur simultaneously, the condition tends to have a chronic course.

In approximately 15% to 25% of patients with chronic urticaria, an eliciting stimulus or underlying predisposing condition can be identified (3). The various causes of urticaria include soluble antigens in foods, drugs, and insect venom; contact allergens; physical stimuli such as pressure, vibration, solar radiation, or cold temperature; occult infections and malignancies; and some hereditary syndromes such as familial cold urticaria and Muckle-Wells syndrome (amyloidosis, nerve deafness, and urticaria), which are both inherited as an autosomal dominant trait and linked to chromosome 1q44. Schnitzler's syndrome is characterized by a chronic urticaria and a monoclonal gammopathy with evolution in 15% of patients to lymphoplasmacytic neoplasms (4).

Recent evidence suggests that at least 30% to 50% of chronic idiopathic urticarias may have an autoimmune basis for their condition (5,6) (see pathogenesis discussion).

In *hereditary angioedema,* a rare form of dominantly inherited angioedema, recurrent attacks of edema involve not only the skin, but also the oral, upper respiratory, and gastrointestinal tracts. Itching is absent, and there is no associated urticaria. However, lesions may be painful. Attacks are commonly precipitated by trauma, such as dental extraction or emotional stress. Hereditary angioedema manifesting in late middle age after angiotensin-converting enzyme inhibitor therapy has been reported (7). Patients may later manifest autoimmune disorders such as systemic or discoid lupus erythematosus.

Urticarial vasculitis is a syndrome consisting of recurrent episodes of urticarial lesions often associated with arthralgia and abdominal pain and rarely with glomerulonephritis and obstructive pulmonary disease (8). The individual skin lesions tend to persist for 1 to 3 days and may resolve with purpura or hyperpigmentation (9). Lesions in urticarial vasculitis are not necessarily acral in distribution. Urticarial vasculitis should be suspected when individual lesions persist for more than 24 hours and produce burning or stinging sensations (10). Urticarial vasculitis may be normo- or hypocomplementemic. The latter is less frequent and can occur in up to 30% of the cases (11). Organ involvement is more common in hypocomplementemic urticarial vasculitis than in the normocomplementemic form (9). Urticarial vasculitis is usually idiopathic but may be associated with infectious mononucleosis, infectious hepatitis, serum sickness, systemic lupus erythematosus, Sjögren's syndrome, mixed cryoglobulinemia, polycythemia rubra vera (12), and B-cell lymphoma (13). Urticarial vasculitis may antedate other manifestations of collagen vascular disease by months or years (14). Accordingly, the appropriate serologic studies should be performed and periodically monitored. Other associations with urticarial vasculitis include drugs, especially selective serotonin reuptake inhibitors (15,16).

Histopathology. In *acute urticaria* one observes interstitial dermal edema, dilated venules with endothelial swelling, and a paucity of inflammatory cells. In *chronic urticaria* interstitial dermal edema and a perivascular and interstitial mixed-cell infiltrate with variable numbers of lymphocytes, eosinophils, and neutrophils are present (17) (Figs. 7-1 and 7-2).

In *angioedema* the edema and infiltrate extend into the subcutaneous tissue. In *hereditary angioedema* there is subcutaneous and submucosal edema without infiltrating inflammatory cells (18).

In *urticarial vasculitis* the dermis shows an early leukocytoclastic vasculitis characterized by (a) an infiltrate predominantly within and around the walls of small blood vessels composed largely of neutrophils, some of which show fragmentation of their nuclei (leukocytoclasis); (b) minimal deposits of fibrin in the vessel walls; and (c) slight to moderate extravasation of erythrocytes (19).

Pathogenesis. Electron microscopic examination reveals mast cell and eosinophil degranulation in common urticaria. In chronic urticaria, immunoglobulin G (IgG) autoantibodies cross-link the α chain of the high-affinity receptor for IgE on

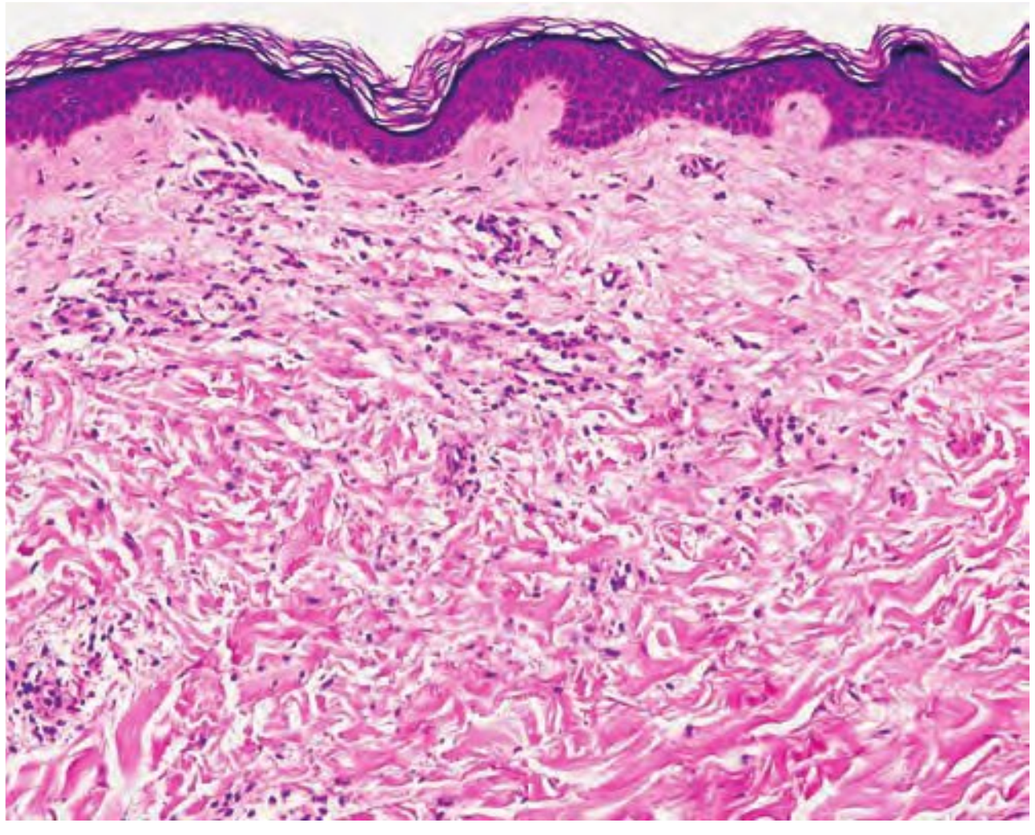


FIGURE 7-1. Urticaria. Sparse superficial perivascular and interstitial inflammatory infiltrate.

mast cells (FcεRI), which results in histamine release. It appears that complement, especially C5a, augments histamine release (20,21). In addition, recent studies have shown that CD203c is a basophil activation marker that is upregulated by cross-linking of the FcεRI α-receptor and may serve as a useful marker to identify patients with chronic urticaria (22). In addition, chemotactic mediators are released from mast cells that induce a sequential upregulation of endothelial adhesion molecules (P-selectin, E-selectin, intercellular adhesion molecule-1 [ICAM-1], and vascular cell adhesion molecule-1) and of β2-integrins on leukocytes (23). The presence of these autoantibodies against the FcεRI α-subunit of the IgE receptor or IgE itself is detected in approximately 30% to 40% of patients with chronic urticaria (22).

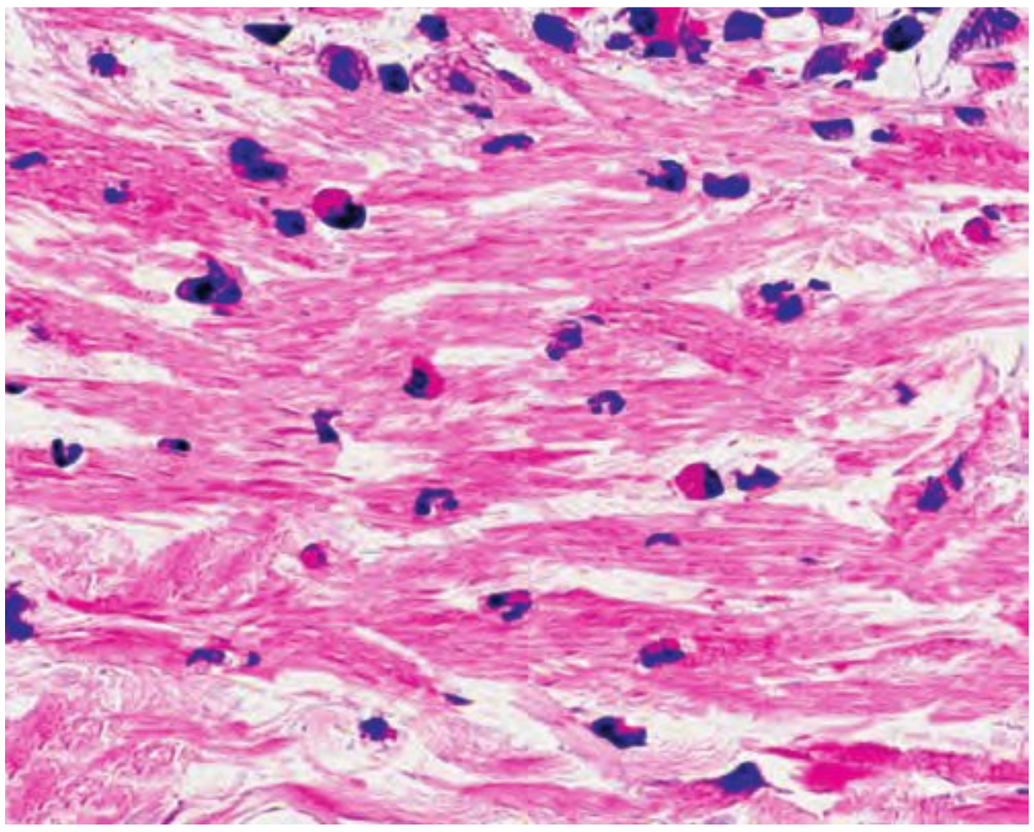


FIGURE 7-2. Urticaria. Interstitial infiltrate of eosinophils, neutrophils, and lymphocytes.

Most patients with hereditary angioedema have a low serum level of the esterase inhibitor of the first component of complement (C1-INH). Exhaustion of this inhibitor allows activation of C1. This leads to activation of C4 and C2, with the generation of a C2 fragment possessing kinin-like activity and causing increased vascular permeability (3). A smaller proportion of patients with hereditary angioedema have a deficit in functional C1-esterase inhibitor.

In urticarial vasculitis, circulating immune complexes are found in about one half of the patients. By direct immunofluorescence testing, strong granular deposits of immunoreactants are seen along the dermoepidermal junction and perivascular areas (14,24). Positive immunofluorescence findings are more common in patients with the hypocomplementemic form of urticarial vasculitis (10). Renal biopsy in patients with hypocomplementemia frequently shows glomerulonephritis (8).

PRURITIC URTICARIAL PAPULES AND PLAQUES OF PREGNANCY

Pruritic urticarial papules and plaques of pregnancy (PUPPP) is a fairly common entity first described in 1979 by Lawley et al. (25) The condition has a predilection for primigravidas in the third trimester of pregnancy. The rash usually starts on the abdomen and is composed of intensely pruritic erythematous urticarial papules, which may be surmounted by vesicles. The proximal parts of the extremities are also affected. There is no increased incidence of the rash in subsequent pregnancies (26). The rash usually involutes spontaneously after delivery. Fetal outcome appears to be unaffected. Unusual clinical presentations have recently been reported as involvement of palmoplantar surfaces and also initial manifestation of the disease in the postpartum period (27,28).

Histopathology. Microscopic findings most commonly show a superficial and middermal perivascular lymphohistiocytic infiltrate with variable numbers of eosinophils and neutrophils together with edema of the superficial dermis. Epidermal involvement is variable and consists of focal spongiosis, parakeratosis, and mild acanthosis (25,26,29).

Pathogenesis. A possible correlation has been proposed between susceptibility to develop PUPPP and increased maternal weight gain and twin/triplet pregnancies (30,31). In cultures of human keratinocytes, lesional epidermis of PUPPP has shown positive progesterone receptor (PR) expression detected by immunohistochemistry and reverse transcriptase polymerase chain reaction (RT-PCR). Nonlesional epidermis, however, has not revealed any PR positivity (32). In addition, a paternal factor hypothetically generated or expressed by the fetal portion of the placenta has been invoked as the cause of PUPPP in two families with unusual conjugal patterns (33). Direct immunofluorescence studies may be negative or show nonspecific immunoreactants on dermal blood vessels or at the dermoepidermal junction (34).

ERYTHEMA ANNULARE CENTRIFUGUM

Erythema annulare centrifugum is also known as gyrate erythema and represents a hypersensitivity reaction manifesting as arcuate and polycyclic areas of erythema. The condition has been categorized into superficial and deep variants. The deep form was originally described by Darier and is characterized by annular areas of palpable erythema with central clearing and absence of surface changes (35). The superficial variant differs only by the presence of a characteristic trailing scale—a delicate annular rim of scale that trails behind the advancing edge of erythema (36,37) (Fig. 7-3A). Small vesicles may occur.

The lesions may attain considerable size (up to 10 cm across) over a period of several weeks, may be mildly pruritic, and have a predilection for the trunk and proximal extremities. Most cases resolve spontaneously within 6 weeks; however, the condition may persist or recur for years. In a recent study of 66 patients with erythema annulare centrifugum, the lower extremities were the most frequently involved area and the superficial variant was more common than the deep form, 78% versus 22%, respectively (38).

Histopathology. In the superficial variant of gyrate erythema, there is a superficial perivascular tightly cuffed lymphohistiocytic infiltrate with endothelial cell swelling and focal extravasation of erythrocytes in the papillary dermis. In addition, there is focal epidermal spongiosis and focal parakeratosis (36,37).

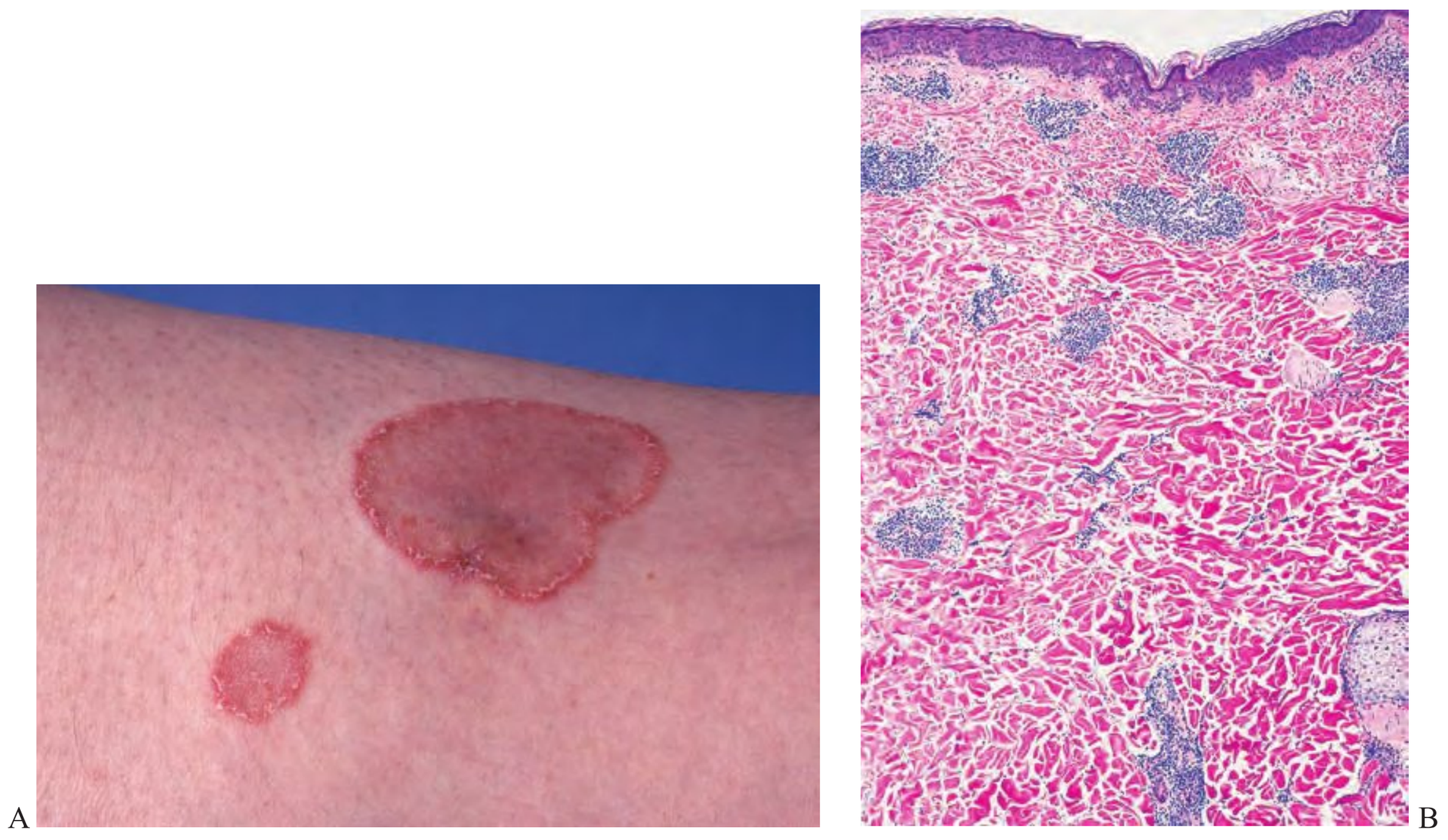
In the classic deep form or indurated type, a superficial and deep perivascular lymphocytic infiltrate characterized by a tightly cuffed "coat-sleeve–like" pattern is present in the mid and deep dermis (39) (Figs. 7-3B and 7-4). Occasionally, focal vacuolar alteration of the basal layer keratinocytes may be noted in the deep variant (40).

Pathogenesis. The exact pathogenesis of erythema annulare centrifugum is not clear. It has been associated with occult infections, dermatophytosis, candidiasis, medications, and, rarely, an underlying malignancy (41–43). The rash responds poorly to topical steroids. Treatment of any underlying disorder, if identifiable, is indicated.

Differential Diagnosis. The rather striking coat-sleeve—like perivascular arrangement of the infiltrate seen in the deep form of gyrate erythema is encountered also in secondary syphilis. However, in secondary syphilis numerous plasma cells and histiocytes are usually present, and the endothelial cells are swollen. The presence of increased deposits of connective tissue mucin distinguishes tumid lupus erythematosus from deep gyrate erythema.

ERYTHEMA GYRATUM REPENS

Erythema gyratum repens is a very rare but clinically highly characteristic dermatosis that was originally reported in 1952 by Gammel (44). It mostly represents a paraneoplastic



A B

FIGURE 7-3. A: Erythema annulare centrifugum. Characteristic delicate annular rim of scale trailing behind the edge of erythema. (Courtesy of Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, New York.) B: Gyrate erythema, deep form. Superficial and deep, dense perivascular lymphocytic infiltrate.

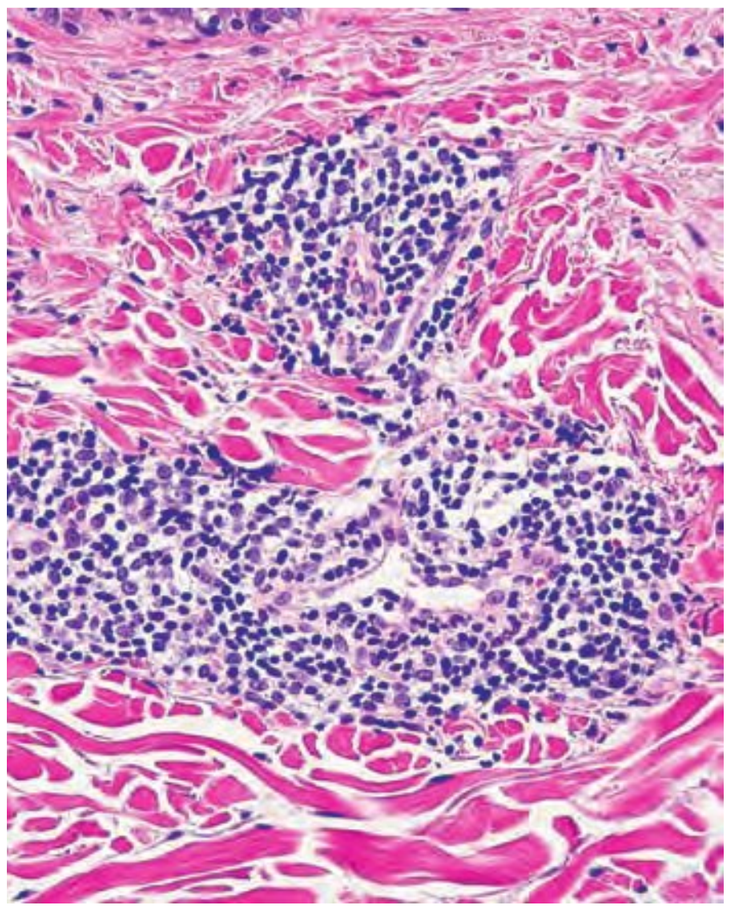


FIGURE 7-4. Gyrate erythema, deep form. Dense perivascular lymphocytic infiltrate.

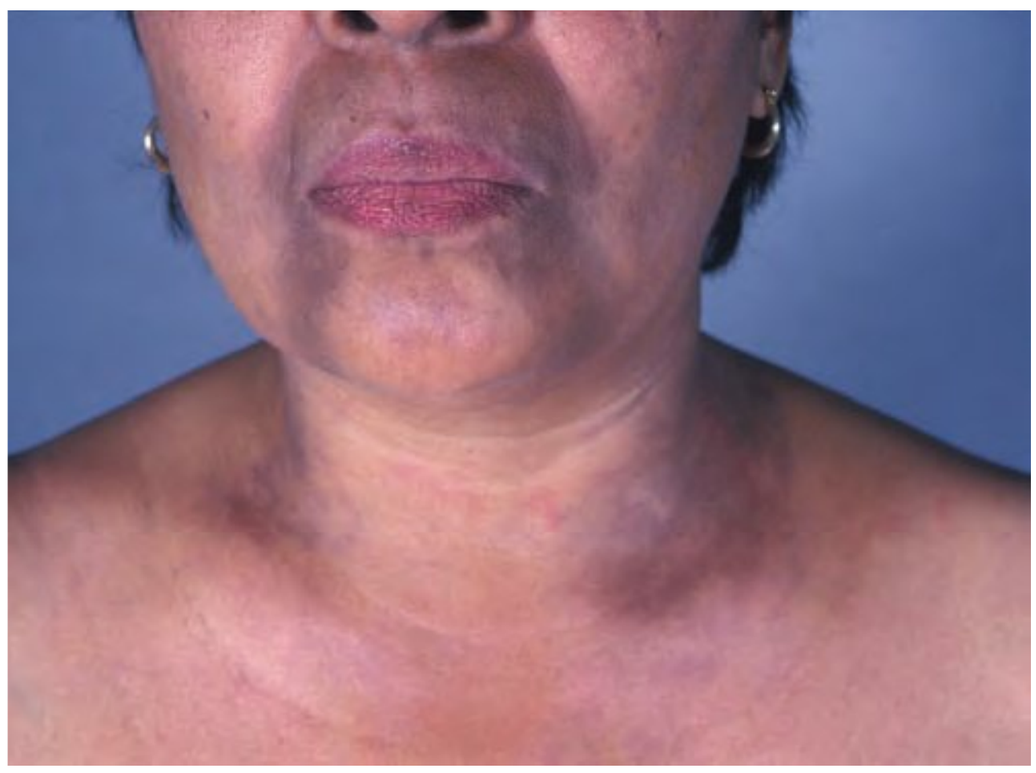


FIGURE 7-5. Erythema dyschromicum perstans. Disseminated blue-gray macules on face, neck, and chest. (Courtesy of Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, New York.)

syndrome that is associated with an internal malignancy in 82% of patients (45). The most common associated malignancies include lung/bronchial, esophageal, and breast carcinomas. Occurrence of erythema gyratum repens as a nonparaneoplastic phenomenon has also been described (46). The eruption typically is very pruritic and is composed of concentric and parallel bands of erythema and scale producing a "wood-grain" pattern on the skin. The trunk and extremities are preferentially involved; however, the entire integument may be affected. The rash of erythema gyratum repens constantly migrates at a fairly rapid rate (up to 1 cm/day). Ichthyosis and palmar/plantar hyperkeratosis have been observed concomitantly in 16% and 10% of patients, respectively (47). The condition is known to remit with treatment and eradication of the associated malignancy.

Histopathology. The histologic picture usually shows mild acanthosis, spongiosis, focal parakeratosis, and a superficial perivascular lymphohistiocytic infiltrate that may also include eosinophils, neutrophils, and melanophages (47,48).

Pathogenesis. Several authors have described granular deposition of C3, C4, or IgG at the basement membrane zone on direct immunofluorescence, suggesting that erythema gyratum repens may have an immunologic basis (49–51). In particular, Caux et al., using immunoelectron microscopy, noted that the deposits are located in the sublamina densa region (51).

ERYTHEMA DYSCHROMICUM PERSTANS

Erythema perstans, also called ashy dermatosis, is an extensive asymptomatic eruption. It begins with disseminated macules showing an elevated red active border, which by peripheral extension and coalescence form large patches with a polycyclic outline (Fig. 7-5). Although the macules may at first be erythematous before assuming their characteristic bluish gray color, they often appear blue-gray from the very beginning. The disease progresses slowly, and the discoloration persists. The most common areas of involvement are the trunk, arms, and face. Most patients with this disorder are Latin Americans (52). A genetic susceptibility to develop the disease in Mexican mestizo patients has been associated with the HLA-DR4 DRB1(*)0407 allele (53).

Histopathology. In the early active stage or in the erythematous active border, there is vacuolar alteration of the basal layer. The papillary dermis shows a mild to moderate perivascular infiltrate of lymphocytes and histiocytes intermingled with melanophages (54,55). There may also be exocytosis of lymphocytes into the basal layer, and occasional necrotic keratinocytes or colloid bodies resembling those seen in lichen planus may be present (56). Late lesions show aggregates of melanophages in the papillary dermis (54).

Pathogenesis. Electron microscopic examination reveals many vacuoles delimited by a membrane within the affected keratinocytes as the ultrastructural counterpart of the vacuolar alteration. This is associated with widening of the intercellular spaces and retraction of desmosomes to either one cell or the other. Additional findings include discontinuities in the subepidermal basement membrane and the presence in the dermis of melanophages containing aggregates of melanosomes enclosed by a lysosomal membrane (57). It can be assumed that the vacuolar alteration of basal keratinocytes is the cause of the pigmentary incontinence and of the formation of the colloid bodies.

Direct immunofluorescence studies have shown IgG deposition on necrotic keratinocytes at the dermal—epidermal junction. Immunohistochemical studies have revealed that in

early lesions, the dermal inflammatory infiltrate is composed primarily of T lymphocytes, both $CD4^+$ (helper-inducer) and $CD8^+$ (cytotoxic-suppressor) subtypes (58).

It has been shown that the expression of ICAM-1 and HLA-DR on basal layer keratinocytes is increased. The activation molecule AIM/CD69 and the cytotoxic cell marker CD94 have been seen to be expressed in the inflammatory cell infiltrate (59). Damage and necrosis of the basal keratinocytes resulting in formation of colloid bodies and pigmentary incontinence suggests a possible relationship of erythema dyschromicum perstans to lichen planus pigmentosus, also called lichen planus actinicus or subtropicus (56,60,61). However, lichen planus pigmentosus shows a different clinical presentation, characterized by dark brown macules located predominantly on exposed areas and flexural folds. Histologically, it shows a more pronounced lichenoid distribution of the infiltrate (55,62). Erythema dyschromicum perstans coexisting with lichen planopilaris has been reported (63).

Differential Diagnosis. Erythema dyschromicum perstans may show similarities with the inflammatory infiltrate and pigmentary incontinence seen in interface drug reactions, especially in the late stage of fixed-drug eruption (54).

PRURIGO SIMPLEX

Prurigo simplex is characterized by intensely pruritic, erythematous urticarial papules that are seen in symmetric distribution, especially on the trunk and extensor surfaces of the extremities of middle-aged patients. Some patients may have an atopic background or may exhibit dermographism (64). In contrast with dermatitis herpetiformis, which prurigo simplex may resemble in clinical appearance, there is no grouping of lesions (65). In other cases, prurigo simplex greatly resembles arthropod bites (papular urticaria).

Histopathology. The histologic picture of the early papules shows mild acanthosis, spongiosis with an occasional small spongiotic vesicle, and parakeratosis. The upper dermis contains a mild lymphocytic inflammatory infiltrate in a largely perivascular arrangement (66). An admixture of eosinophils is present in some cases (65,67). Excoriated papules show partial absence of the epidermis, and they are covered with a crust containing degenerated nuclei of inflammatory cells (65). On serial sectioning, most of the histologic changes may be found to be located around hair follicles, which then show spongiosis and exocytosis of lymphocytes in the follicular infundibulum, and a perifollicular infiltrate (68). In other instances, there is distinct sparing of the follicular structures (67).

Differential Diagnosis. The diagnosis of dermatitis herpetiformis is easily excluded by the absence in prurigo simplex of neutrophilic microabscesses at the tips of dermal papillae and of neutrophils, eosinophils, and nuclear dust in the dermal infiltrate. A negative direct immunofluorescence study of perilesional skin excludes dermatitis herpetiformis or urticarial bullous pemphigoid (64). The histologic picture of prurigo simplex resembles that of a subacute eczematous dermatitis, except that the extent of its papular lesions is much more limited. Histologic differentiation from papular urticaria is not possible (65).

PRURIGO NODULARIS

Prurigo nodularis is a chronic dermatitis characterized by discrete, raised, firm hyperkeratotic papulonodules, usually from 5 to 12 mm in diameter but occasionally larger. They occur chiefly on the extensor surfaces of the extremities and are intensely pruritic. The disease usually begins in middle age, and women are more frequently affected than men (69). Prurigo nodularis may coexist with lesions of lichen simplex chronicus, and there may be transitional lesions (70).

The cause is unknown, but local trauma, insect bites, atopic background, and metabolic or systemic diseases have been implicated as predisposing factors in some cases (70–73).

Histopathology. One observes pronounced hyperkeratosis and irregular acanthosis. In addition, there may be papillomatosis and irregular downward proliferation of the epidermis and adnexal epithelium (74) approaching pseudoepitheliomatous hyperplasia (75) (Fig. 7-6). The papillary dermis shows a predominantly lymphocytic inflammatory infiltrate and vertically oriented collagen bundles. Occasionally, prominent neural hyperplasia may be observed (75); however, this is an uncommon finding and is not considered to be an essential feature for the diagnosis of prurigo nodularis (76). In some cases, silver stains or cholinesterase stains demonstrate the increased number of cutaneous nerves (69).

Eosinophils and marked eosinophil degranulation may be seen more frequently in patients with an atopic background (71). Dermal Langerhans cells are shown to be increased in prurigo nodularis compared to normal controls (77). The

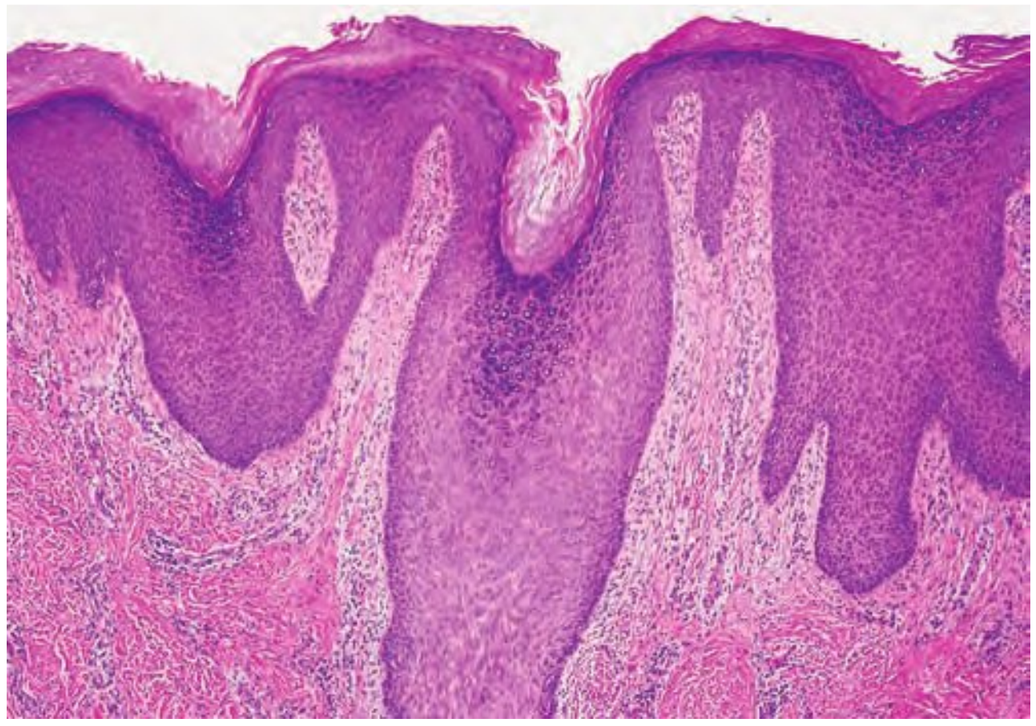


FIGURE 7-6. Prurigo nodularis. Marked irregular acanthosis, focal hypergranulosis, and compact orthokeratosis with parakeratosis.

identification of enlarged dendritic mast cells containing fewer cytoplasmic granules within the lesional dermis has recently been described (78).

Pathogenesis. It is generally assumed that the neural proliferation in prurigo nodularis is a secondary phenomenon due to chronic trauma by scratching. Still, it may be that the extreme pruritus is related to the increased number of dermal nerves (75). A recent study showed that nerve growth factor (NGF) and its receptors are overexpressed in lesional skin of prurigo nodularis compared to normal controls, with the inflammatory cell infiltrate being the source of NGF with resulting neural hyperplasia (79).

Calcitonin gene–related peptide and substance P are markedly increased in prurigo nodularis compared to normal skin. These neuropeptides may mediate the pruritus in prurigo nodularis (80). On electron microscopic examination, it is evident that the neural proliferation involves both axons and Schwann cells (75). Many nerve fibers are also demonstrable with immunostains for S100 protein (81), neurofilament, and myelin basic protein (82). Immunohistochemical analysis has confirmed that they are mostly sensory nerves by demonstrating the presence of sensory neuropeptides (83). In addition, Merkel cells are reported to be increased in number in the basal cell layer of the affected interfollicular epidermis, suggesting that these specialized sensory receptors interacting with the neural fibers may participate in the pathogenesis of the disease (84).

Differential Diagnosis. Lichen simplex chronicus may have a similar histologic picture, although less exuberant and less circumscribed (76). Multiple keratoacanthomas, which often show less of a central crater than solitary keratoacanthomas, may be difficult to distinguish from prurigo nodularis because both show marked epidermal and epithelial hyperplasia (85).

PSORIASIS

Psoriasis may be divided into psoriasis vulgaris, generalized pustular psoriasis, and localized pustular psoriasis.

Psoriasis Vulgaris

Clinical Features

Psoriasis vulgaris is a common chronic inflammatory skin disorder that affects approximately 1.5% to 2% of the population in the Western countries. It is characterized by pink to red scaly papules and plaques (Fig. 7-7). The lesions are of variable size, sharply demarcated, dry, and usually covered with layers of fine, silvery scales. As the scales are removed by gentle scraping, fine bleeding points are usually seen—the so-called Auspitz sign. The scalp, sacral region, and extensor surfaces of the extremities are commonly involved, although in some patients the flexural and intertriginous areas are mainly affected (inverse psoriasis). An acute variant—guttate or eruptive psoriasis—is often seen in younger patients and is characterized by



FIGURE 7-7. Psoriasis vulgaris. Sharply demarcated erythematous scaly papules and plaques on the upper extremity. (Courtesy of Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.)

an abrupt eruption of small lesions associated with acute group A β-hemolytic streptococcal infections (86). Involvement of the nails is common; the most frequent alteration of the nail plate surface is the presence of pits (87). In severe cases, the disease may affect the entire skin and present as generalized erythroderma. Pustules are generally absent in psoriasis vulgaris, although pustules on palms and soles occasionally occur. Rarely, one or a few areas show pustules, and this is referred to as "psoriasis with pustules." Also rarely, severe psoriasis vulgaris develops into generalized pustular psoriasis. Oral lesions such as stomatitis areata migrans (geographic stomatitis) and benign migratory glossitis (geographic tongue) may be seen in psoriasis vulgaris as well as in generalized pustular psoriasis (88,89).

Psoriatic arthritis characteristically involves the terminal interphalangeal joints, but frequently the large joints are also affected, so that a clinical differentiation from rheumatoid arthritis is often difficult. However, the rheumatoid factor is generally absent.

Generalized Pustular Psoriasis

Clinical Features

Generalized pustular psoriasis includes (a) acute generalized pustular psoriasis (von Zumbusch type and acute exanthematous type), (b) generalized pustular psoriasis of pregnancy (impetigo herpetiformis), (c) infantile and juvenile pustular psoriasis, and (d) subacute annular or circinate pustular psoriasis (90).

This cutaneous eruption is characterized by the presence of variable numbers of sterile pustules appearing in erythematous and scaly lesions associated with moderate to severe constitutional symptoms (91). Several exacerbations may occur, and lesions of ordinary psoriasis may be seen in the intervals between them.

The four variants of generalized pustular psoriasis show considerable resemblance and overlapping in their clinical picture and also have a similar histologic appearance. They differ

mainly in the mode of onset and the distribution of the lesions. Frequently, all four diseases show oral pustules, particularly on the tongue (92).

Acute generalized pustular psoriasis of von Zumbusch is generally diagnosed when the pustular eruption occurs in patients with preexisting psoriasis, either of the plaque type (93) or of the erythrodermic type (94). Frequently, the eruption occurs after systemic steroid therapy withdrawal (90,95). The *exanthematous type of generalized pustular psoriasis* refers to a group of patients with later onset of psoriasis, atypical distribution of the lesions, and a rapid and apparently spontaneous pustular eruption (96).

Generalized pustular psoriasis of pregnancy is a rare pustular eruption that appears during the last trimester of pregnancy. It starts with flexural lesions of psoriasis followed by a generalized pustular eruption. It may occur repeatedly during successive pregnancies (97). Some authors have considered it to be the same disease as *impetigo herpetiformis* (90), but others claim that they stand as separate entities (98,99).

In some instances of *subacute annular pustular psoriasis* the annular or gyrate lesions show a clinical resemblance to subcorneal pustular dermatosis (100,101). Figurate lesions are more frequently seen in subacute or chronic forms of generalized pustular psoriasis (90). Annular pustular psoriasis, although usually generalized, in some instances may be localized (102).

Very rarely, children develop generalized pustular psoriasis, also known as *infantile and juvenile pustular psoriasis*. In these patients the disease has a benign course with frequent spontaneous remissions (103).

Localized Pustular Psoriasis

Clinical Features

There are three types of localized pustular psoriasis: (a) "psoriasis with pustules" (95,96), in which only one or a few areas of psoriasis show pustules and the tendency to change into a generalized pustular psoriasis is low; (b) localized acrodermatitis continua of Hallopeau, which occasionally evolves into generalized acrodermatitis continua; and (c) pustular psoriasis of the palms and soles, with two variants: the chronic palmoplantar pustulosis, also called pustulosis palmaris et plantaris, and the acute palmoplantar pustulosis, or "pustular bacterid." Both are occasionally seen in association with psoriasis vulgaris (90). The relationship of Reiter's disease to psoriasis is discussed in the description of Reiter's disease.

Acrodermatitis continua of Hallopeau is the term used when the pustular eruption involves the distal portions of the hands and feet. In the localized type of acrodermatitis continua, these are the only areas affected, whereas in the generalized type of acrodermatitis continua, extensive areas of the skin in addition to the acral portions of extremities are involved (96). Atrophy of the skin and permanent nail loss may occur on the fingers and toes.

Pustulosis palmaris et plantaris is a chronic, relapsing disorder occurring on the palms, soles, or both (Fig. 7-8). Crops of small, deep-seated pustules are seen within areas of erythema and scaling. In the earliest stage, the lesions may appear as vesicles or vesiculopustules. During the subsiding stage, the pustules appear as brown macules. The sites of predilection are the midpalms and thenar eminences of the hands and the heels and insteps of the feet (104). In pustulosis palmaris et plantaris, in contrast to acrodermatitis continua of Hallopeau, the acral portions of the fingers and toes are spared. An acute variant called "pustular bacterid" (105) describes a rare eruption of large and sterile pustules on hands and feet.



FIGURE 7-8. Pustular psoriasis (palmar pustulosis). Confluent pustules on erythematous scaly skin of the palm. (Courtesy of Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.)

Psoriasis and Acquired Immunodeficiency Syndrome

Clinical Features

The association between psoriasis and human immunodeficiency virus (HIV) infection is commonly seen. The prevalence of psoriasis is reported to be 1.3% to 2.5% in HIV-positive patients (106,107). Clinically, psoriasis may have a more severe course with sudden exacerbations and may be refractory to treatment (106,108). Extensive erythrodermic psoriasis may occur (109). Palmoplantar involvement, flexural (inverse) psoriasis, and psoriatic arthritis were found to be more frequent in patients who developed psoriasis after HIV infection (107). Although a direct relation between the stage of HIV infection and the severity of psoriasis has not been found, a trend of low peripheral T-cell $CD4^+$ (helper-inducer) counts and a more severe clinical course have been noted (107).

Psoriasis Vulgaris

Histopathology

The histologic picture of psoriasis vulgaris varies considerably with the stage of the lesion and usually is diagnostic only in early, scaling papules and near the margin of advancing plaques.

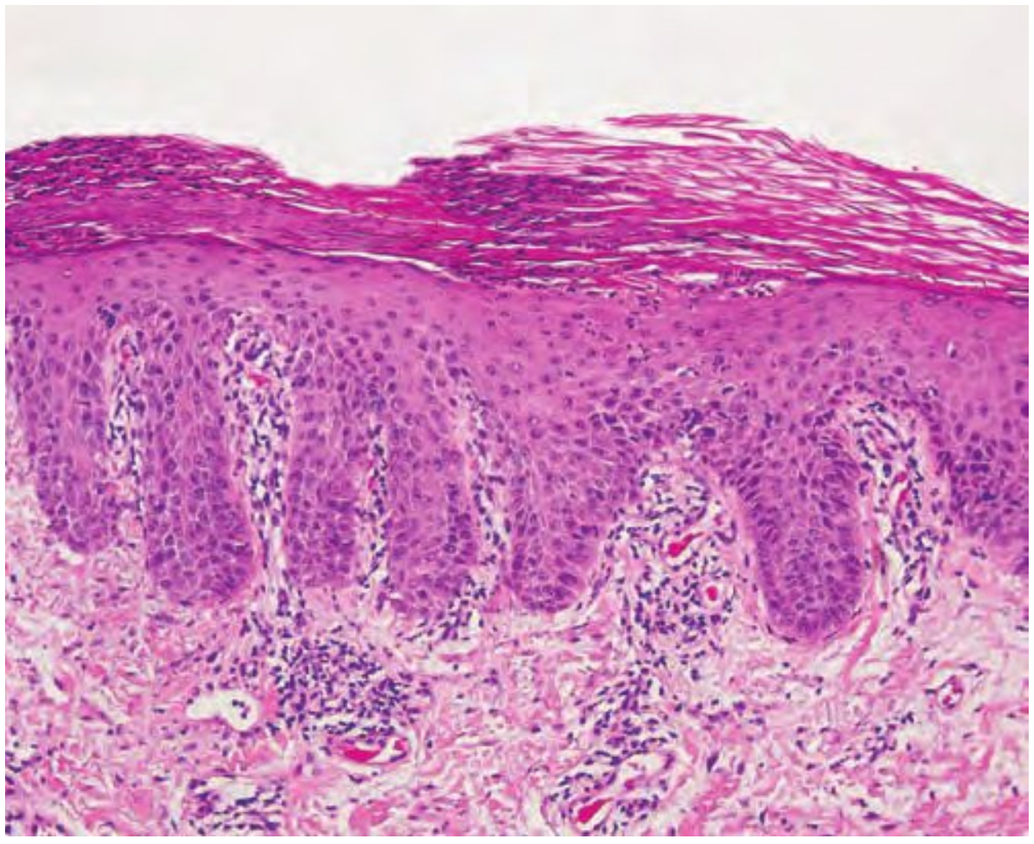


FIGURE 7-9. Early psoriasis. Mounds of parakeratosis with neutrophils, thin granular layer, moderate acanthosis, focal spongiosis, increased mitotic figures, dilated blood vessels at the tip of the dermal papillae, and perivascular infiltrate of lymphocytes and a few neutrophils.

The earliest pinhead-sized macules or smooth-surfaced papules show subtle histologic changes with a preponderance of dermal changes (110,111). At first, there is capillary dilation and edema in the papillary dermis, with a lymphocytic infiltrate surrounding the capillaries. The lymphocytes extend to the lower portion of the epidermis, where slight spongiosis develops. Then focal changes occur in the upper portion of the epidermis, where granular cells become vacuolated and disappear, and mounds of parakeratosis are formed. Neutrophils are usually seen only at the summits of some of the mounds of parakeratosis and appear scattered through an otherwise orthokeratotic cornified layer (Fig. 7-9). These mounds of parakeratosis with neutrophils represent the earliest manifestation of Munro microabscesses (111). At this stage, which is characterized clinically by an early scaling papule, a histologic diagnosis of psoriasis can often be made. In some cases, when there is marked exocytosis of neutrophils, they may aggregate in the uppermost portion of the spinous layer to form small spongiform pustules of Kogoj. Lymphocytes remain confined to the lower epidermis, which, as more and more mitoses occur, becomes increasingly hyperplastic. The epidermal changes are at first focal, but later become confluent, leading clinically to plaques.

In the fully developed lesions of psoriasis, as best seen at the margin of enlarging plaques, the histologic picture is characterized by (a) acanthosis with regular elongation of the rete ridges with thickening in their lower portion; (b) thinning of the suprapapillary epidermis with the occasional presence of small spongiform pustules; (c) pallor of the upper layers of the epidermis; (d) diminished to absent granular layer; (e) confluent parakeratosis; (f) the presence of Munro microabscesses;

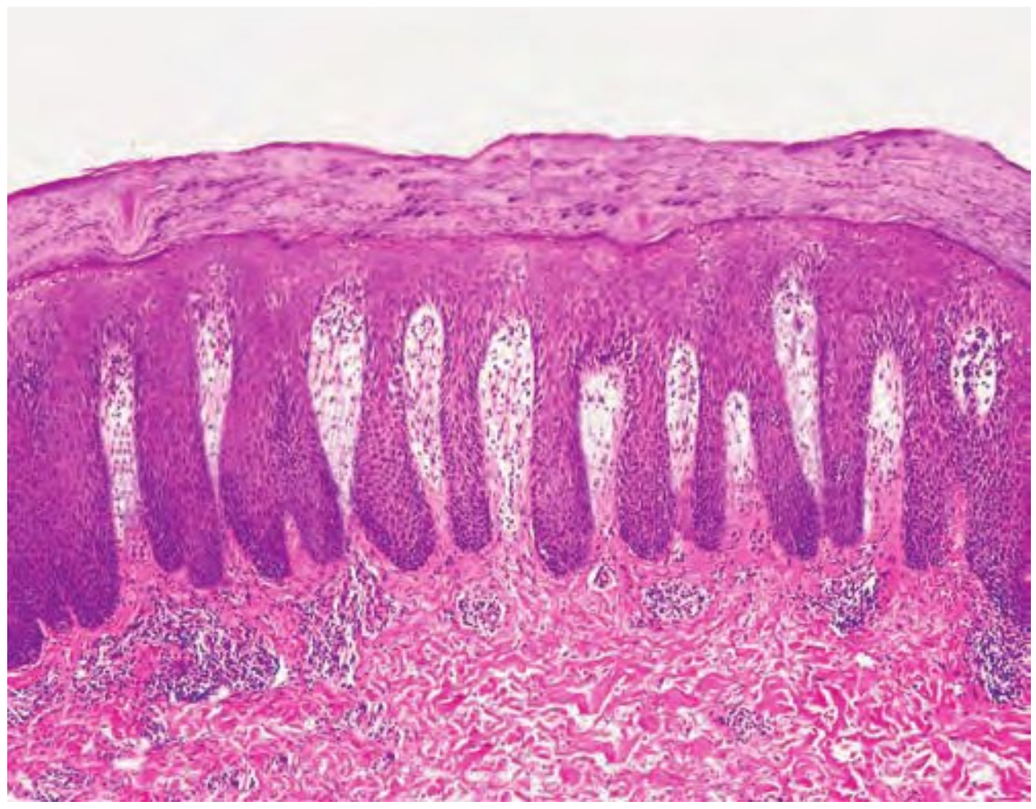


FIGURE 7-10. Psoriasis, well-developed plaque. Markedly elongated rete ridges, absent granular layer, parakeratosis with neutrophils, and dilated tortuous vessels in the dermal papillae.

(g) elongation and edema of the dermal papillae; and (h) dilated and tortuous capillaries (Fig. 7-10).

Of the listed features, only the spongiform pustules of Kogoj and Munro microabscesses are truly diagnostic of psoriasis, and, in their absence, the diagnosis can rarely be made with certainty on a histologic basis. The changes in active psoriasis are discussed in detail later.

The rete ridges show considerable elongation and extend downward to a uniform level, resulting in regular acanthosis (Fig. 7-11). They are often slender in their upper portion but

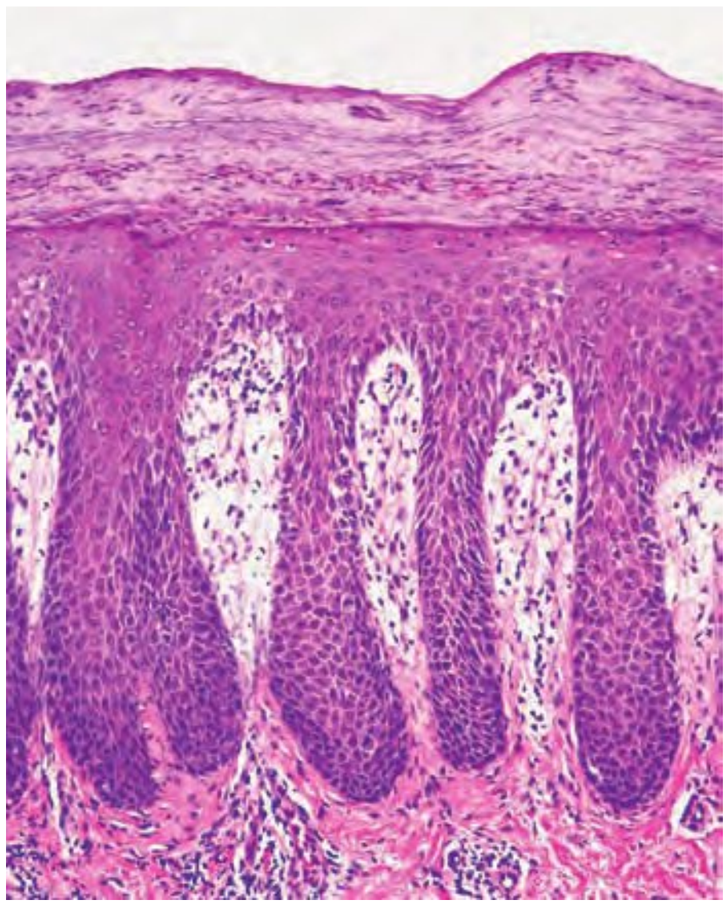


FIGURE 7-11. Psoriasis, well-developed plaque. Acanthosis with club-shaped rete ridges of even length, suprabasal mitoses, thin suprapapillary epidermal plates, absent granular layer, pallor of the upper epidermis, and confluent parakeratosis with collections of neutrophils.

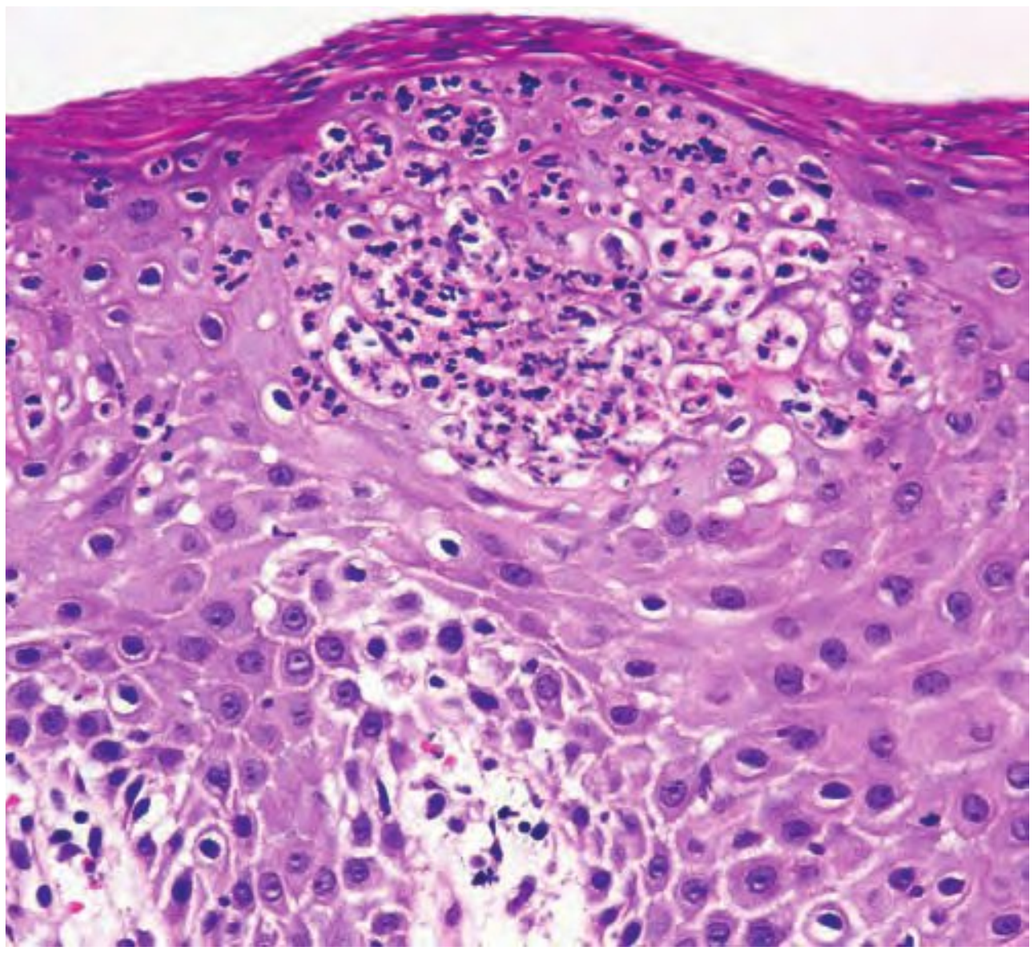


FIGURE 7-12. Psoriasis. Closer view of a spongiform pustule of Kogoj formed by collections of neutrophils in the spinous and granular layers.

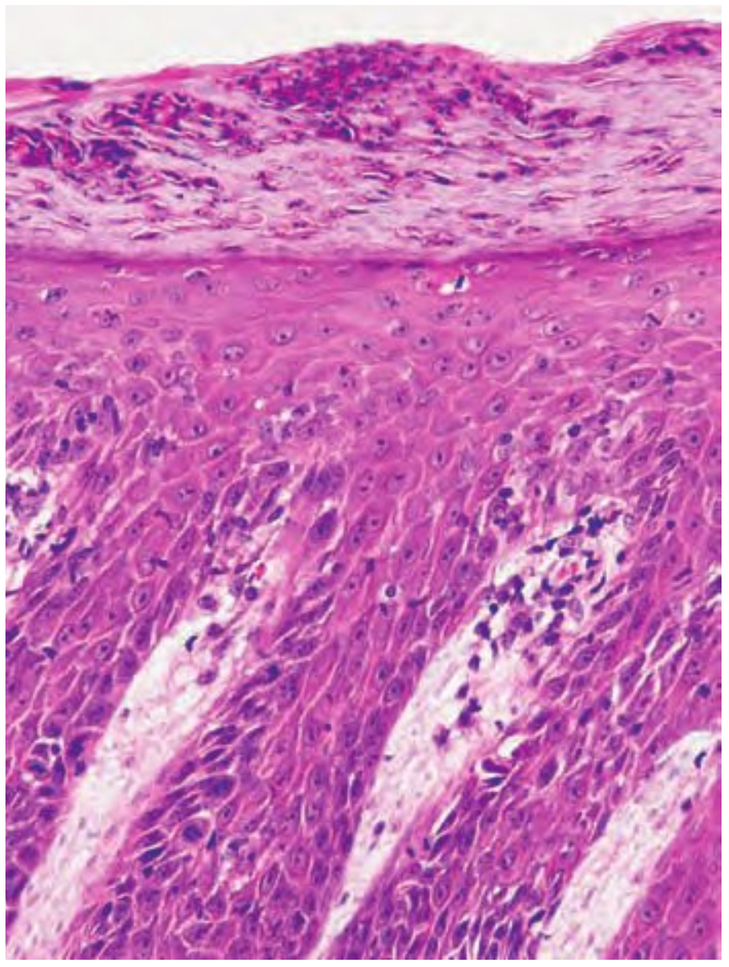


FIGURE 7-13. Psoriasis, plaque lesion. Closer view of the neutrophilic collections within the parakeratotic cornified layer (Munro microabscess). Note the thin suprapapillary epidermal plates and dilated blood vessels in the dermal papillae.

show thickening ("clubbing") in their lower portion. Not infrequently, adjacent rete ridges seem to coalesce at their bases due to tangential sectioning. Usually, intercellular and intracellular edema is absent in the rete ridges, and keratinocytes located well above the basal layer show deep basophilia. In addition, mitoses are not limited to the basal layer as in normal skin but are also seen above the basal layer. This, together with a considerable lengthening of the basal cell layer due to elongation of the rete ridges, results in a marked increase in the number of mitoses. This increase has been calculated to be 27 times the number of mitoses in uninvolved skin (112).

The suprapapillary epidermis appears relatively thin in comparison with the markedly elongated rete ridges, and the cells in the upper layers of the epidermis may appear enlarged and pale stained as a result of intracellular edema and hypogranulosis. Keratinocytes beneath the parakeratotic cornified layer may be intermingled with neutrophils (113). The histologic picture is then that of a small spongiform pustule of Kogoj (Fig. 7-12). Although it is only a micropustule, it is nevertheless of the same type as the much larger macropustules seen in pustular psoriasis. Such a spongiform pustule, highly diagnostic for psoriasis and its variants, shows aggregates of neutrophils within the interstices of a spongelike network formed by degenerated and thinned epidermal cells (114).

In some instances the cornified layer consists entirely of confluent parakeratosis forming a platelike scale with a concomitant absence or diminution of the granular layer. However, occasional focal orthokeratosis with preservation of the underlying granular cells is present.

Munro microabscesses are located within the parakeratotic areas of the cornified layer (Fig. 7-13). They consist of accumulations of neutrophils and pyknotic nuclei of neutrophils that have migrated there from capillaries in the papillae through the suprapapillary epidermis. As a rule, Munro microabscesses are easily found in early lesions but are few in number or absent in longstanding lesions (115).

The dermal papillae, in accordance with the elongation and basal thickening of the rete ridges, are elongated and club shaped. They show edema, and the capillaries within them appear dilated and tortuous. A relatively mild inflammatory infiltrate is present in the upper dermis and the papillae. It consists of lymphocytes, except in early lesions, in which neutrophils are also present in the upper portion of the papillae (116).

An entirely typical histologic picture as described earlier is not always found, even if the biopsy specimens are taken from clinically typical lesions of psoriasis (117). Orthokeratosis often appears intermingled with parakeratosis. In such cases, one may see vertically adjoining areas of orthokeratosis and parakeratosis, focal parakeratosis, or, occasionally, alternating layers of orthokeratosis and parakeratosis. The last-named pattern indicates a fluctuation in the activity of the psoriasis.

The bleeding points that may be produced by gentle scraping of the skin (Auspitz sign) correspond to the tips of dermal papillae. They are attributable to the following histologic changes: parakeratosis, intracellular edema of keratinocytes in the suprapapillary epidermis, thinning of the suprapapillary plates, and dilation of the capillaries in the upper portion of the papillae.

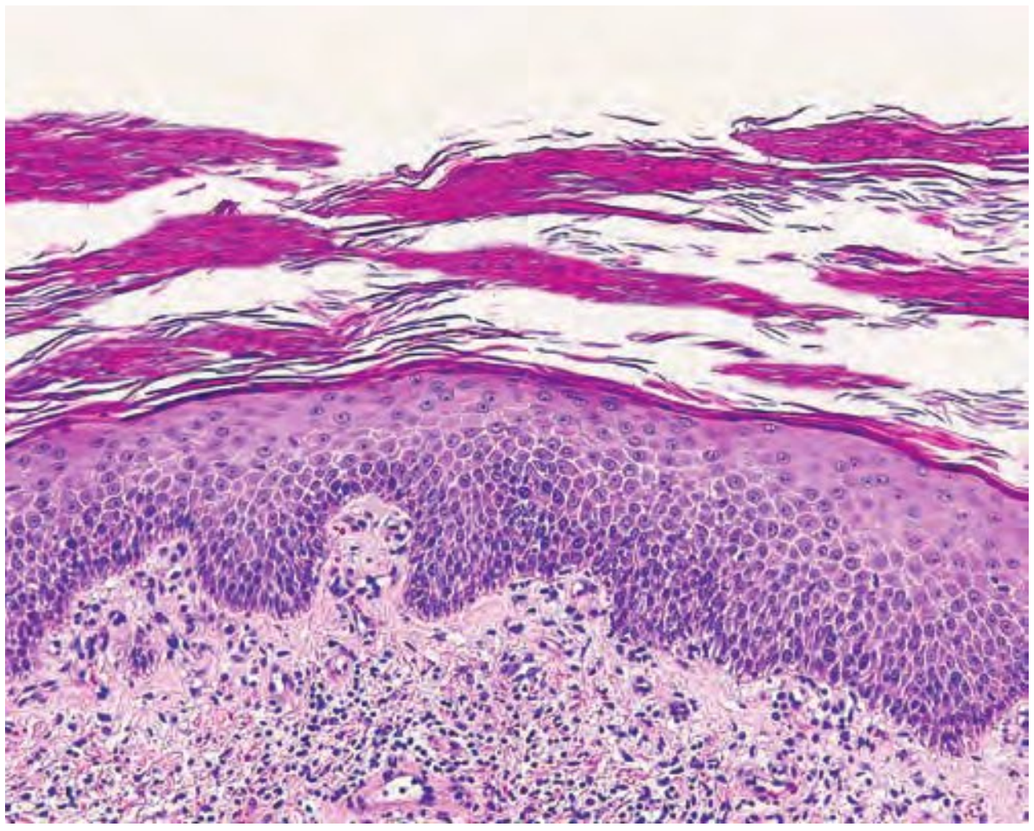


FIGURE 7-14. Eruptive psoriasis. Multilayered mounds of parakeratosis admixed with basket-weave orthokeratosis, slight acanthosis, and dilated blood vessels in the dermal papillae.

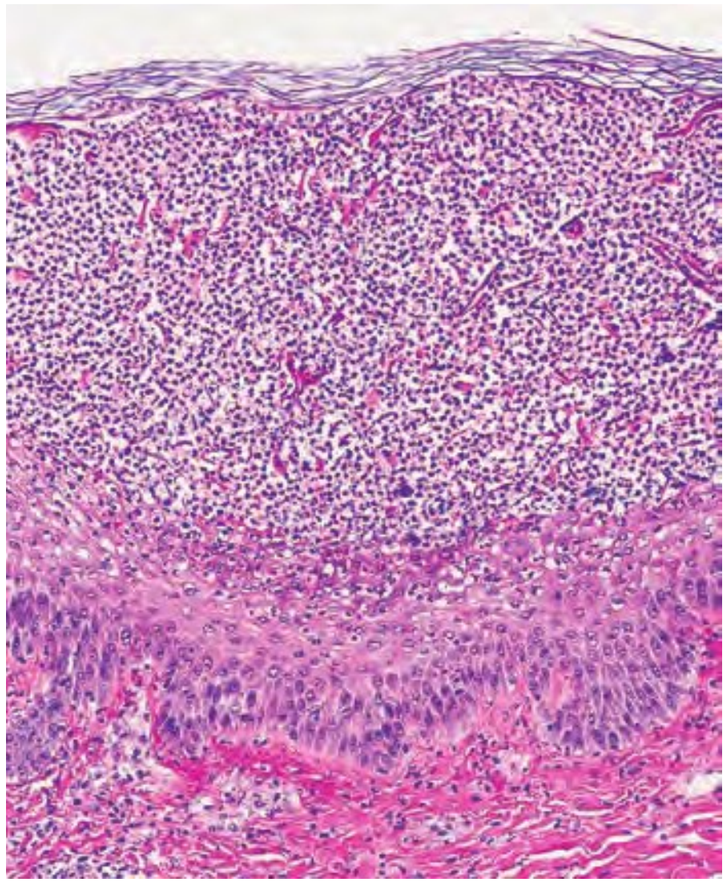


FIGURE 7-15. Pustular psoriasis. Large collections of neutrophils with spongiosis in the upper spinous layer and granular layer.

Guttate or eruptive psoriasis shows the histologic features of an early or active lesion of psoriasis, where there is more pronounced inflammatory infiltrate and less acanthosis as compared with a well-developed chronic plaque of psoriasis. Because of its acute onset, one may observe the remaining normal basket-weave orthokeratotic cornified layer overlying the mounds of parakeratosis with neutrophils, which, in turn, may appear loosely arranged (Fig. 7-14).

The histologic picture of *erythrodermic psoriasis* in some instances shows enough of the characteristics of psoriasis to allow this diagnosis. Frequently, however, the histologic appearance is indistinguishable from that of a chronic eczematous dermatitis (118).

Generalized Pustular Psoriasis

Histopathology

Whereas in ordinary psoriasis the spongiform pustule of Kogoj is a very small micropustule and is seen only in early, active lesions, it occurs as a macropustule in all variants of generalized pustular psoriasis and represents their characteristic histologic lesion. The spongiform pustule forms through the migration of neutrophils from the papillary dermal capillaries to the upper layer of epidermis, where they aggregate within the interstices of a spongelike network formed by degenerated and thinned epidermal cells (114). As the size of the pustule increases, the epidermal cells in the center of the pustule undergo complete cytolysis so that a large single cavity forms (Fig. 7-15). At the periphery of the pustule, however, the network of thinned epidermal cells persists for a much longer time. As the neutrophils of the spongiform pustule move up into the cornified layer, they become pyknotic and assume the appearance of a large Munro abscess (93,119).

In addition to the large spongiform pustules, the epidermal changes in generalized pustular psoriasis are very much like those seen in psoriasis vulgaris, consisting of parakeratosis and elongation of the rete ridges. The upper dermis contains an infiltrate of lymphocytes, and neutrophils can often be seen migrating from the capillaries in the papillae into the epidermis (120). The oral lesions show the same spongiform pustule formation as those seen on the skin (92).

In the healing stage, the lesions of all types of generalized pustular psoriasis may present the same histologic appearance as ordinary psoriasis (93).

Localized Pustular Psoriasis

Histopathology

In the variants of localized pustular psoriasis "psoriasis with pustules" (95,96) and localized annular pustular psoriasis, the histologic picture is the same as that described for generalized pustular psoriasis.

In localized acrodermatitis continua of Hallopeau, the nail bed is mainly affected, showing marked epithelial hyperplasia with variable numbers of spongiform pustules, hypogranulosis, and hyperkeratosis with mounds of parakeratosis with neutrophils. The nail matrix is only occasionally involved (121).

In pustulosis palmaris et plantaris there is a fully developed large intraepidermal unilocular pustule. It is elevated only slightly above the surface but presses onto the underlying dermis. Many neutrophils are present within the cavity of the pustule. The epidermis surrounding the pustule shows slight acanthosis, and an inflammatory infiltrate can be seen beneath the pustule (122). In many instances one can observe typical, although small, spongiform pustules in the epidermal wall of

the pustule, most commonly at the junction of the lateral walls and the overlying epidermis (122–126). These spongiform pustules are identical to those seen in the walls of the pustules of generalized pustular psoriasis.

Very early lesions may show spongiosis and exocytosis of lymphocytes in the lower epidermis overlying the tips of dermal papillae (125). This may be followed by the formation of a small intraepidermal vesicle containing mostly lymphocytes (122,125). Subsequently, there is a massive exocytosis of neutrophils, which penetrate the intercellular spaces of the vesicle wall, where the histologic picture of spongiform pustules is then seen (122). In the acute form, pustular bacterid, leukocytoclastic vasculitis has been described (127).

Psoriasis and Acquired Immunodeficiency Syndrome

Histopathology

The histologic picture in most cases is similar to that of psoriasis. In others, the histologic sections may show acanthosis without thinning of the suprapapillary epidermis, slight spongiosis, rare necrotic keratinocytes, and a superficial perivascular infiltrate of lymphocytes and histiocytes that occasionally contains some plasma cells (128). As in other dermatitides related to AIDS, eosinophils may be present in the inflammatory infiltrate.

Pathogenesis of Psoriasis Vulgaris

Although the cause of psoriasis is unknown, there is increasing evidence of a complex interaction among altered keratinocytic proliferation and differentiation, inflammation, and immune dysregulation.

Electron Microscopy

The earliest recognizable morphologic events in psoriasis have been investigated in lesions that cleared with corticosteroid under occlusion and then were allowed to relapse. The earliest indications of relapse, as seen by electron microscopy, are swelling and intercellular widening of endothelial cells. This is followed by the appearance around postcapillary venules of mast cells showing degranulation. Hours later, activated macrophages migrate into the lower epidermis, where there is loss of desmosome-tonofilament complexes. Only then are lymphocytes and neutrophils seen (129). Ultrastructurally, in well-developed lesions, psoriatic keratinocytes from the suprabasal layers of the epidermis show significant abnormalities. The tonofilaments are decreased in number and in diameter and lack their normal aggregation. The size and number of keratohyaline granules are greatly reduced, and occasionally these are absent (130,131). The cornified cells possess thin tonofilaments and often retain organelles and a nucleus as parakeratotic cells. They often fail to form a marginal band and to lose their outer plasma membrane (132). Basal keratinocytes may show cytoplasmic processes protruding into the dermis through gaps in the basal lamina. These are more numerous in active and untreated lesions and are absent in completely resolved and uninvolved psoriatic skin (133). The intercellular spaces between all epidermal cells are widened because of a deficiency in the glycoprotein-rich cell surface coat, so that intercellular adhesion is limited to the desmosomes (132,134). Electron microscopic studies have confirmed the view that the keratinocytes in psoriasis are defective and not just immature owing to accelerated epidermal proliferation. Although a correlation exists in psoriasis between an increased rate of mitosis and parakeratosis, rapid proliferation of the epidermis does not cause parakeratosis (135).

Ultrastructural studies of the spongiform pustule of Kogoj, one of the most characteristic histologic structures encountered in psoriasis, reveal that it is located in the uppermost portion of the spinous and granular layers, where neutrophils lie intercellularly in a multilocular pustule in which the spongelike network is composed of degenerated and flattened keratinocytes (114).

The ultrastructure of the capillary loops in the dermal papillae shows them to be different from normal capillary loops. In psoriasis, the capillaries show a wider lumen, bridged fenestrations and gaps between endothelial cells, edematous areas in the cytoplasm of endothelial cells, pericytes and myocytes, extravasation of red blood cells and inflammatory cells, and a thickened multilayered basement membrane (136). This finding may be a result of the deposition of amorphous substances and accumulation of collagen fibrils in the basement membrane zone (137).

Epidermal Cell Cycle Kinetics

The rate of epidermal cell replication is markedly accelerated in active lesions of psoriasis, as shown by the higher than normal number of basal and suprabasal mitotic figures and the greater number of premitotic cells labeled by tritiated thymidine (138). The mitotic activity within different lesions of psoriasis and even within the same lesion can vary considerably and seems to be correlated with the degree of parakeratosis. Thus, psoriatic epidermis with 91% to 100% parakeratosis shows on average five times as many mitotic figures as psoriatic epidermis with only 0% to 20% parakeratosis (117). The frequent finding in psoriasis of alternating layers of orthokeratosis and parakeratosis suggests that epidermal growth activity fluctuates in the lesions (117). Step sections of early "punctate" papules show a mitotically very active parakeratotic center surrounded by a zone of a thickened granular layer with a relatively low mitotic rate (139).

Early calculations made it appear likely that in psoriatic lesions there was a great acceleration of the transit time of cells from the basal cell layer to the uppermost row of the squamous cell layer, from approximately 53 days in normal epidermis to only 7 days in the epidermis of active psoriatic lesions (138).

Further investigations (140) have found that (a) the germinative cell cycle is shortened from 311 to 36 hours, indicating that psoriatic keratinocytes proliferate approximately eightfold faster than do normal keratinocytes, (b) there is a doubling of the proliferative cell population in psoriasis from 27,000 to 52,000 cells/mm^2 of epidermal surface area, and (c)

100% of the germinative cells of the epidermis enter the growth fraction instead of only 60% for normal subjects. However, in another study (141), it was shown that the germinative cell cycle time is around 200 hours in normal epidermis and about 100 hours in psoriatic epidermis, a twofold rather than an eightfold acceleration.

The source of the cycling cells in the suprabasal layers of the epidermis is not well defined. They could be an expanded population of basal keratinocytes or could be recruited from the transient-amplifying cells (TAC)—suprabasal keratinocytes committed to terminal differentiation—that might undergo rounds of amplifying divisions above the basal layer (142). Based on keratin studies, it is believed that proliferating keratinocytes may result from recruitment of TAC (142) because they express K1/K10 and predominantly K6/K16 keratins and not K5/ K14 as basal keratinocytes do (143).

Recent studies suggested that psoriatic epidermis shows aberrant expression of apoptosis-related molecules representing suppressed apoptotic process, which might be related to proliferative characteristic of the epidermis in this disease (144).

Keratinocyte Differentiation

Keratinocytes undergo the process of differentiation as they migrate upward through the epidermis from the basal layer to the cornified layer. During this process, different structural proteins are synthesized. One such protein family is the keratins, which are intermediate filaments found in the cytoplasm of all epithelial cells. Studies revealed that the keratin pair K5/K14 is expressed in basal keratinocytes (145) and keratins K1/K10 are found in the suprabasal layers. Involucrin, one of the major precursor proteins of the cornified cell envelope, is detected higher in the granular and cornified layers (146). In psoriatic skin, basal keratinocytes continue to express K5/K14; however, keratins K1/K10 are replaced by the so-called hyperproliferation-associated keratins K6 and K16. In addition, involucrin is expressed prematurely in the lower suprabasal layers (143,147). Keratin 17, normally expressed in the deep outer root sheath of the hair follicle, has been found also in the upper suprabasal keratinocytes within the interfollicular psoriatic epidermis (143).

Immunopathology

Immunologic factors play a very important role in the pathogenesis of psoriasis. Psoriasis is now regarded as a T-cell—mediated disorder. It has been shown that both $CD4^+$ and $CD8^+$ T lymphocytes are found in the papillary dermis and the epidermis of the psoriatic lesions. $CD8^+$ T cells seem to be dominant in the epidermis, whereas the $CD4^+$ T lymphocytes are the predominant subset in the dermis. Presence of $CD8^+$ T cells within the epidermis is believed to be a key event in the pathogenesis of psoriasis (148), with up to one third of them expressing the activation markers (149). Recent data suggest that lesions of psoriasis exhibit clonal expansion of epidermal T lymphocytes. Recurrent lesions also show the recruitment of the identical expanded T-cell clones. Nonlesional skin did not show the presence of the same T-cell receptor rearrangements. These findings suggest that a stable antigen-specific pathogenic T-cell response may play a role in disease perpetuation in psoriasis (150–152). The activation of T lymphocytes may be due to bacterial superantigens such as group A β-hemolytic streptococci. It is suggested that amino acid sequences from streptococcal M-protein share sequences with keratin 17, and therefore an epitope on keratin 17 or keratin 6 may be a target for autoreactive lymphocytes in psoriasis (153,154). Group A streptococcal–reactive $CD8^+$ and to a lesser extent $CD4^+$ T cells in psoriatic epidermis may play a role in the pathogenesis of both poststreptococcal guttate psoriasis (155) and chronic plaque psoriasis (156). Activated $CD4^+$ T cells produce a variety of cytokines, including interleukin-2 (IL-2), tumor necrosis factor-α (TNFα), and γ-interferon (γIFN), which is also produced by $CD8^+$ T lymphocytes (157).

Keratinocytes stimulated by TNFα may produce IL-8, which is a potent T-lymphocyte and neutrophil chemoattractant present in increased amounts in psoriatic epidermis. This cytokine may be involved in the formation of Munro microabscesses (158).

γIFN is believed to play an important role in the initiation of psoriatic lesions as demonstrated by the induction of pinpoint lesions of psoriasis at sites of γIFN injection in previously uninvolved skin (159).

γIFN induces the expression of the ICAM-1 in keratinocytes and endothelial cells. This molecule mediates the adhesion and trafficking of lymphocytes into the epidermis by binding to its ligand lymphocyte function-associated antigen-1 (LFA-1) expressed on lymphocyte membranes (158). In addition, γIFN-inducible protein (IP-10) is overexpressed by keratinocytes in psoriatic lesional skin (160). IP-10 is detected in epidermis during cellular immune responses and may have chemotactic as well as mitogenic properties. Psoriatic keratinocytes are shown not to be responsive to the growth inhibition effects of γIFN, leading to their hyperproliferative state in the disease (161).

Increased expression of p53 and downregulation of Bcl-2, consistent with the dynamics of psoriasis, have been shown (162). In addition, aberrant cytokine expression has been proposed as an underlying cause of psoriasis, with IL-23 being considered as a master regulator cytokine in the pathogenesis of the disease (163).

Pathogenesis of Localized Pustular Psoriasis

A relationship of pustulosis palmaris et plantaris with psoriasis is not generally accepted, although two facts favor a close relationship: the relatively common occurrence of psoriasis in patients with pustulosis palmaris et plantaris, reported in 19% to 48% of patients (164–166), and the common presence of spongiform pustules in the walls of the pustules of pustulosis palmaris et plantaris. In addition, a leukotactic factor identical to that noted in psoriasis has been found in pustulosis palmaris et plantaris (167).

Pathogenesis of Psoriasis and AIDS

There is evidence of the role of both $CD8^+$ and $CD4^+$ T lymphocytes and γIFN in the pathogenesis of psoriasis in AIDS

(128,168). Paradoxically, as T-helper cell counts decline, it appears that psoriatic lesions exacerbate until a preterminal stage, when the dermatitis improves. The latter event is probably a consequence of a decreased local production of γIFN due to the increasing number of infected T-helper lymphocytes or a diminished number of dermal lymphocytes available to produce this cytokine (115). However, in a recent study, it was shown that γIFN serum levels were much higher in HIV-positive psoriatic patients than HIV-negative subjects (169).

The immunodysregulation resulting from HIV infection may trigger psoriasis in those genetically predisposed by carrying the HLA-Cw□0602 allele. HLA-Cw□0602 could act as a cross-reactive target for cytotoxic T lymphocytes responding to peptides from microorganisms. Human retrovirus-5 has been implicated in the pathogenesis of psoriatic arthropathy but not psoriasis (168). Immunohistochemical studies showed similar proportions of T-lymphocyte subtypes in psoriasis of HIV-positive patients and in psoriasis of immunocompetent hosts (170). Furthermore, there is evidence of identical keratinocyte expression of γIFN-induced IP-10 in both groups (128). These two findings suggest that the cellular immune reactions involved in the pathogenesis of psoriasis may be similar in AIDS and non-AIDS patients (170).

Differential Diagnosis

Two histologic features are of great value in the diagnosis of psoriasis vulgaris: (a) mounds of parakeratosis with neutrophils at their summits (Munro microabscesses) and (b) spongiform micropustules of Kogoj in the uppermost layers of the spinous layer. Dilation and tortuosity of capillaries in the papillae may also help in the diagnosis. All other features, such as acanthosis with elongation of the rete ridges and parakeratosis, can be found also in chronic eczematous dermatitis, such as *atopic dermatitis*, *nummular dermatitis,* or *allergic contact dermatitis*, which then may appear to be "psoriasiform." However, the elongation of rete ridges is uneven. Although mild spongiosis may be seen in psoriasis, the presence of marked spongiosis and especially of coagulated serum as evidence of crusting in the cornified layer are features speaking against psoriasis, except in psoriasis on volar skin, in which spongiosis may be prominent. In addition, eosinophils, which are commonly found in allergic contact dermatitis and mainly in HIV-positive patients, are rarely seen in the psoriatic infiltrate. Difficulties may arise in treated lesions of psoriasis and in those with superimposed allergic contact dermatitis secondary to topical treatments. *Lichen simplex chronicus* is considered in the differential diagnosis of fully developed psoriatic plaques. In contrast to psoriasis, it shows a prominent granular layer, more irregular acanthosis, and fibrosis of the papillary dermis with collagen bundles aligned perpendicular to the skin surface. *Seborrheic dermatitis* may be very difficult to distinguish from psoriasis vulgaris, especially if overlap occurs. Accentuated spongiosis, mounds of parakeratosis with neutrophils predominantly at the follicular ostia, and more irregular acanthosis are histologic features suggestive of seborrheic dermatitis. *Pityriasis rubra pilaris* shares some histologic features with psoriasis, namely, acanthosis and parakeratosis. However, it could be differentiated from well-developed lesions of psoriasis by the presence of thick suprapapillary plates, broader and shorter rete ridges, and a preserved granular layer and alternating ortho- and parakeratosis. It also lacks Munro microabscesses and neutrophils in the infiltrate (171). Although the Kogoj spongiform pustule is highly diagnostic of the psoriasis group of diseases, including Reiter's disease, histologically typical spongiform pustules may occur also in *pustular dermatophytosis*, *bacterial impetigo*, *pustular drug eruptions*, and *candidiasis*, particularly if pustules are clinically present (172). Periodic acid-Schiff (PAS) and Gram stains are useful for identifying the infectious microorganisms. Aggregates of neutrophils with pyknotic nuclei within areas of parakeratosis may occur in conditions other than psoriasis, but they generally differ from Munro microabscesses by being larger and less well circumscribed and by often showing crusting.

Because of the clinical and, particularly, the histologic resemblance of the tongue lesions in pustular psoriasis with those seen in geographic tongue, it has been suggested that geographic tongue represents an abortive form of pustular psoriasis (173).

REITER'S DISEASE

Reiter's disease is a sterile arthritis associated in most cases with a distant infection causing enteritis or urethritis. Reiter's disease predominantly affects young men and consists of the triad of urethritis, arthritis, and conjunctivitis. Although as a rule the arthritis occurs in attacks and is followed by recovery, it progresses in some cases to cause permanent damage to the affected joints (174,175). Cutaneous lesions occur in about half of affected patients. Lesions have a predilection for glans penis (balanitis circinata), palms and soles (keratoderma blennorrhagicum), and the subungual regions (Fig. 7-16).



FIGURE 7-16. Reiter's disease. Confluent erythematous scaly papules and plaques on the dorsum of feet and toes, with nail dystrophy. (Courtesy of Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.)

In uncircumcised men, balanitis circinata presents as superficial crusted erosions forming a serpiginous pattern. In circumcised men the condition presents as erythematous hyperkeratotic and coalescent papules on the glans. Lesions on the palms and soles are erythematous, mollusk-like plaques with central keratotic excrescences. Pustular lesions may also develop. The subungual lesions consist of hyperkeratosis with opacification of the nail plate, and eventual shedding of the nail plate may occur. The prevalence of Reiter's disease in HIV-infected individuals is less than 1%; however, the disease appears to be more severe in immunocompromised patients (176).

Histopathology. Early pustular lesions on the palms or soles show a spongiform macropustule in the upper epidermis (174,177). In addition, one observes parakeratosis and elongation of the rete ridges.

As the lesions age, the parakeratotic cornified layer thickens considerably, which correlates with the keratotic excrescences seen clinically. The parakeratotic cornified layer is intermingled with the pyknotic nuclei of neutrophils. In old lesions, spongiform pustules are no longer seen, and the histologic picture shows acanthosis and orthokeratosis with only a few areas of parakeratosis, but occasionally the histologic picture resembles that of psoriasis (174).

Pathogenesis. Most cases of Reiter's disease are probably caused by microorganisms that infect the urogenital or gastrointestinal systems, such as *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and *Shigella*, *Salmonella*, *Campylobacter*, *Cyclospora*, and *Yersinia* species. *Chlamydia trachomatis* has been cultured from urethral samples in nearly half of the patients and is believed to be capable of triggering Reiter's syndrome in susceptible men (178). Although joint cultures are negative for bacteria in Reiter's disease, hybridization studies have detected chlamydial RNA in synovial specimens (179). The occurrence of Reiter's syndrome after bacille Calmette-Guérin immunotherapy for bladder cancer has been reported (180). Eighty percent of Reiter's disease patients are HLA-B27 positive (176); however, the precise role of this major histocompatibility class I antigen in the development of this disease is unclear.

A close relationship to psoriasis has been assumed for the cutaneous lesions because of their clinical resemblance to psoriasis and the presence of spongiform pustules (174). Similarly, the arthritis of Reiter's disease resembles that of psoriasis not only clinically but also by the absence of rheumatoid factor (175).

Differential Diagnosis. The early spongiform pustule seen in Reiter's disease is indistinguishable from the spongiform pustule seen in pustular psoriasis. Slightly older lesions often can be identified as representing Reiter's disease, in contrast to psoriasis, by the presence of a markedly thickened cornified layer.

PARAPSORIASIS

There are three entities described as parapsoriasis: small-plaque parapsoriasis, large-plaque parapsoriasis, and parapsoriasis variegata.

Large-plaque parapsoriasis and *parapsoriasis variegata* are best considered as early stages of cutaneous T-cell lymphoma/mycosis fungoides (181). These are discussed further in Chapter 31.

The *small-plaque parapsoriasis* is also known as xanthoerythrodermia perstans of Crocker (182) and as digitate dermatosis (183). Pink-to-yellow, slightly scaly, oval or elongated, often fingerprint-like patches 1 to 5 cm in diameter are symmetrically distributed over the trunk and the proximal portions of the extremities following the tension lines of the skin (184). The eruption is usually asymptomatic, has a chronic course, and tends to persist. In some instances, cases diagnosed originally as small-plaque type later showed reticulate pigmentation and atrophy and were reclassified as the large-plaque type (185).

Histopathology. The small-plaque parapsoriasis shows focal epidermal involvement consisting of slight spongiosis, exocytosis of lymphocytes, mild acanthosis, and parakeratosis (183,186). Elongated mounds of parakeratosis with collections of plasma above a basket-weave cornified layer is a characteristic finding (Fig. 7-17). In the papillary dermis, there is a mild superficial perivascular lymphocytic infiltrate that in some instances is more pronounced and resembles that seen in the large plaque type; such cases require inclusion in the large-plaque category (185,187). It must be conceded that, in some instances, a clinical or histologic distinction of small-plaque parapsoriasis from large-plaque parapsoriasis is difficult, so that only the subsequent course decides the issue (185).

Pathogenesis. The inflammatory infiltrate in small-plaque parapsoriasis is dominated by $CD4^+$ (helper-inducer) T lymphocytes with a small proportion of the $CD8^+$ (cytotoxic-suppressor)

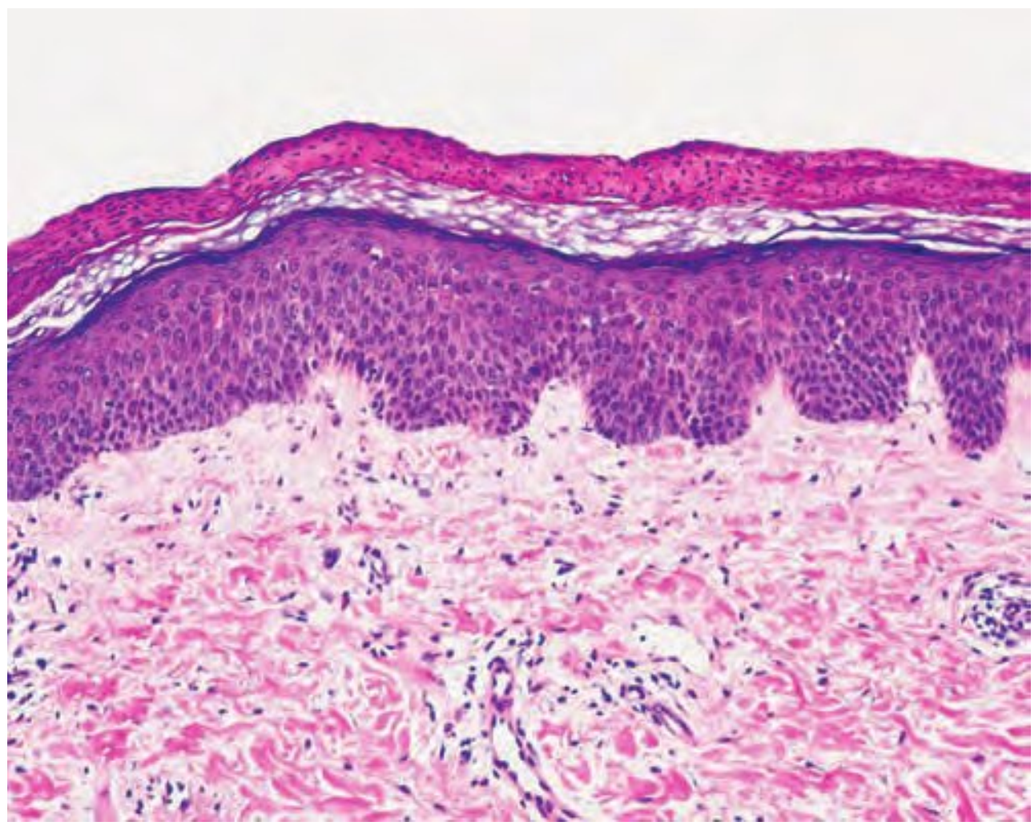


FIGURE 7-17. Digitate dermatosis (small-plaque parapsoriasis). Characteristic elongated mound of parakeratosis with collections of plasma above a basket-weave cornified layer, preserved granular layer, and minimal acanthosis. There is a sparse superficial perivascular lymphocytic infiltrate.

T lymphocytes subset. Langerhans cells are increased in the epidermis and dermis (188).

Relationship to Lymphoma. Although it is generally accepted that small-plaque parapsoriasis, or digitate dermatosis, is a benign disorder without the potential for transformation into mycosis fungoides (181,183,185,189,190), it has been shown that in some cases there is a dominant clonal rearrangement of the infiltrating T lymphocytes (188). Accordingly, some authors hypothesize that small-plaque parapsoriasis could be placed into the category of "abortive lymphomas," which includes conditions in which clonality can be demonstrated but conversion into a systemic lymphoma does not occur (191). However, some believe that small-plaque parapsoriasis is a form of mycosis fungoides (192), and in a retrospective cohort study of more than 100 patients in a 26-year follow-up period, 10% of those diagnosed with small-plaque parapsoriasis and 35% of those diagnosed with the large-plaque variant developed histologically confirmed mycosis fungoides (193). Another study detected a clonal T-cell proliferation in the peripheral blood but not in the skin of patients with small-plaque parapsoriasis, suggesting that this disorder is not strongly related to mycosis fungoides, where there is clonal T-cell proliferation in both peripheral blood and skin (194).



FIGURE 7-18. Pityriasis rosea. Round to oval, salmon-colored patches following the lines of cleavage on the trunk. (Courtesy of Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, New York.)

PITYRIASIS ROSEA

Pityriasis rosea is a self-limited dermatitis usually lasting from 4 to 7 weeks. It frequently starts with a herald patch, followed by a disseminated eruption. The lesions, found chiefly on the trunk, neck, and proximal extremities, consist of round to oval salmon-colored patches following the lines of cleavage and showing peripherally attached thin, cigarette paper—like scales (Fig 7-18). Several typical and atypical clinical variants have been described, including papular, vesicular, urticarial, purpuric, and recurrent forms (195,196).

Histopathology. The patches of the disseminated eruption show a superficial perivascular dermal infiltrate that consists predominantly of lymphocytes, with occasional eosinophils and histiocytes. Lymphocytes extend into the epidermis (exocytosis), where there is spongiosis, intracellular edema, mild to moderate acanthosis, areas of decreased to absent granular layer, and focal parakeratosis with plasma (197–199). Intraepidermal spongiotic vesicles (197,198) and a few necrotic keratinocytes (200) are found in some cases. A common feature is the presence of extravasated erythrocytes in the papillary dermis, which sometimes extend into the overlying epidermis (200,201) (Fig. 7-19). Occasionally, multinucleated keratinocytes in the affected epidermis can be seen (201). Late lesions from the disseminated eruption are more likely to have a psoriasiform pattern (197) and a slight increased number of eosinophils in the inflammatory infiltrate (199). The herald patch may have, in addition to the histopathologic changes described earlier, more pronounced acanthosis, deeper and

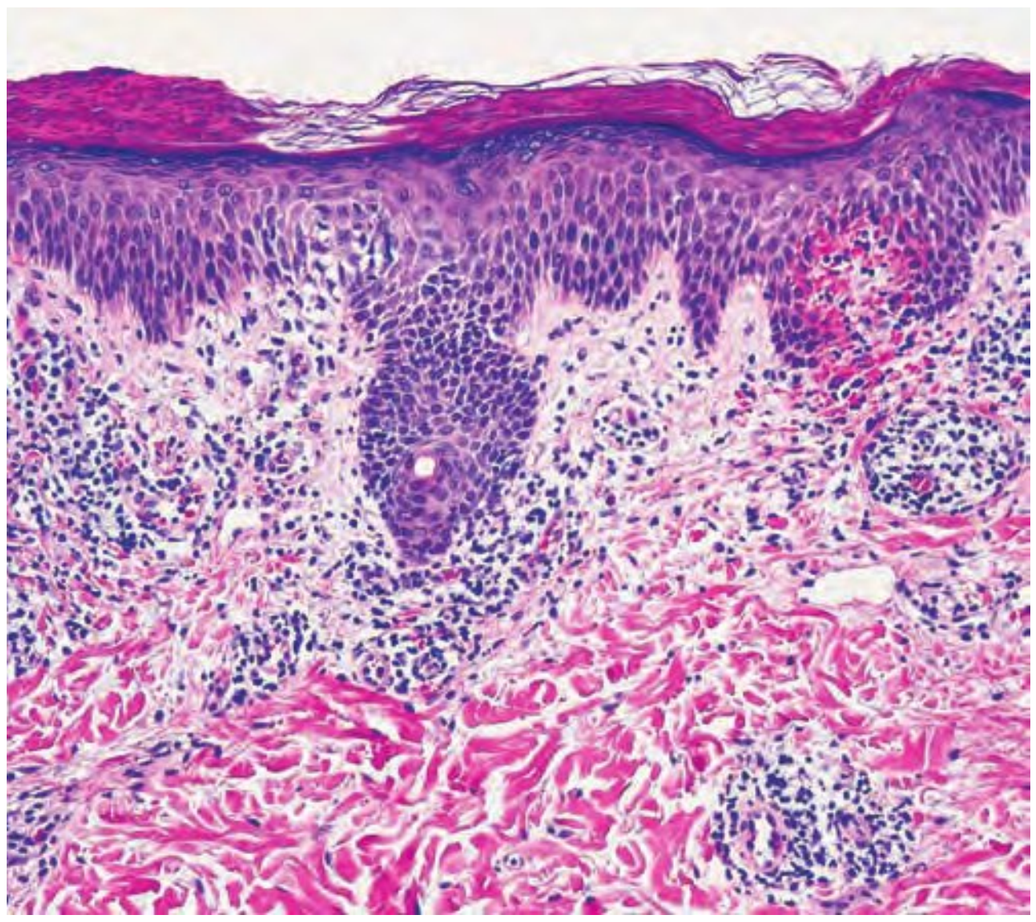


FIGURE 7-19. Pityriasis rosea. Superficial perivascular infiltrate of lymphocytes and extravasated erythrocytes that extend to the epidermis, where there is moderate acanthosis, spongiosis, decreased granular layer, and mounds of parakeratosis.

denser perivascular inflammatory infiltrate, and papillary dermal edema (201).

Pathogenesis. The cause of pityriasis rosea is unknown, although a viral etiology such as human herpesvirus 7 is highly suspected (202). Enterovirus infection has also been proposed as a possible cause of the disease (203). Several drugs have produced pityriasis rosea–like reactions that on their withdrawal have subsided (204). Cell-mediated immunity may be involved in the pathogenesis of pityriasis rosea due to the presence of activated helper-inducer T lymphocytes ($CD4^+$/HLA-DR^+) in the epidermal and dermal infiltrate (205) in association with a highly increased number of Langerhans cells ($CD1a^+$) (206) and the expression of HLA-DR^+ antigen on the surface of keratinocytes located around the area of lymphocytic exocytosis (207).

Differential Diagnosis. The differential diagnosis includes superficial gyrate erythema and small-plaque parapsoriasis (digitate dermatosis). The histopathologic picture in superficial gyrate erythema could be identical to that seen in milder forms of pityriasis rosea. Elongated mounds of parakeratosis with plasma, sparse superficial perivascular lymphocytic infiltrate, minimal exocytosis, and spongiosis are features of small-plaque parapsoriasis (186).

GIANOTTI-CROSTI SYNDROME (PAPULAR ACRODERMATITIS OF CHILDHOOD AND PAPULOVESICULAR ACROLOCATED SYNDROME)

Papular acrodermatitis of childhood was first described by Gianotti in 1955 (208). It is clinically characterized by a nonpruritic, symmetric eruption of monomorphic erythematous papules on the face, extremities, and buttocks lasting about 3 weeks. It was originally described in association with lymphadenopathy and hepatitis B viral infection (209). However, in recent years, it has become apparent that similar acral papular eruptions may occur with several other viruses, such as Epstein-Barr virus, coxsackie virus, parainfluenza virus, vaccine-related virus, and cytomegalovirus, among others (210–213). In such cases, there is often no hepatitis or lymphadenopathy. These eruptions were classified by Gianotti (209) in a separate category as "papular or papulovesicular acrolocated syndrome." However, further studies (213,214) failed to identify repeatable clinical differences between papular acrodermatitis of childhood and papulovesicular acrolocated syndrome. The term Gianotti-Crosti syndrome now applies to all self-limited, acrolocated, papular eruptions that occur in association with an underlying viral infection (215). Atopic background has recently been shown to have a significant association with this syndrome (216).

Histopathology. There is a superficial and middermal perivascular infiltrate of lymphocytes and histiocytes with some lymphocytes extending to the overlying epidermis, where there is focal spongiosis and parakeratosis. In some cases, there is associated papillary dermal edema and extravasation of erythrocytes. In some instances, true lymphocytic vasculitis has been described with lymphocytes in the vessel walls and extravasated erythrocytes into the upper dermis (210). Gianotti-Crosti syndrome associated with Epstein-Barr virus is reported to have marked papillary dermal edema with minimal spongiosis and rare eosinophils in the dermal infiltrate (217). The inflammatory pattern may also present as a lichenoid interface dermatitis (218).

Pathogenesis. Immunohistochemical stains have shown that the inflammatory infiltrate is composed predominantly of $CD4^+$ (helper-inducer) T lymphocytes and about 20% of $CD8^+$ (suppressor-cytotoxic) T lymphocytes. There is also an increased number of Langerhans cells in the epidermis. A virus-induced type IV hypersensitivity reaction has been proposed (219). The surface antigen of the hepatitis B virus is detectable in the sera of all cases of papular acrodermatitis of childhood due to hepatitis B virus by radioimmunoassay. Cases in which serologic studies for hepatitis B virus are negative require studies for other viruses by means of throat swabs and stool samples and by testing for antibodies (211).

MUCOCUTANEOUS LYMPH NODE SYNDROME (KAWASAKI'S DISEASE)

The mucocutaneous lymph node syndrome, first reported in 1967 (220), is most common in Japanese or Korean children younger than 5 years of age, although it can occur in all races (221) either sporadically or epidemically. A definitive diagnosis is established by the presence of unexplained fever lasting 5 or more days and of at least four of five clinical criteria: (a) bilateral conjunctivitis; (b) erythematous oral mucosa, injected or dry fissured lips, and "strawberry tongue"; (c) erythema and indurated edema of hands and feet, often followed by periungual desquamation; (d) polymorphous skin rash; and (e) cervical nonsuppurative lymphadenopathy (222). Measles and group A β-hemolytic streptococcal infections may closely resemble Kawasaki's disease and must be excluded (223).

The course of the disease could be divided in three clinical phases: acute, subacute, and convalescent. The first phase is the febrile period, in which all the diagnostic signs may be seen (224). The rash appears around the third to fifth day of illness and may have different morphologic patterns, such as maculopapular, morbilliform, scarlatiniform, or urticarial (225). It involves the trunk and extremities and in some cases has a peculiar perineal distribution (226).

Recently a psoriasiform skin eruption that occurs during either the acute or convalescent phase has been described, with some lesions being pustular (227,228). There are many other associated systemic manifestations, but cardiovascular complications account for the death of 2% of the children with the disease (220). Twenty percent of untreated patients may develop coronary artery aneurysms (229), and myocardial infarction secondary to aneurysmal thrombosis is the principal cause of death (230). A rare and serious complication is the development of peripheral ischemia and gangrene (231).

Histopathology. The histologic changes in the skin consist of a sparse perivascular infiltrate of lymphocytes and histiocytes

(220), marked papillary dermal edema, and dilation of blood vessels (232). Mild exocytosis of lymphocytes can be seen (233). An uncommon pustular variant of Kawasaki's disease shows sterile intraepidermal spongiform pustules with neutrophils (234).

Pathogenesis. Electron microscopic studies have revealed swelling and focal degenerative changes of endothelial cells from the superficial and deep vascular plexuses of the skin (232). Immunohistochemical stains have shown that the inflammatory infiltrate has predominantly $CD4^+$ (helper-inducer) T lymphocytes and $CD13^+$ macrophages, with only a few $CD8^+$ (suppressor-cytotoxic) T lymphocytes and no $CD20^+$ B lymphocytes. There is also expression of HLA-DR by keratinocytes and endothelial cells (233). In the acute stage of the disease, IL-1α and TNFα can be detected in the epidermis. TNFα is also found on blood vessel walls (233). All of these findings support the hypothesis of a cell-mediated immune reaction in the pathogenesis of the disease, possibly triggered by a virus (235), conventional antigen (236), or superantigen (237). It has been suggested that vascular endothelial growth factor, also known as vascular permeability factor, together with hepatocyte growth factor might play an important role in the pathophysiology of Kawasaki's disease, and their serum levels could be a powerful predictor for the development of coronary artery lesions (238). The detection of autoantibodies against a 70-kD protein from vascular smooth muscle cells may also contribute to the coronary and systemic vasculitis in Kawasaki's disease (239).

LICHEN PLANUS

Lichen planus is a subacute or chronic dermatosis that may involve skin, mucous membranes, hair follicles, and nails (240).

In glabrous skin, the eruption is characterized by small, flat-topped, shiny, polygonal, violaceous papules that may coalesce into plaques. The papules often show a network of white lines known as Wickham's striae (Fig. 7-20). Pruritus is usually

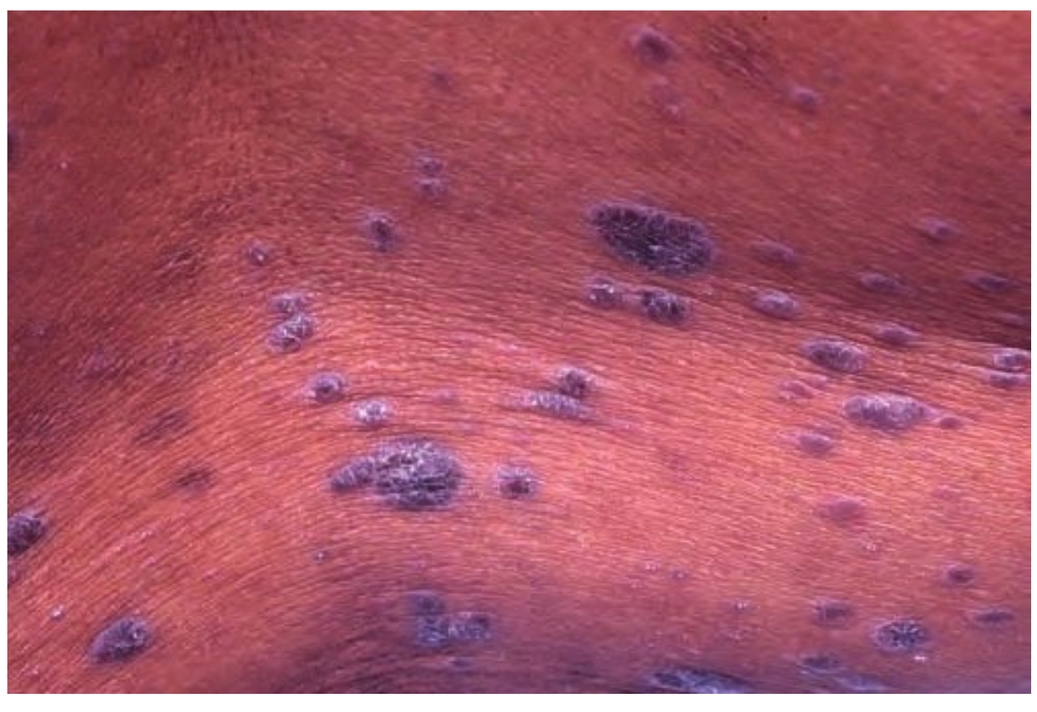


FIGURE 7-20. Lichen planus. Flat-topped, shiny, violaceous papules with white Wickham's striae. (Courtesy of Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, New York.)



FIGURE 7-21. Oral lichen planus. Lacy reticular network of white coalescent papules involving the buccal and labial mucosa. (Courtesy of Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.)

pronounced. The disease has a predilection for the flexor surfaces of the forearms, legs, and glans penis. The eruption may be localized or extensive, and Koebner's phenomenon is commonly seen (241).

The oral lesions of lichen planus are frequently seen as either sole manifestation of the disease or associated with cutaneous involvement (242). They usually involve the buccal and glossal mucosa and most often consist of a lacy reticular network of white coalescent papules (Fig. 7-21) (243). Besides the reticular type, other lesional patterns have been described, such as plaquelike, atrophic, papular, erosive, and bullous (240,244).

The nails are involved in about 10% of cases and show roughening, longitudinal ridging, and, rarely, thinning with destruction (245). Pterygium formation is a frequent finding.

A common variant is *hypertrophic lichen planus*, which is usually found on the shins and consists of thickened, often verrucous plaques. In contrast, *vesicular lichen planus* is rare. It shows vesicles situated only on some of the preexisting lesions (246). It is different from the so-called *lichen planus pemphigoides* in which the eruption is more disseminated and the bullae are more extensive, arising from the papules of lichen planus or from normal-appearing skin (247–250). Lichen planus pemphigoides manifesting exclusively in the oral mucosa has recently been reported (251). Although lichen planus pemphigoides and bullous pemphigoid manifest in different ways clinically, the same antigen may be involved in the immunopathogenesis of these two diseases (see pathogenesis discussion).

Lichen planopilaris designates the folliculotropic variant of lichen planus, which predominantly involves the scalp. Initially, there may only be follicular papules or perifollicular erythema; however, with progressive hair loss, irregularly shaped atrophic patches of scarring alopecia develop on the scalp. The axillae and the pubic region may also be affected, and the alopecia in these areas may be cicatricial (252). Hyperkeratotic follicular papules may also be seen on glabrous skin. The association of scarring alopecia of hair-bearing areas and hyperkeratotic follicular papules on glabrous skin is known as

Graham-Little syndrome. Lichen planopilaris may also coexist with typical lesions of lichen planus on skin, mucous membranes, or nails. Linear lichen planopilaris of the face resolving with scarring has also been described (253).

Ulcerative lichen planus, a rare but quite characteristic variant of lichen planus, shows bullae, erosions, and painful ulcerations on the feet and toes resulting in atrophic scarring and permanent loss of the toenails. It is usually associated with patches of atrophic alopecia of the scalp and with cutaneous and oral lesions of lichen planus (254,255).

Lichen planus actinicus, or *pigmentosus*, occurs mainly in Middle Eastern countries, where between 20% and 30% of the cases of lichen planus are of this type (256,257). It tends to be more common in children or young adults. The lesions develop in spring and summer on sun-exposed areas, especially the face. Three different forms have been described: annular (the most common type), pigmented (resembling melasma) (258), and dyschromic (259). The lesions are typically annular plaques with central slate blue to light brown pigmentation and well-defined, slightly raised hypopigmented borders. Pruritus is minimal or absent.

The *overlap syndrome*, or *lichen planus/lupus erythematosus,* refers to a heterogeneous group of patients bearing at the same time skin lesions with clinical, histologic, and/or immunologic features typical of both diseases (260). The cutaneous findings in these unusual cases consist of erythematous to purplish scaly patches and plaques, some of which show central atrophy, with a predilection for photodistributed areas or acral portions of extremities (260,261).

Twenty-nail dystrophy may be encountered in adults as well as children. The nails have longitudinal ridging and distal notching and splitting. With time, they become thin and roughened. Clinically, the nail changes resemble those seen in lichen planus (262,263). Other manifestations of lichen planus are usually absent. In children, the nail changes tend to involute spontaneously after a few years. In familial cases, it tends to have an unremitting course. Congenital cases have been described (264). Twenty-nail dystrophy may be idiopathic or may be associated with alopecia areata, atopic dermatitis, lichen planus, or psoriasis.

The coexistence of *lichen nitidus* with lichen planus is frequent enough that some authors have suggested that both entities are variants of the same disease (265).

Malignant transformation of cutaneous lichen planus occurs in less than 1% of cases (266). In hypertrophic lichen planus of the leg, development of squamous cell carcinoma, verrucous carcinoma, or keratoacanthoma is an exceptional occurrence (267–269). There have been reports of squamous cell carcinoma arising occasionally on long-standing lesions of lichen planus situated on mucous membranes or the vermillion border (270,271). The incidence of carcinoma evolving in oral lichen planus is about 0.5% (272), with a range of 0.3% to 3%. Development of carcinoma in ulcers of the feet in ulcerative lichen planus has been reported to occur rarely in lesions that had not been previously grafted (273).

Histopathology. Typical papules of lichen planus show (a) compact orthokeratosis, (b) wedge-shaped hypergranulosis, (c) irregular acanthosis, (d) vacuolar alteration of the basal layer, and (e) a bandlike dermal lymphocytic infiltrate in close approximation to the epidermis (Fig. 7-22). This constellation of findings is sufficiently diagnostic that a histologic diagnosis can be rendered in more than 90% of the cases (274).

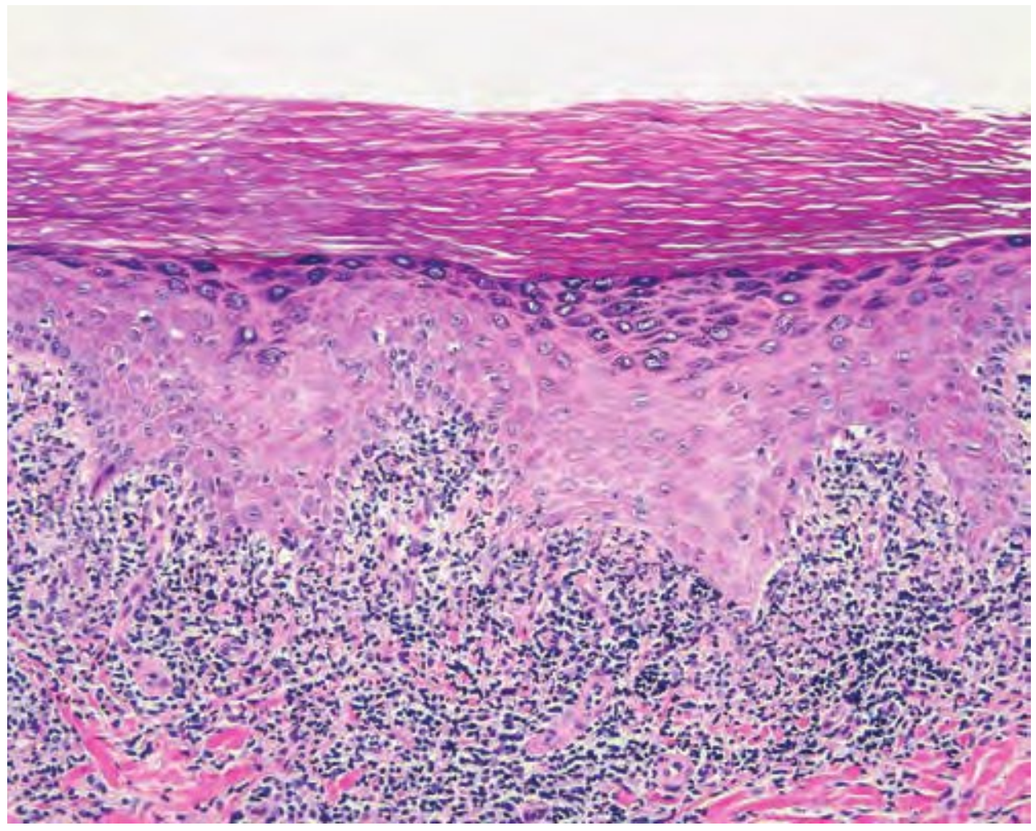


FIGURE 7-22. Lichen planus. Dense, bandlike infiltrate predominantly of lymphocytes in the papillary dermis that extends to the epidermis, where there is vacuolar alteration of the basal layer, necrotic keratinocytes, irregular acanthosis, wedge-shaped hypergranulosis, and compact orthokeratosis.

The cornified layer shows compact orthokeratosis and contains very few, if any, parakeratotic cells, a fact that is important for the diagnosis. The thickening of the granular layer is uneven and wedge shaped. The granular cells appear increased in size and contain coarse and more abundant keratohyaline granules. On step sectioning, the areas of wedge-shaped hypergranulosis are found to be contiguous to intraepidermal adnexal structures, namely acrosyringia and acrotrichia (275). Wickham's striae are believed to be caused by focal increase in the thickness of the granular layer and the entire epidermis (276).

The acanthosis in lichen planus is irregular and affects the spinous layer and the suprapapillary plates. Keratinocytes of the spinous layer often appear larger and eosinophilic, possibly because of advanced keratinization. The rete ridges show irregular lengthening, and some are pointed at their lower end, giving them a saw-toothed appearance. The dermal papillae between elongated rete ridges are often dome shaped (277).

The basal layer keratinocytes are not clearly visible in early lesions because the dense dermal infiltrate obscures the dermal–epidermal junction with vacuolar alteration and necrosis of these cells. In fully developed lesions, the basal layer keratinocytes appear as flattened squamous cells.

The infiltrate in the upper dermis is bandlike and sharply demarcated at its lower border and is composed almost entirely of lymphocytes intermingled with macrophages. A few eosinophils and/or plasma cells may be seen. Melanophages are seen in the upper dermis, often in considerable number, as a result of damage to the basal cells with subsequent pigment

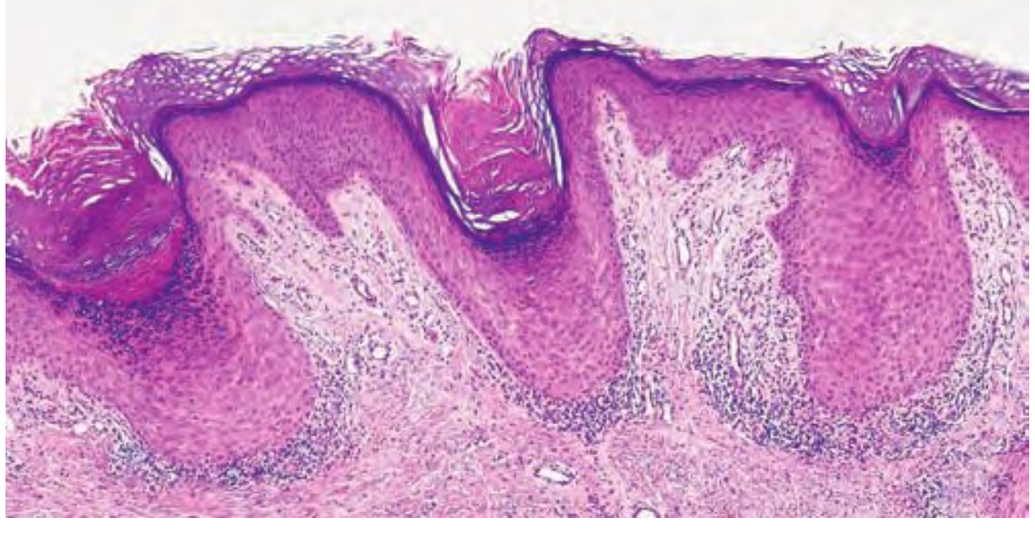


FIGURE 7-23. Hypertrophic lichen planus. Marked irregular acanthosis, hypergranulosis, and compact orthokeratosis. The vacuolar alteration and the lymphocytic inflammatory infiltrate are accentuated at the base of the rete ridges.

incontinence. In some instances, the dermal lymphocytic infiltrate is seen in juxtaposition to the acrosyringium, and vacuolar alteration of the acrosyringeal basal cell layer is a prominent finding (*acrosyringeal lichen planus*) (278).

In old lesions, the cellular infiltrate decreases in density, but the number of melanophages increases. In areas in which a basal cell layer has regenerated, the dermal infiltrate no longer lies in close approximation to the epidermis. *Hypertrophic lichen planus* shows considerable acanthosis, papillomatosis, hypergranulosis, and hyperkeratosis (Fig. 7-23). The interface vacuolar changes are discrete and often limited to the base of the rete ridges.

Necrotic keratinocytes are present in most of the cases in the lower epidermis and especially in the papillary dermis. They are also referred to as colloid, hyaline, cytoid, or Civatte bodies. They average 20 μm in diameter and have a homogeneous, eosinophilic appearance (Fig. 7-24). They are PAS positive and

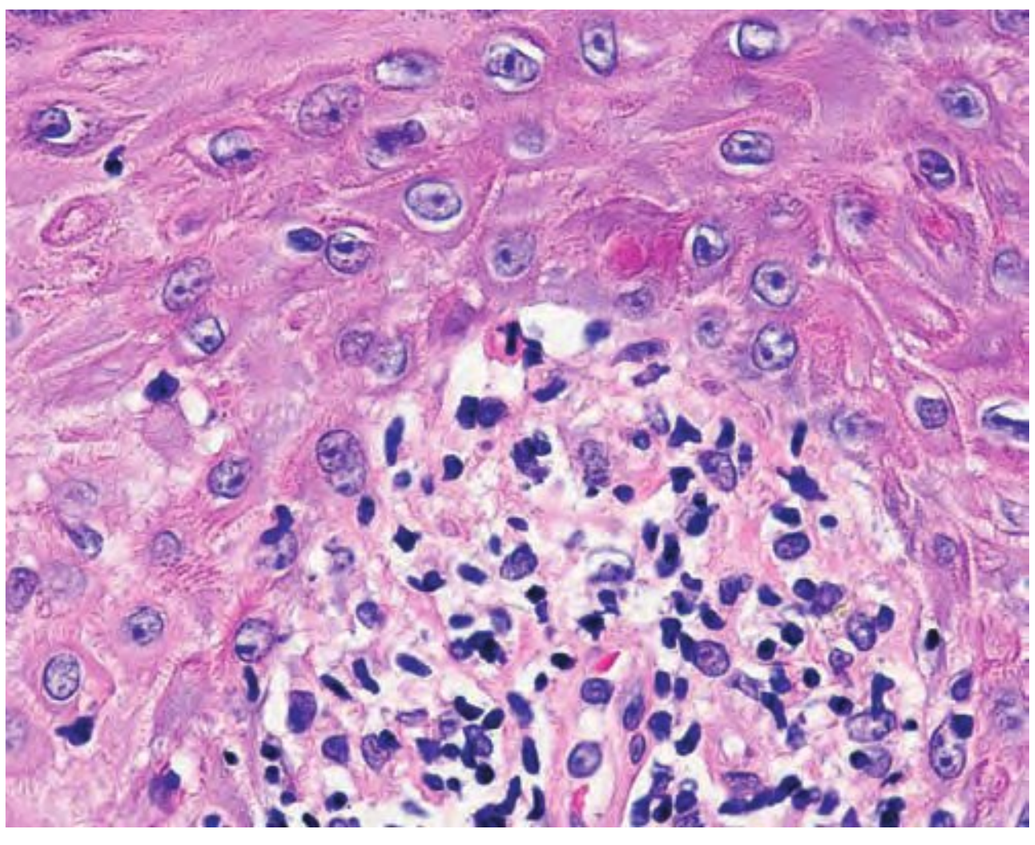


FIGURE 7-24. Lichen planus. Closer view shows lymphocytes and melanophages in the papillary dermis, vacuolar alteration of the basal layer, necrotic keratinocytes (Civatte bodies), and enlarged keratinocytes with eosinophilic cytoplasm.

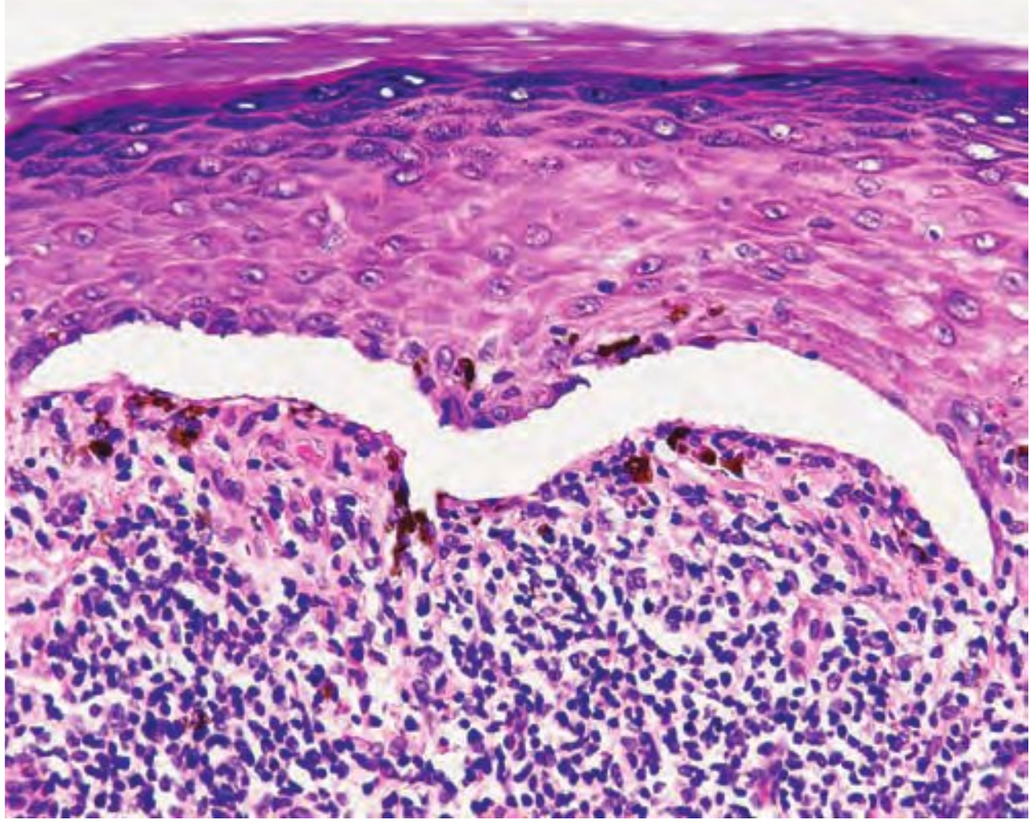


FIGURE 7-25. Lichen planus. Artifactual cleft between the epidermis and the lichenoid infiltrate known as the Max-Joseph space.

diastase resistant. Even though necrotic keratinocytes are found most commonly in lichen planus, they may occur in any interface dermatitis in which damage to the basal cells occurs, including graft-versus-host disease, lichen nitidus, lupus erythematosus, and drug reactions, as well as in inflamed keratoses such as lichenoid actinic keratosis and lichen planus–like keratosis. They may even be seen in normal skin (279). In lichen planus, the number of necrotic keratinocytes may be so large that they are seen lying as clusters in the uppermost dermis (260). Their aggregation may result in the perforation of the epidermis with subsequent transepidermal elimination (280).

Occasionally, small areas of artifactual separation between the epidermis and the dermis, known as Max-Joseph spaces, are seen (274) (Fig. 7-25). In some instances, the separation occurs *in vivo* and subepidermal blisters form (*vesicular lichen planus*). These vesicles develop as a result of extensive damage to the basal cells (246,247).

Oral Lichen Planus

The oral lesions of lichen planus differ in their histologic appearance from those of the skin, as one would expect, because the oral mucosa normally shows parakeratosis without the presence of a granular layer. Thus, the lesions of the oral mucosa often show parakeratosis rather than orthokeratosis without a granular layer, although alternating areas of both types of keratinization with the presence of a granular layer may also be observed (244) (Fig. 7-26). In addition, rather than showing acanthosis, the epithelium is often atrophic. Ulcerations may develop either through the rupture of vesicles or as a result of necrosis of the atrophic epithelium.

Lichen Planopilaris

Most early lesions of lichen planopilaris show a focally dense, bandlike perifollicular lymphocytic infiltrate at the level of the

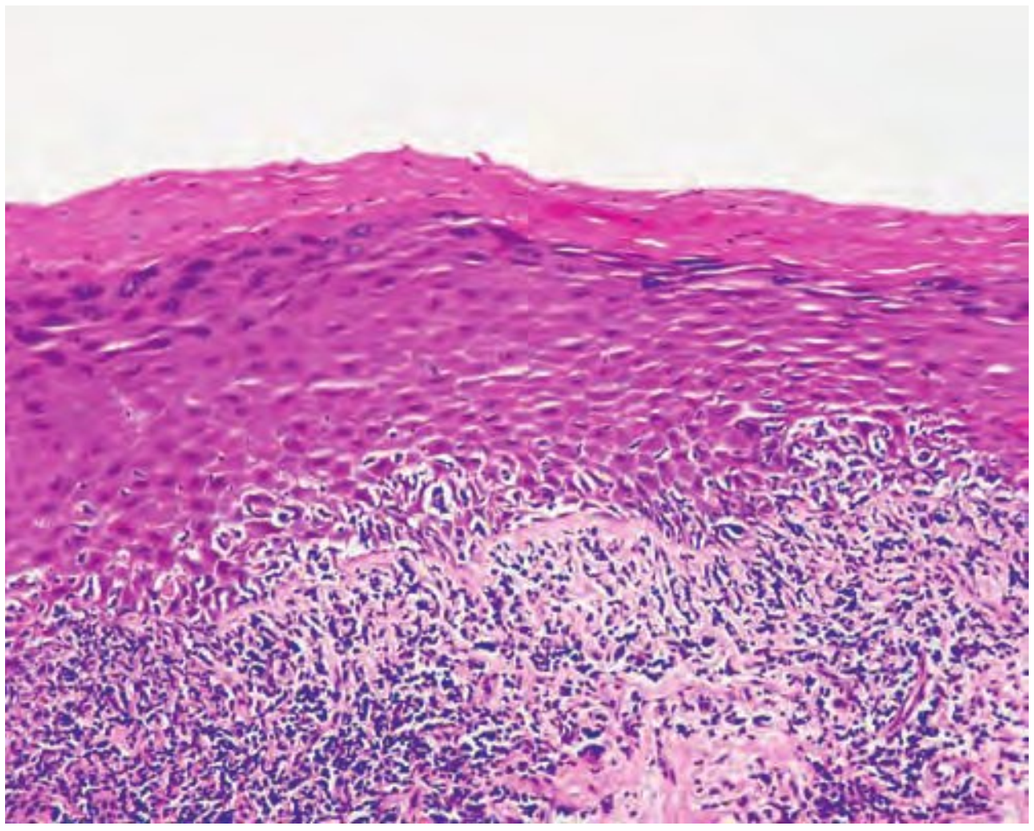


FIGURE 7-26. Oral lichen planus. Similar lichenoid inflammatory pattern as seen in the skin except for less hypergranulosis and confluent parakeratosis.

infundibulum and the isthmus where the hair "bulge" is located. Initially, the inferior segment of the hair follicle is spared. Vacuolar changes of the basal layer of the outer root sheath and necrotic keratinocytes are often seen. In addition, orthokeratosis, follicular plugging, and wedge-shaped hypergranulosis of the infundibulum are observed (Fig. 7-27). Interfollicular epidermis is often spared, but it can occasionally be involved (281). In more developed lesions, perifollicular fibrosis and epithelial atrophy at the level of the infundibulum and isthmus are characteristic findings and give rise to an hourglass



FIGURE 7-27. Lichen planopilaris. Follicular plugging, hypergranulosis, and dense, bandlike perifollicular lymphocytic infiltrate that obscures the infundibular epithelium.

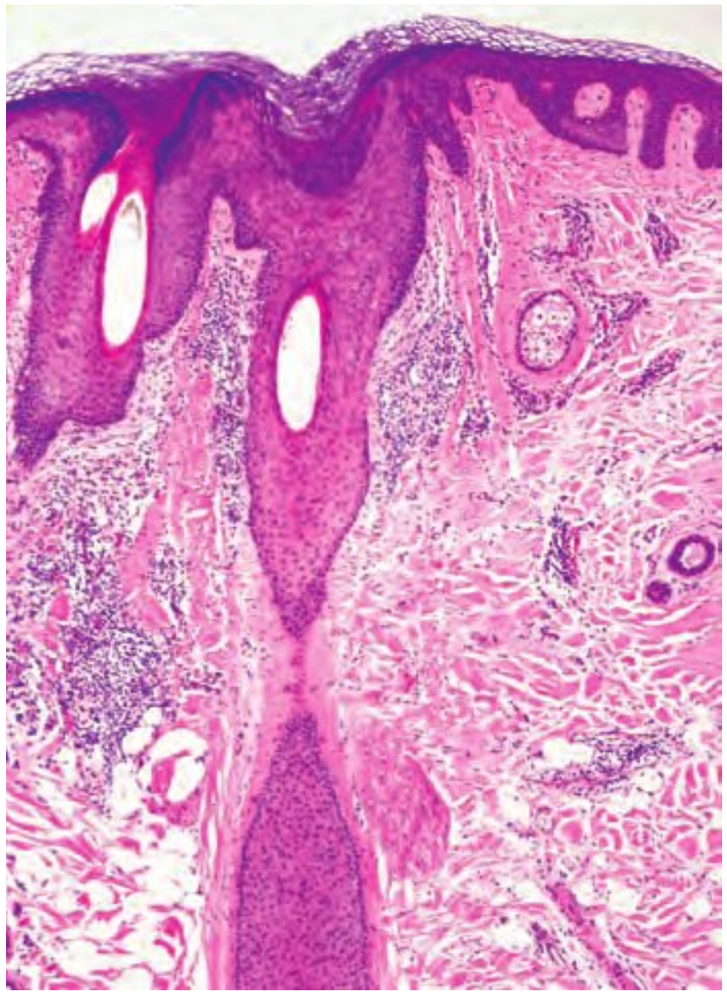


FIGURE 7-28. Lichen planopilaris, developed lesion. Perifollicular fibrosis and inflammation with epithelial atrophy at the infundibuloisthmic portion give rise to an hourglass configuration.

configuration (Fig. 7-28). It is hypothesized that damage to the hair bulge, where the stem cells of the hair follicle supposedly reside, results in permanent scarring alopecia (282). Advanced cases show alopecia with vertically oriented fibrotic tracts containing clumps of degenerated elastic fibers that had replaced the destroyed hair follicles. This end-stage scarring alopecia in which no visible hair follicles remain is called pseudopelade of Brocq (283).

The hyperkeratotic follicular papules that are occasionally seen on glabrous skin in association with lichen planopilaris of the scalp exhibit similar changes; however, perifollicular fibrosis is usually slight, and the process does not eventuate in scarring (284).

Ulcerative Lichen Planus

In ulcerative lichen planus, samples taken from the skin adjacent to the ulcer generally show changes of an established lichen planus (254).

Lichen Planus Actinicus

In some instances, the histologic picture of lichen planus actinicus is similar to that of the typical lichen planus but with a tendency toward thinning of the epidermis at the center of the lesion and more evident pigmentary incontinence in the upper dermis (55,257). Because of the histologic resemblance in some cases, a relationship between lichen planus actinicus and erythema dyschromicum perstans has been postulated (285); however, they have significant clinical differences (55).

Overlap Syndrome–Lichen Planus/Lupus Erythematosus

In some cases of the overlap syndrome, the histologic features and direct immunofluorescence findings are more consistent with lichen planus. In others, the immunofluorescence testing favors lupus erythematosus (261), and still in another subset of patients, there are lesions of lichen planus that coexist rather than overlap with those of lupus erythematosus (286).

Twenty-Nail Dystrophy

Histologic data on twenty-nail dystrophy are available in only a few cases. Twenty-nail dystrophy is a manifestation of diverse underlying processes; therefore, its histology varies (263,264). Biopsies may show typical lichen planus involving the nail matrix (262). However, spongiosis may be prominent as in cases associated with atopic dermatitis.

Lichen Planus Pemphigoides

In lichen planus pemphigoides, biopsies taken from blisters arising from uninvolved skin show subepidermal bullae with an infiltrate that is not bandlike and that contains eosinophils (287).

Pathogenesis

The eosinophilia of the keratinocytes and the increase in thickness of the granular and cornified layers suggest a decreased epidermal turnover. However, in spite of severely damaged basal cells, measurements of cell proliferation in lichen planus with tritiated thymidine have shown an increase in cell proliferation (288).

Electron Microscopy

On electron microscopy, the basal keratinocytes in lichen planus, together with their desmosomes and hemidesmosomes, show degenerative changes (289). Whereas the tonofilaments in the basal cells are decreased in early lesions, they are increased in later lesions (290). Because of the presence of degenerated and necrotic keratinocytes in the basal layer, it is assumed that the basal cells in later lesions are largely regenerated cells. The dermal infiltrate, extending to the epidermis, causes damage to the lamina densa such as fragmentation (EM 12). This may be followed by duplication and irregular folding of the lamina densa (291). The dermal infiltrate contains mainly lymphocytes, but it also contains macrophages. Some of the lymphocytes have hyperconvoluted nuclei and appear indistinguishable from Sézary cells.

Necrotic keratinocytes or colloid bodies are located largely in the papillary dermis but also in the lowermost epidermis (EM 12). They can be seen to develop from damaged keratinocytes through filamentous degeneration. This is followed by their discharge into the dermis. Necrotic keratinocytes consist of aggregates of filament bundles, with each filament measuring approximately 10 nm in diameter. The use of antikeratin immune sera has resulted in their intense staining (292). Necrotic keratinocytes often still contain cell organelles, such as melanosomes and mitochondria, but only rarely contain nuclear material (293). Fibrin deposits in the upper dermis are a common finding in electron microscopy studies (EM 12).

In the vesicular lesions of lichen planus, electron microscopic examination shows cytolysis of basal keratinocytes; therefore, the blister cavity is situated below the spinous layer (294).

Immunofluorescence

In lichen planus, fibrinogen deposition can be demonstrated by direct immunofluorescence as shaggy deposits at the dermal–epidermal junction (295). Only occasionally are there granular deposits of IgM (296) or linear deposits of C3 (297), or both IgG and C3 (298) in the basement membrane zone. Necrotic keratinocytes are demonstrable in lichen planus by direct immunofluorescence staining in about 87% of the cases (295). They stain mainly for IgM but often also for IgG, IgA, C3, and fibrin. Although necrotic keratinocytes are found occasionally in many other conditions with damage to the basal cell layer, such as lupus erythematosus, they are highly suggestive of lichen planus if they are present in large numbers or arranged in clusters. Their staining for IgM facilitates their recognition (279).

In lichen planopilaris, direct immunofluorescence in many specimens shows deposition of IgM and/or IgA, IgG, and, rarely, C3 at the level of the infundibulum and isthmus (299). The necrotic keratinocytes may react with anti-IgM antibody. There is often deposition of fibrinogen in a shaggy pattern surrounding the affected follicles. The dermal–epidermal junction is virtually always negative for deposition of immunoreactants (281).

In lichen planus pemphigoides, direct immunofluorescence of perilesional skin shows the presence of IgG and C3 in a linear arrangement along the basement membrane zone (287,300), and on immunoelectron microscopy, C3 is seen to be localized within the lamina lucida, analogous to its location in bullous pemphigoid (248). It has been shown that circulating IgG autoantibodies are directed against the bullous pemphigoid antigen 180 (BP180, type XVII collagen), a transmembrane hemidesmosomal glycoprotein of the basal keratinocytes that spans the lamina lucida (301,302). Immunoelectron microscopic studies have also confirmed that the location of the antigen is at the same site as the bullous pemphigoid antigen, the basal cell hemidesmosomes on the epidermal side of salt-split skin (303). However, it is suggested that the immunoglobulin subclass of the autoantibody and/or the epitope that is recognized may be different in these two diseases (301). One study has shown that in addition to BP180 antigen, the autoantibodies were also directed against a 200-kD antigen (304).

In the overlap syndrome lichen planus/lupus erythematosus, some patients show immunofluorescence testing consistent with lichen planus; yet another group demonstrates deposition of immunoglobulins and C3 at the dermal–epidermal junction in a linear granular pattern as in cutaneous lupus erythematosus (261).

Immunohistochemistry

The infiltrating cells in lichen planus are predominantly T lymphocytes with very few B lymphocytes. More than 90% are activated T lymphocytes expressing HLA-DR antigen and some interleukin-2 receptor (305). The identification of various subtypes of T lymphocytes has given contradictory results with regard to the predominance of $CD4^+$ helper-inducer T lymphocytes and $CD8^+$ suppressor-cytotoxic T lymphocytes in the infiltrate (306–308). It is likely that both subsets participate in the immunologic reaction. It has been shown that in older lesions of oral lichen planus, the suppressor T lymphocytes predominate. The epitheliotropic lymphocytes have also been shown to be of the same subtype, supporting a cell-mediated cytotoxic mechanism against epithelial cells (307,309). In the epidermis adjacent to the infiltrate, basal keratinocytes express HLA-DR surface antigen and ICAM-1 (310), both of which are implicated in the enhancement of the interaction between lymphocytes and their epidermal targets resulting in keratinocyte destruction (308). It is probable that these surface antigens are induced by cytokines (γIFN and TNFα) released by lymphocytes from the infiltrate (311,312). Immunophenotyping studies on T lymphocytes extracted from specimens of lichen planus have shown that the majority of clones were $CD8^+$ T lymphocytes, displayed suppressor activity, and expressed $\alpha\beta$ T-cell receptor (313) or a distinctive $\gamma\delta$T-cell receptor (314). Clonal expansion of $\alpha 2\beta 3$ T-cell receptor of the V-gene family has been reported, suggesting that a superantigen could be involved in the pathogenesis of the disease (315).

The number of Langerhans cells in the epidermis is increased very early in the disease, especially near keratinocytes expressing $HLA\text{-}DR^+$ antigen (275,316). Immunoelectron studies have shown close contacts of lymphocytes with Langerhans cells and macrophages. Specific conjugations between $CD4^+$ T lymphocytes and dendritic ($HLA\text{-}DR^+$) cells and between $CD8^+$ T lymphocytes and degenerated basal keratinocytes have been observed in lesional epithelium of oral mucosa. These cell-to-cell interactions suggest that a cell-mediated immune mechanism is operative (317). Recent studies have shown that lesional type I interferons produced by plasmacytoid dendritic cells play an important role in chronic cytotoxic inflammation of lichen planus by recruiting cytotoxic effector lymphocytes via IP10/CXCR3 interactions (318).

Differential Diagnosis

It should be borne in mind that parakeratosis is not a feature of lichen planus of the skin and that if more than focal parakeratosis is present, a diagnosis of lichen planus should not be made on histologic grounds.

Focal parakeratosis and adjacent solar lentigines in an otherwise typical histologic picture of lichen planus should be regarded as lichen planus–like keratosis, even more so if there is a solitary and nonpruritic lesion (319). Lichenoid drug eruptions may be differentiated from lichen planus by the presence of focal parakeratosis with concomitant absence of the granular layer, necrotic keratinocytes in the basal and spinous layers, exocytosis of lymphocytes to the upper layers of the epidermis, and a deeper inflammatory infiltrate with numerous eosinophils (320).

Differentiation from lichenoid lupus erythematosus is based on (a) atrophy of the epidermis in addition to acanthosis, (b) absence of eosinophilia of the keratinocytes in the spinous layer, (c) a superficial bandlike infiltrate with a superficial and deep perivascular and periadnexal infiltrate, (d) the presence of a thickened, PAS-positive basement membrane, and (e) dermal mucin deposits. Direct immunofluorescence findings may also be helpful; in lupus erythematosus linear or granular deposits of immunoglobulins and C3 predominate in lesional skin, whereas in lichen planus clusters of necrotic keratinocytes with absorbed immunoglobulins and complement are found. Langerhans cells are decreased in number in discoid and systemic lupus erythematosus; in contrast, they are increased in early lichen planus (308). The epidermal changes in chronic graft-versus-host disease may be similar to those in lichen planus; however, the inflammatory infiltrate tends to be perivascular instead of bandlike. In addition, the number of Langerhans cells in graft-versus-host disease is decreased, and nearly all intraepidermal lymphocytes are cytotoxic-suppressor T cells (321). In long-standing hypertrophic lichen planus, the basal layer may show hardly any residual damage and the infiltrate may no longer be bandlike, rendering differentiation from lichen simplex chronicus at times difficult. However, in hypertrophic lichen planus, deeper sections still may show areas of damage to the basal layer at the base of the rete ridges.

On the lips and in the mouth, the differentiation of lichen planus from early squamous cell carcinoma *in situ* ("dysplastic leukoplakia") may cause difficulties clinically as well as histologically. Both diseases may show hyperkeratosis and an inflammatory infiltrate close to the epidermis/epithelium. However, thorough microscopic study reveals more atypical keratinocytes in squamous cell carcinoma *in situ*. Furthermore, squamous cell carcinoma *in situ* is more apt than lichen planus to show irregular downward proliferation of the rete ridges and numerous plasma cells.

Lichen planopilaris of the scalp must be differentiated in its early phase from discoid lupus erythematosus, which affects the hair follicles as well as the interfollicular epidermis. Lupus erythematosus shows vacuolar alteration of the basal cells both in the epidermis and in the hair follicles without disappearance of basal cells. In addition, it also shows a thickened basement membrane and an interfollicular superficial and deep perivascular infiltrate. There is also an increase in connective tissue mucin. In their late stages, both lichen planopilaris and lupus

erythematosus may result in permanent scarring alopecia, which is known as pseudopelade of Brocq (283).

LICHEN PLANUS–LIKE KERATOSIS

Lichen planus–like keratosis (LPLK), also known as "benign lichenoid keratosis," was originally described in 1966 as "solitary lichen planus" (322) and as "solitary lichen planus–like keratosis" (323). It is a common lesion that occurs predominantly on the trunk and upper extremities of adults between the fifth and seventh decades. Occurrence on the face and lower extremities has also been reported (324–327). LPLK consists of a nonpruritic papule or slightly indurated plaque that is nearly always solitary, although cases with more than one skin lesion have been reported (328). It usually measures 5 to 20 mm in diameter, and its color varies from bright red to violaceous and brown. Its surface may be smooth or slightly verrucous. Lichen planus–like keratosis probably represents the inflammatory stage of involuting solar lentigines (329).

Histopathology. Histologic examination shows, at least in a part of the lesion, a lichenoid pattern that may be indistinguishable from lichen planus (319,322,323). As in lichen planus, there is vacuolar alteration of the basal cell layer and a bandlike lymphocytic infiltrate that obscures the dermal–epidermal junction. Necrotic keratinocytes are commonly seen and may be numerous. As in lichen planus, the epidermis often shows increased eosinophilia, hypergranulosis, and hyperkeratosis (330). In contrast to lichen planus, parakeratosis is fairly common (Fig. 7-29) and ranges from focal to prominent (319,325). In addition, eosinophils and plasma cells in the infiltrate are more frequently found in some cases of LPLK, as opposed to lichen planus, in which they are rarely seen (319). A residual solar lentigo at the edge of the lesion supports the diagnosis of LPLK (331). Regressed LPLK represents the involuted and late-stage lesion with atrophic epidermis, patchy lymphocytic infiltrate in the papillary dermis, and pigment incontinence, associated with dermal fibrosis. Bullous LPLK has also been described as a histopathologic variant (328). Immunohistochemical studies have shown that LPLK has significantly fewer Langerhans cells in the epidermis compared to lichen planus (332). The epidermal and dermal lymphocytes were shown to mainly consist of $CD8^+$ T cells and partly $CD20^+$ B cells with only scarce $CD4^+$ T cells. However, epidermal lymphocytes in lichen planus are mainly $CD8^+$ T cells and dermal lymphocytes are $CD4^+$ or $CD8^+$ T cells. In addition, in lichen planus, $CD20^+$ B cells are scarcer than in LPLK. Memory T cells express a skin homing receptor called cutaneous lymphocyte associated antigen. This antigen is strongly expressed in lichen planus but not in LPLK, suggesting that in lichen planus, disease-related lymphocytes infiltrate the epidermis, whereas in LPLK, the lymphocytes may be nonspecific infiltrating cells (327).

Direct immunofluorescence studies have revealed the linear deposition of IgM at the basement membrane zone (333). Even though some keratinocytes may show pyknotic hyperchromatic nuclei, no definite nuclear atypia is seen. If marked keratinocytic atypia is found in association with a lichenoid inflammatory pattern, a lichenoid actinic keratosis should be considered in the differential diagnosis.

Pathogenesis. LPLK has been noted to involute spontaneously (334). LPLK may be the inflammatory stage of regressing solar lentigines and reticulated seborrheic keratoses (329,331). These precursor lesions could be the targets of an immune cell–mediated reaction (319).

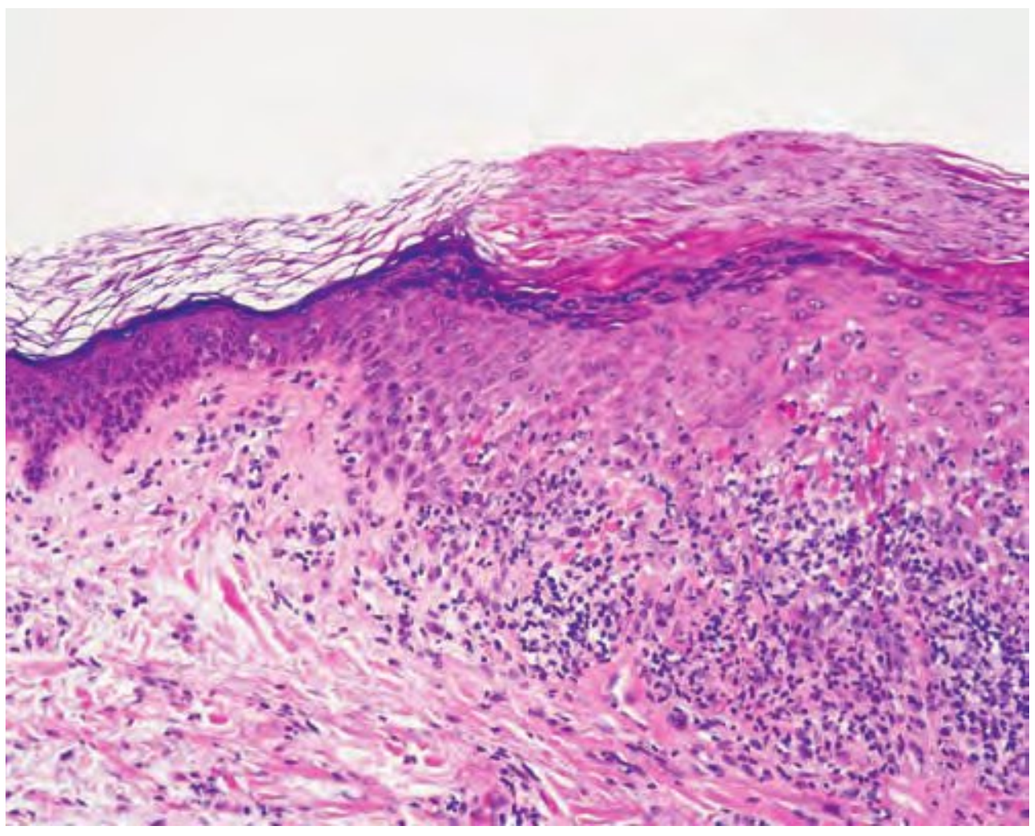


FIGURE 7-29. Lichen planus–like keratosis. Lichenoid inflammatory pattern with numerous necrotic keratinocytes, granular layer of uneven thickness, orthokeratosis, and parakeratosis with a residual solar lentigo.

KERATOSIS LICHENOIDES CHRONICA

A rare asymptomatic dermatosis, keratosis lichenoides chronica was first described by Kaposi in 1895 as "lichen ruber acuminatus verrucosus et reticularis" (335) and received its present name in 1972 (336). It usually begins in adulthood between 20 and 50 years of age and is extremely rare in children (337). There is an extensive, symmetrically distributed eruption predominantly on the dorsal aspects of extremities and trunk. It mainly consists of red to violaceous papulonodules covered with a thick, adherent scale and arranged often in a characteristic linear and occasionally reticular pattern. The lesions may coalesce to form erythematous scaly or hyperkeratotic plaques (338,339). Very frequently there is associated seborrheic dermatitis–like eruption of the face, palmoplantar hyperkeratosis (338), and, in some cases, nail changes with warty hypertrophy of the periungual tissues, which has been described as a distinctive feature of the disease (340). Mucosal membrane involvement is common and includes oral ulcers, nodular infiltration of the epiglottis and

larynx, blepharitis, and keratoconjunctivitis, among others (336,338,339). Although the disease is characterized by a chronic and progressive course, spontaneous resolution has been reported (341).

The disease has been reported in association with lymphoma (342), following trauma (343), and after a drug-induced erythroderma (344).

Histopathology. In most cases, there is a lichenoid inflammatory infiltrate comprised of lymphocytes, histiocytes, and numerous plasma cells that obscures the dermal–epidermal junction with vacuolar alteration of the basal cell layer and necrotic keratinocytes (338,345). The epidermis shows areas of acanthosis as well as atrophy covered by a hyperkeratotic cornified layer with focal parakeratosis and follicular plugging (346). Prominent dilated dermal capillaries are seen in cases with associated telangiectasias (347).

Differential Diagnosis. Although the histologic picture may closely resemble that of lichen planus, the presence of parakeratosis, alternating areas of atrophy and acanthosis, numerous plasma cells, and a heavier infiltrate than is usually seen in lichen planus may help in the differentiation. In addition, the clinical appearance of keratosis lichenoides chronica is quite different from that of lichen planus.

LICHEN NITIDUS

Lichen nitidus is a chronic and usually asymptomatic dermatitis that commonly begins in childhood or early adulthood (348). It is characterized by round, flat-topped, flesh-colored papules 2 to 3 mm in diameter that may occur in groups but do not coalesce (Fig. 7-30). The lesions appear frequently as a localized eruption affecting predominantly the arms, trunk, or penis. Rarely, the eruption may become generalized, and Koebner's phenomenon may be observed (265,349,350). Purpuric generalized variant has also been reported (351). In addition, lesions occurring on the palms, soles, nails, and mucous membranes have been described (352). The clinical course is unpredictable, and spontaneous resolution may be seen (348).



FIGURE 7-30. Lichen nitidus. Cluster of round, flat-topped, flesh-colored papules of a few millimeters in diameter. (Courtesy of Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, New York.)

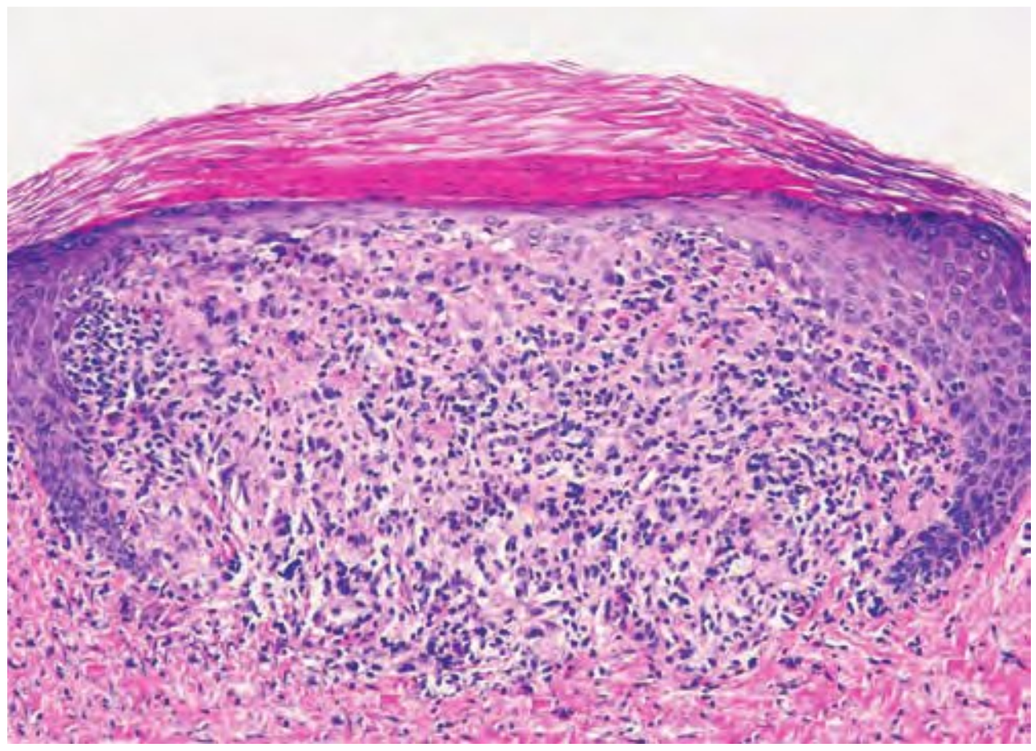


FIGURE 7-31. Lichen nitidus. Dense infiltrate of lymphocytes and histiocytes in an expanded dermal papilla, thin suprapapillary epidermis with vacuolar alteration of the basal layer, and focal parakeratosis.

Histopathology. Each papule of lichen nitidus consists of a well-circumscribed mixed-cell granulomatous infiltrate that is closely attached to the lower surface of the epidermis and confined to a widened dermal papillae. The infiltrate is composed of lymphocytes and mono- and a few multinucleated epithelioid histiocytes. The dermal infiltrate often extends slightly into the overlying epidermis, which is flattened and shows vacuolar alteration of the basal cell layer, focal subepidermal clefting, diminished granular layer, and focal parakeratosis (348). Transepidermal perforation of the infiltrate through the thinned epidermis may occur (353). At each lateral margin of the infiltrate, rete ridges tend to bend downward and inward and seem to clutch the infiltrate in the manner of a "claw clutching a ball" (Fig. 7-31). The palmar lesions have the infiltrate mostly disposed around the bases of the rete ridges, similar to that found in hypertrophic lichen planus (354). Follicular involvement in lichen nitidus has also been described (355).

Relationship Between Lichen Planus and Lichen Nitidus

There are controversial facts regarding the relationship that might exist between lichen planus and lichen nitidus. The view that lichen nitidus represents a variant of lichen planus has been supported by several authors because the two diseases are occasionally present simultaneously (265), ultrastructural findings are similar (356), and, in some cases of lichen planus, small miliary papules may have a histologic appearance consistent with lichen nitidus (357). However, the subsequent

evolution is different; in lichen nitidus, the papule remains small and develops parakeratosis with epidermal flattening, whereas in lichen planus, the papule develops acanthosis and hyperkeratosis (265). Occasional deposits of fibrinogen can be observed by direct immunofluorescence in lichen nitidus, in contrast to lichen planus, where most of the lesions have globular deposits of immunoglobulins at the dermal–epidermal junction (358). Furthermore, immunohistochemical studies have revealed different cell populations in the inflammatory infiltrate of each disease. Lichen nitidus has a significantly smaller proportion of $CD4^+$ (helper-inducer) and HECA-452^+ (skin-homing receptor) T lymphocytes than lichen planus, suggesting different immunologic pathways (359).

LICHEN STRIATUS

Lichen striatus is a fairly uncommon dermatitis that, as a rule, occurs in children from 5 to 15 years of age but may be seen in adults (360). It usually manifests as a unilateral eruption along Blaschko's lines on the extremities, trunk, or neck as either a continuous or an interrupted band composed of minute, slightly raised erythematous papules, which may have a scaly surface (361) (Fig. 7-32). The lesions appear abruptly and usually involute within a year. They are occasionally pruritic (362). Hypopigmented lesions may be seen in dark-skinned patients (363). A few cases with associated onychodystrophy, rare cases of multiple or bilateral presentations, and simultaneous occurrence of lichen striatus in siblings have been reported (364–368).

Histopathology. Although lichen striatus has been recognized by its variable histologic picture (360,363,369), some constant microscopic findings may be present (370). There is usually a superficial perivascular inflammatory infiltrate of lymphocytes admixed with variable number of histiocytes. Plasma cells and eosinophils are rarely seen (360) (Fig. 7-33). Focally, in the papillary dermis, the infiltrate may have a bandlike distribution with extension into the lower portion of the epidermis, where there is vacuolar alteration of the basal layer and necrotic keratinocytes. In these areas, the papillary dermis occasionally contains melanophages (360,369). Additional epidermal changes consist of spongiosis and intracellular edema often associated with exocytosis of lymphocytes and focal parakeratosis (Fig. 7-34). Less frequently, there are

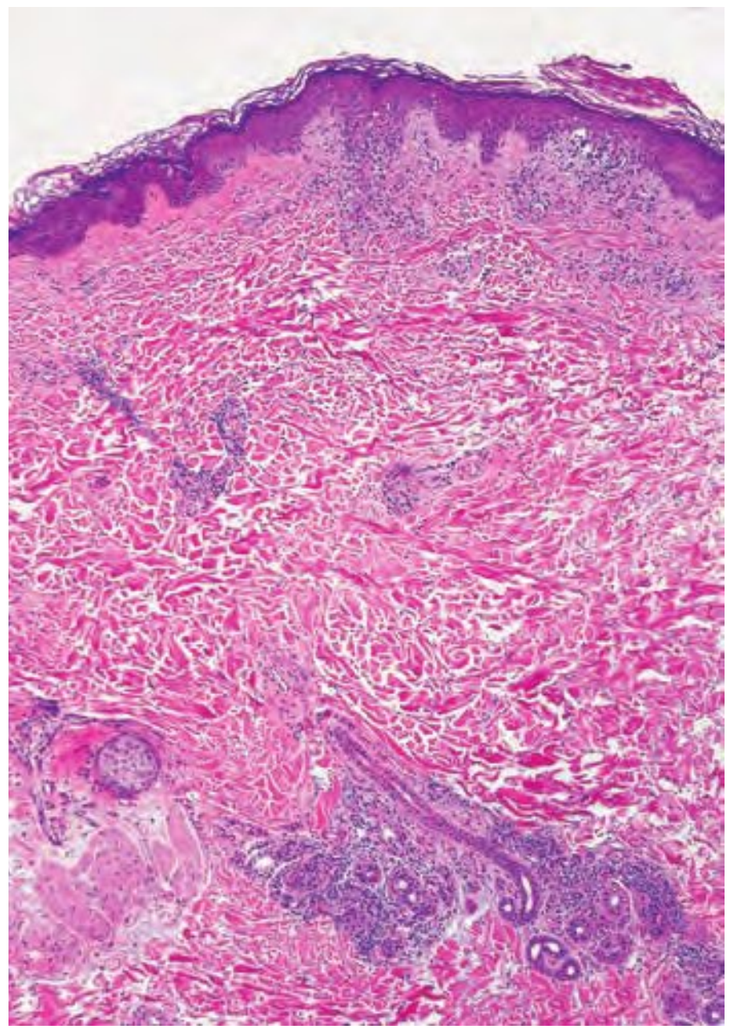


FIGURE 7-33. Lichen striatus. Superficial and deep perivascular, perieccrine, and perifollicular infiltrate of lymphocytes and histiocytes that extends to the epidermis, which shows acanthosis and spongiosis.



FIGURE 7-32. Lichen striatus. Linear band of confluent small papules following a Blaschko's line. (Courtesy of Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.)

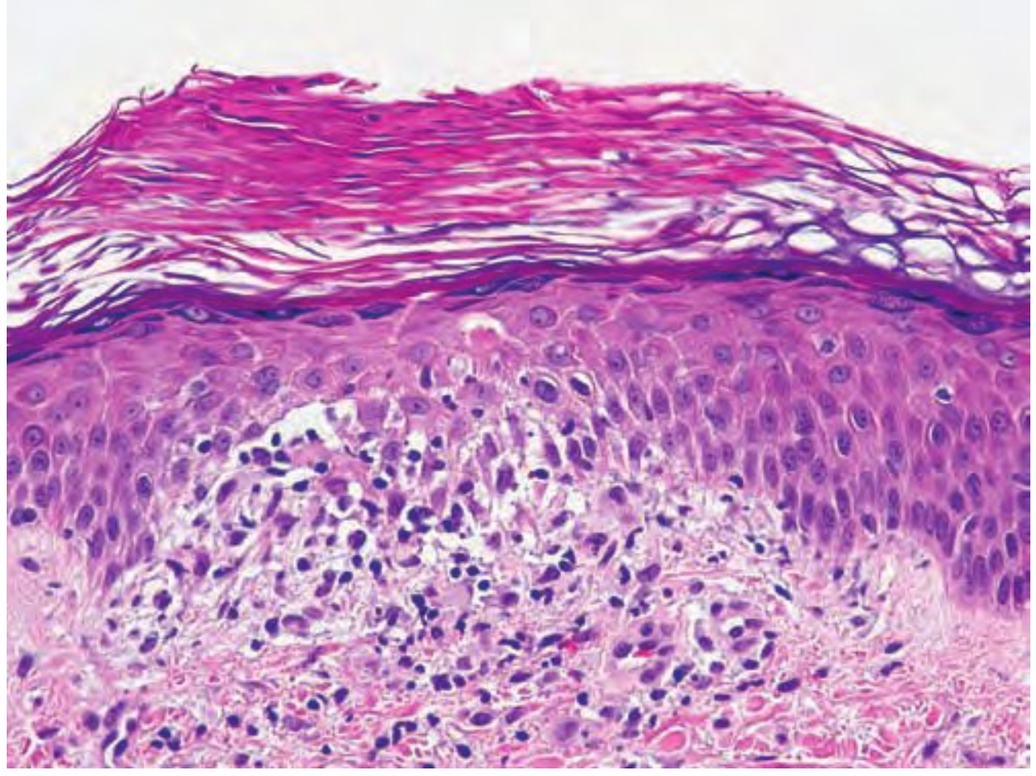


FIGURE 7-34. Lichen striatus. Closer view shows an infiltrate of lymphocytes and histiocytes, exocytosis of lymphocytes, acanthosis, spongiosis, and focal parakeratosis.

scattered necrotic keratinocytes in the spinous layer as well as subcorneal spongiotic vesicles filled with Langerhans cells (370). A very distinctive feature is the presence of inflammatory infiltrate in the reticular dermis around hair follicles and eccrine glands (Fig. 7-33) (360,370). An unusual perforating variant of lichen striatus has been described, which shows transepidermal elimination of clusters of necrotic keratinocytes (371).

Pathogenesis. It has been demonstrated in lichen striatus that the inflammatory cells reaching the epidermis are $CD8^+$ T lymphocytes (370,372) with the Langerhans cell population in the epidermis being either decreased or increased. These findings suggest a cell-mediated immunologic mechanism in which cytotoxic events against keratinocytes could be taking place during the evolution of the disease (370).

Differential Diagnosis. Lichen striatus may show histologic features similar to those of other interface dermatitides such as lichen planus, lichen nitidus, or graft-versus-host disease. In contrast to lichen striatus, the inflammatory infiltrate of lichen nitidus is only focally present in a widened dermal papillae and contains more histiocytes. The presence of epidermal spongiosis and a deeper dermal inflammatory infiltrate around adnexal structures are features rarely seen in lichen planus. In secondary syphilis, the infiltrate mainly comprises plasma cells.

INFLAMMATORY LINEAR VERRUCOUS EPIDERMAL NEVUS

Inflammatory linear verrucous epidermal nevus (ILVEN) presents as a persistent, linear, intensely pruritic lesion. It is composed of erythematous, slightly verrucous, scaly papules arranged in one or several lines. Although the usual time of onset is early childhood, the disease may arise in adults (373). The most common location is on a lower extremity. On rare occasions the lesions are bilateral (374).

ILVEN in association with arthritis (375) and lichen amyloidosus (376) has been reported. ILVEN is considered to be a variant of epidermal nevi; however, it is described and included in the papulosquamous disorders due to its clinical and histologic similarities to psoriasis and lichen striatus.

Histopathology. There is hyperkeratosis with foci of parakeratosis, moderate acanthosis, elongation and thickening of the rete ridges with a "psoriasiform" appearance, papillomatosis, and, occasionally, slight spongiosis with exocytosis of lymphocytes (377).

Frequently, a rather characteristic histologic feature is a sharply demarcated alternation of orthokeratosis and parakeratosis in the cornified layer (Fig. 7-35). The parakeratotic areas are slightly raised, lack a granular layer, and show a compact eosinophilic cornified layer with nuclear preservation. The orthokeratotic areas instead are slightly depressed with underlying hypergranulosis (374,378,379). Underneath the parakeratotic areas, there is mild exocytosis of lymphocytes and slight spongiosis (380). The papillary dermis shows a mild to moderate perivascular inflammatory infiltrate of lymphocytes and histiocytes.

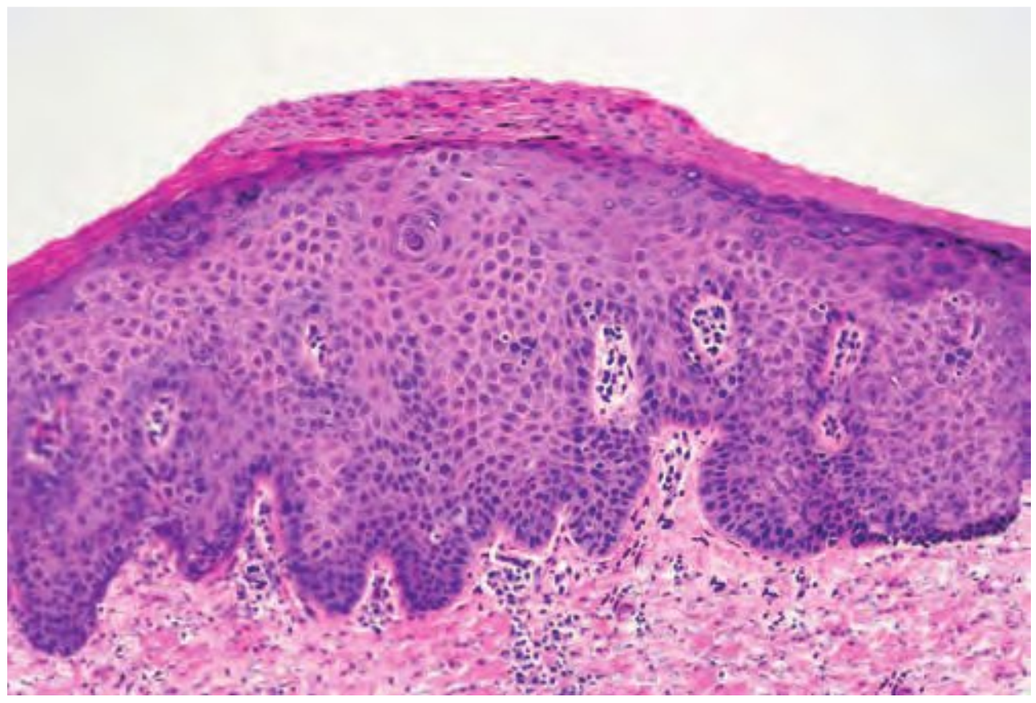


FIGURE 7-35. Inflammatory linear verrucous epidermal nevus. Moderate acanthosis with elongated rete ridges and alternating elevated foci of parakeratosis with absent granular layer and depressed foci of orthokeratosis with preserved granular layer.

Pathogenesis. Electron microscopy and immunohistochemical studies have shown that keratinocyte differentiation is altered in the parakeratotic areas.

Ultrastructurally, keratinocytes have prominent Golgi apparatus and vesicles in their cytoplasm. The intercellular spaces in upper layers of the epidermis are widened by deposits of an electron-dense homogeneous substance. The cytoplasm of parakeratotic corneocytes contains remnants of nucleus and membrane structures and a few lipid droplets. The marginal band formation inside the plasma membrane is incomplete, suggesting a deficient keratinization process (380).

Involucrin expression has a very characteristic pattern in ILVEN. The orthokeratotic epidermis shows increased involucrin expression, whereas the parakeratotic areas are almost negative for involucrin staining (380). This pattern differs from that of psoriasis, in which involucrin is expressed prematurely in most of the suprabasal keratinocytes (381).

More than 90% of the mononuclear cells in the dermal infiltrate are $CD4^+$ T lymphocytes; in contrast, the majority of the epidermal infiltrating T lymphocytes are CD4 negative (382).

Differential Diagnosis. The clinical appearance of lichen striatus and that of ILVEN may be indistinguishable. However, ILVEN, in contrast to lichen striatus, is pruritic and persistent. Histologically, lichen striatus tends to have a lichenoid pattern and ILVEN a psoriasiform pattern. Furthermore, careful search of step sections will usually reveal in ILVEN alternate areas of orthokeratosis with a thickened granular layer and of parakeratosis without a granular layer.

Since alternating orthokeratosis and parakeratosis can be seen in psoriasis and occasionally Munro microabscesses can be

found in ILVEN, the differential diagnosis of these two entities could be sometimes difficult, and a clinicopathologic correlation is necessary (383).

PITYRIASIS RUBRA PILARIS

Pityriasis rubra pilaris is an erythematous squamous disorder characterized by follicular keratotic papules and perifollicular erythema that coalesce to form orange-red scaly plaques that frequently contain islands of normal-appearing skin (384) (Fig. 7-36). As the erythema extends, the follicular component is often lost, but it persists longest on the dorsal aspect of the proximal phalanges. The lesions spread caudally and may progress to a generalized erythroderma (385). Other clinical findings are palmoplantar keratoderma and scaling of the face and scalp. Five types can be recognized (385). Only three types, however, are common enough to deserve mention. *Type I classical adult type* and *type III classical juvenile type* are seen in 55% and 10% of the patients, respectively. They are considered to be the same disease in different age groups (386). In both groups, the majority of the patients clear within 3 years (386,387). *Type IV*, the *circumscribed juvenile type*, accounts for approximately one fourth of the patients. It affects children and is characterized by sharply demarcated areas of follicular hyperkeratosis and erythema on the knees and elbows. It may improve in the late teens (386). There is a familial form of pityriasis rubra pilaris inherited as an autosomal dominant trait (388).

Pityriasis rubra pilaris has been reported to occur in association with malignancies (389–391) and arthritis/arthropathy (392,393). A few cases of pityriasis rubra pilaris with oral involvement have been described (394).

Histopathology. The histologic picture of a fully developed erythematous lesion shows acanthosis with broad and short rete ridges, slight spongiosis, thick suprapapillary plates, focal or confluent hypergranulosis, and alternating orthokeratosis and parakeratosis oriented in both vertical and horizontal directions (171) (Fig. 7-37). In the dermis there is a mild superficial perivascular lymphocytic infiltrate and moderately dilated blood vessels (171,395).

Areas corresponding to follicular papules show dilated infundibula filled out with an orthokeratotic plug and often display perifollicular shoulders of parakeratosis and a mild perifollicular lymphocytic infiltrate (396) (Fig. 7-38). Erythrodermic lesions have a thinned or absent cornified layer with overlying plasma exudate and a diminished granular zone (171).

Differential Diagnosis. Even though pityriasis rubra pilaris and psoriasis bear a similar clinical appearance, they are not alike histologically. Psoriasis differs from pityriasis rubra pilaris



FIGURE 7-36. Pityriasis rubra pilaris. Confluent orange-red scaly plaques with islands of normal-appearing skin. (Courtesy of Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.)

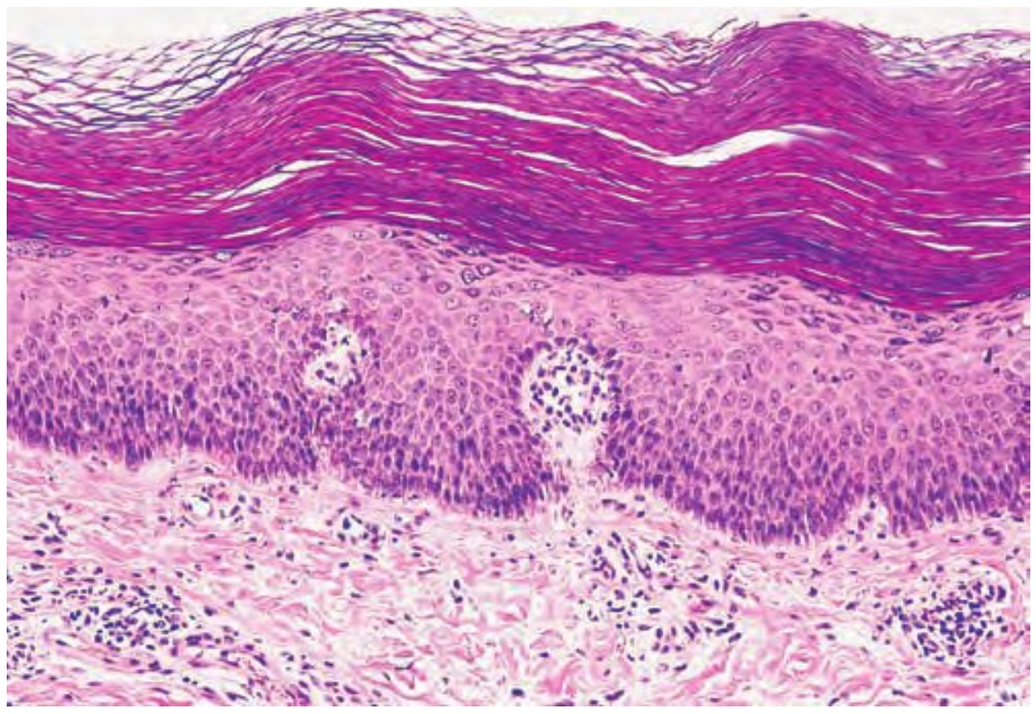


FIGURE 7-37. Pityriasis rubra pilaris. Moderate acanthosis with short and broad rete ridges, focally thin granular layer, and alternating vertical and horizontal foci of orthokeratosis and parakeratosis.

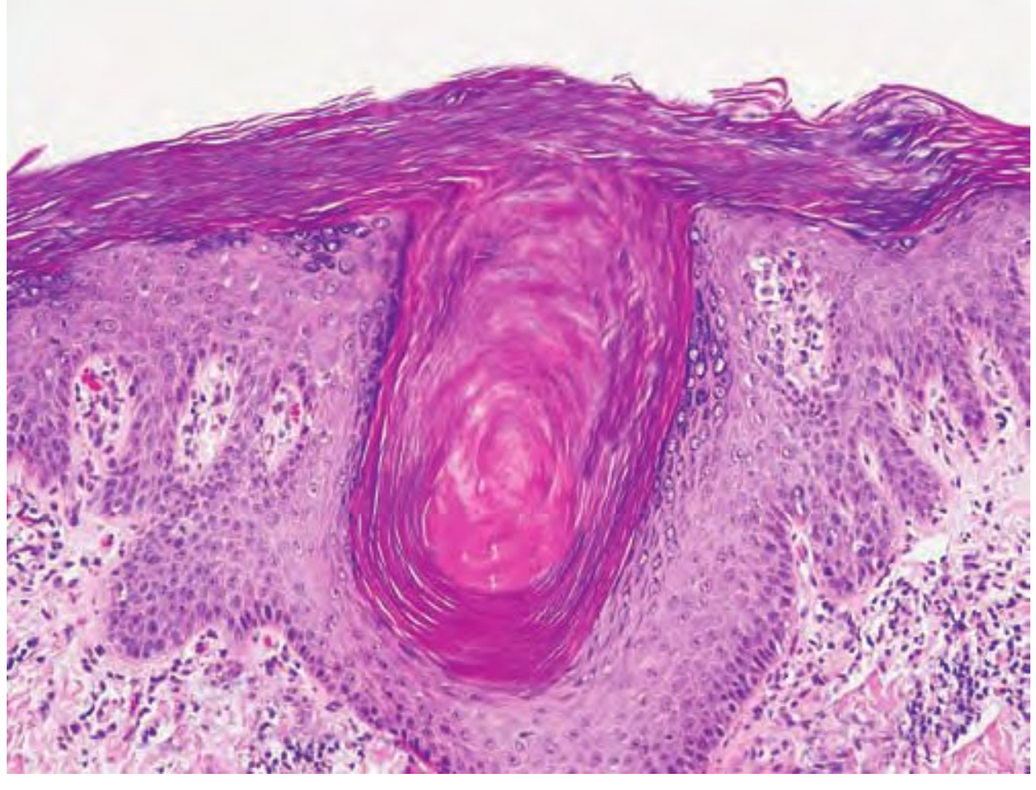


FIGURE 7-38. Pityriasis rubra pilaris, follicular lesion. Dilated follicular infundibulum with hyperkeratotic plug.

by the presence of neutrophils and Munro microabscesses, more pronounced parakeratosis in mounds, thin suprapapillary plates, elongated rete ridges, and tortuous blood vessels (395). Pityriasis rubra pilaris has a more prominent granular layer with less epidermal spongiosis and inflammatory infiltrate (171). Moreover, it has been demonstrated that pityriasis rubra pilaris has a lower keratinocyte proliferation rate than psoriasis, suggesting differences in cell kinetic characteristics (395,397,398).

Pathogenesis. The cause of pityriasis rubra pilaris is unknown. There is evidence that suggests an abnormal epidermal differentiation based on the presence of suprabasal staining with monoclonal antibody against keratin AE1 and the detection of cytokeratins K6 and K16, which are not expressed in normal skin (388).

PITYRIASIS LICHENOIDES

Pityriasis lichenoides is an uncommon cutaneous eruption usually classified in two forms that differ in severity. Simultaneous appearance of the two types and transitions between them often occur, suggesting that they are variants of the same disease (392–401). Both are rarely pruritic or painful, with crops of self-healing lesions affecting mainly young adults and occasionally children (399,400,402,403).

The milder form, called *pityriasis lichenoides chronica*, is characterized by recurrent crops of brown-red papules 4 to 10 mm in size, mainly on the trunk and extremities, that are covered with a scale and generally involute within 3 to 6 weeks with postinflammatory pigmentary changes (186).

The more severe form, called *pityriasis lichenoides et varioliformis acuta* (PLEVA), also referred to as Mucha-Habermann disease, consists of a fairly extensive eruption, present mainly on the trunk and proximal extremities. It is characterized by erythematous papules that develop into papulonecrotic, occasionally hemorrhagic or vesiculopustular lesions that resolve within a few weeks, usually with little or no scarring. Occasionally, some lesions increase in size to necrotic ulcers 1 to 2 cm in diameter, which heal with an atrophic or varioliform scar. Although the individual lesions follow an acute course, the disorder is chronic, extending over several months or even years with development of new lesions and variable periods of remission. Cases of PLEVA occurring during pregnancy and affecting the vagina/cervical mucosa with resultant premature rupture of the membranes and/or premature labor have been reported (404,405). Very rarely, patients with PLEVA have a sudden, severe flare-up of their disease, characterized by innumerable coalescent necrotic ulcerations associated with high fever and systemic manifestations (406–408). Pityriasis lichenoides occurring concurrently with idiopathic thrombocytopenic purpura in childhood has been reported (409).

Histopathology. In pityriasis lichenoides chronica—the mild form—one observes a superficial perivascular and lichenoid infiltrate composed of lymphocytes that extends into the epidermis, where there is vacuolar alteration of the basal layer, mild spongiosis, a few necrotic keratinocytes, and confluent parakeratosis. Melanophages and small numbers of extravasated erythrocytes are commonly seen in the papillary dermis (186,400).

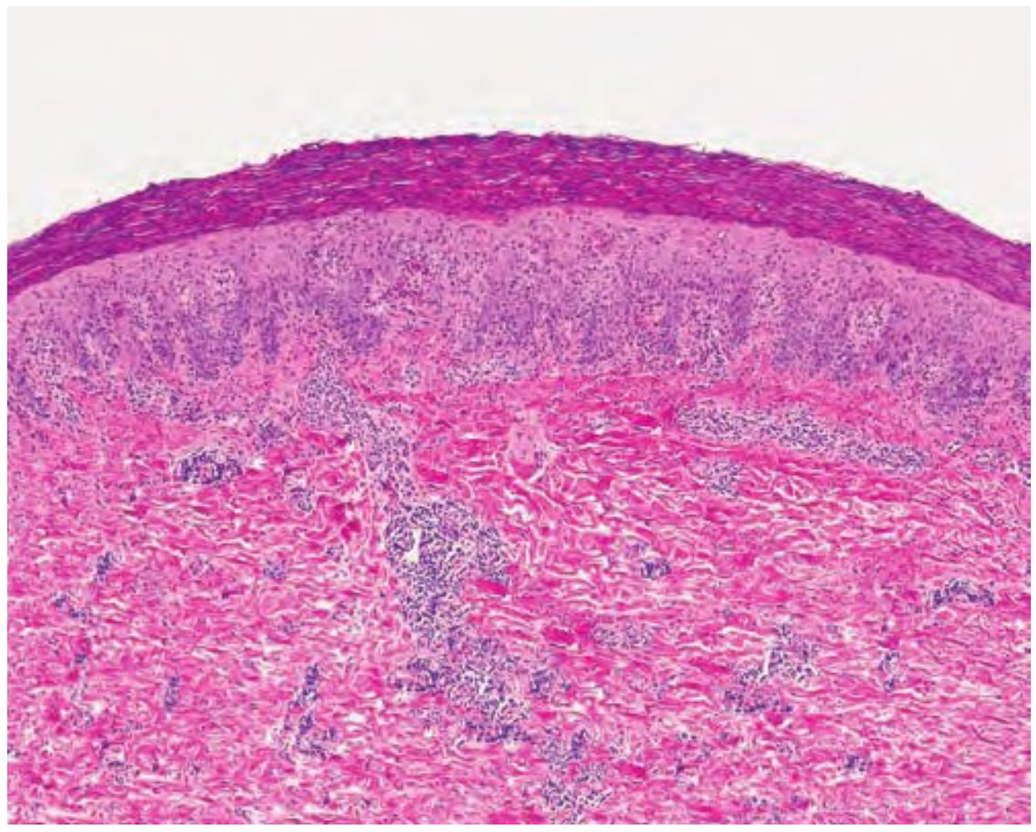


FIGURE 7-39. Pityriasis lichenoides et varioliformis acuta. Lichenoid inflammatory pattern with a superficial and deep perivascular lymphocytic infiltrate.

In PLEVA—the more severe form—there is a perivascular and dense, bandlike, predominantly lymphocytic infiltrate in the papillary dermis that extends into the reticular dermis in a wedge-shaped pattern (Fig. 7-39). The infiltrate obscures the dermal–epidermal junction with pronounced vacuolar alteration of the basal layer, marked exocytosis of lymphocytes and erythrocytes, and intercellular and intracellular edema leading to variable degree of epidermal necrosis (Fig. 7-40). Ultimately,

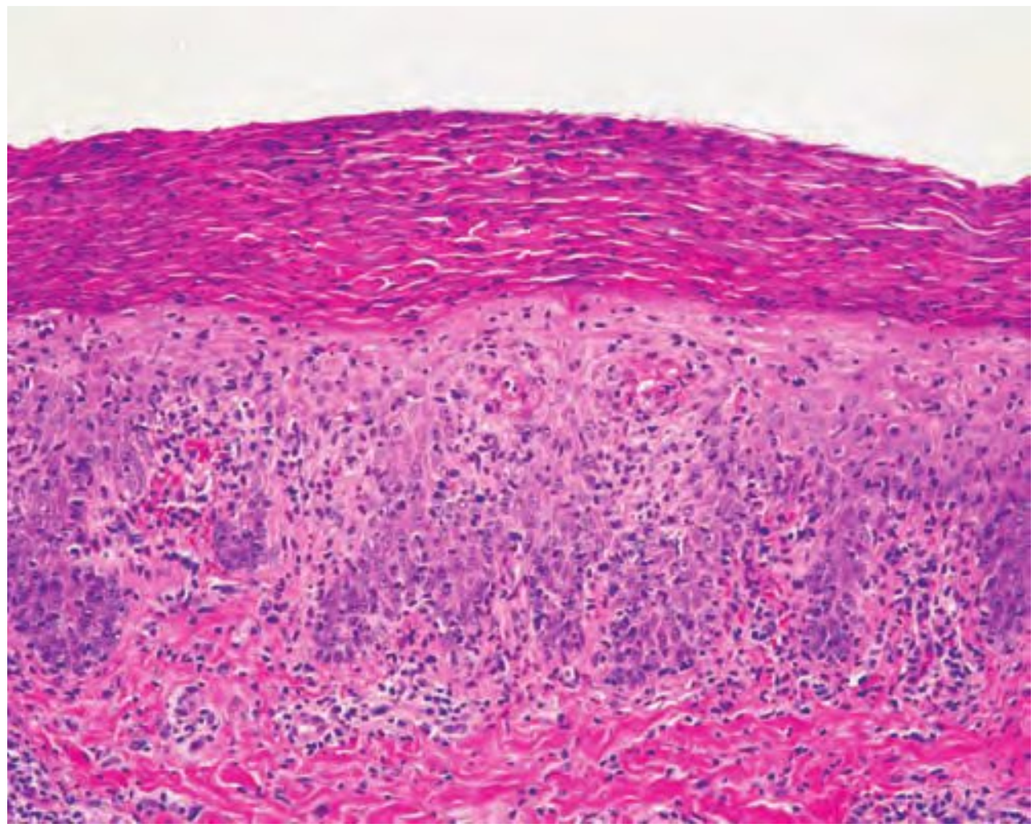


FIGURE 7-40. Pityriasis lichenoides et varioliformis acuta. Closer view reveals lichenoid inflammatory pattern with an infiltrate of lymphocytes, extravasated erythrocytes, irregular acanthosis, pallor of the upper layers of the epidermis, spongiosis, necrotic keratinocytes, and confluent mounds of parakeratosis with plasma, neutrophils, and lymphocytes.

erosion or even ulceration may occur. The overlying cornified layer shows parakeratosis and a scaly crust with neutrophils in the more severe cases (400,410).

Variable degrees of papillary dermal edema, endothelial swelling, and extravasated erythrocytes are seen in the majority of cases. Although occasionally small deposits of fibrin are present within the vessel walls, severe vascular damage is rarely found (400), except in the severe febrile ulceronecrotic variant of PLEVA, in which lymphocytic vasculitis with leukocytoclasis is a fairly common feature (406,408).

Differential Diagnosis. Occasionally, the histologic picture of PLEVA can be mimicked by other diseases such as pityriasis rosea, vesicular insect bites, and subacute eczematous dermatitis. The presence of a deeper inflammatory infiltrate, extensive epidermal necrosis, and the absence of intraepidermal spongiotic microvesicles may help to distinguish PLEVA from pityriasis rosea and subacute eczematous dermatitis. Numerous eosinophils in a vertically oriented dermal infiltrate is more commonly seen in insect bites (411).

Pathogenesis. Most of the cells in the inflammatory infiltrate are activated T lymphocytes (HLA-DR$^+$/CD3$^+$) (401,410,412) that express CD7 and rarely lack other T-cell antigens (CD2, CD5) (401,413). Two constant findings in PLEVA are the predominance of CD8$^+$ (cytotoxic-suppressor) T cells over CD4$^+$ (helper-inducer) T lymphocytes in the infiltrate and the expression of HLA-DR on the surrounding keratinocytes (401,410–412), suggesting a direct cytotoxic immune reaction in the pathogenesis of epidermal necrosis. Recent studies have suggested that PLEVA is a clonal T-cell disorder (414–416). Some cases of pityriasis lichenoides chronica, although less frequent than PLEVA, also exhibited a clonal T-cell receptor gene rearrangement (414,417). Malignant transformation in pityriasis lichenoides is controversial. It does not appear that cases of clonal PLEVA have a higher risk of developing malignant lymphoma (414,418). However, there are a few reports of cases with pityriasis lichenoides that have been associated with cutaneous lymphoma (419–422). It is proposed that pityriasis lichenoides represents an indolent T-cell dyscrasia (423). In conclusion, it is suggested that monoclonal expansion of T cells results most likely from a cellular host immune response to an as-yet-unidentified antigen, perhaps a viral one such as human parvovirus B19 (414,424,425).

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CHAPTER 8

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Vascular Diseases

This chapter discusses vasculitides, vasculopathies, and several other disease processes with vascular injury that can affect the skin. The spectrum of clinical manifestations of such diseases is broad and depends on several factors, including the number, size, and type of vessels involved (arterial vs. venous); the extent of vascular damage; the presence or absence of inflammation; the type of inflammatory infiltrate (neutrophilic vs. lymphocytic); the distribution of the infiltrate (superficial dermis vs. deep dermis or subcutis); and other parameters (1–13).

In general, severe vascular damage with vascular occlusion leads to ischemic damage and may result in necrosis, blister formation, and/or ulceration. Nonocclusive vascular disease may be associated with damage to the structural integrity of the vessel wall and may lead to leakage of blood, resulting in dermal hemorrhage and edema. Dermal hemorrhage is clinically seen as purpura. Hemorrhages less than 3 mm in diameter are called petechiae, and larger lesions are called ecchymoses. If an inflammatory infiltrate is present, purpura may become palpable.

CRITERIA FOR VASCULITIS

Considerable controversy surrounds the criteria for vasculitis. The essential difficulty is the dynamic nature of vascular injury. The appearance of the injured vessels and the inflammatory cells present change as lesions evolve. Furthermore, the degree of vascular injury varies depending on the severity of the insult. The spectrum of vascular reaction to injury ranges from endothelial cell swelling and leakiness to frank fibrinoid necrosis and fibrin deposition. Thus, criteria for recognizing microvascular injury are somewhat arbitrary.

Although the minimum criteria for vasculitis are controversial, in general, vasculitis must have two components: (a) an inflammatory cell infiltrate and (b) evidence of vascular injury (Table 8-1). Vasculitis is an inflammatory process, and thus the absence of inflammation precludes the diagnosis even though vascular alterations may be present. However, in the late, healing state, the inflammatory cell infiltrate may be minimal. The inflammatory cells involved may include neutrophils, eosinophils, lymphocytes, or monocytes/macrophages. The type of infiltrating cell may correlate to some extent with the chronology of the process, but not always.

Evidence of vascular injury is the second major component of vasculitis. Criteria for vascular injury have included (a) evidence of vessel leakiness such as edema and extravasation of erythrocytes, (b) evidence of vessel destruction such as necrosis of endothelium and deposition of fibrinoid material within the vascular lumina or vessel walls, and (c) evidence of inflammatory compromise of the vascular walls, including infiltration by inflammatory cells and leukocytoclasis of the surrounding inflammatory cell infiltrate (Fig. 8-1). As mentioned, there is a continuum of injury. However, for several years pathologists have required a certain degree of injury, as manifested by deposition of fibrinoid material and/or necrosis of the vessel itself, as a primary indicator of a true vasculitis. Certain changes, including edema, extravasation of erythrocytes, infiltration of vessel walls, leukocytoclasis, and thrombosis, may occur with minimal evidence of vascular injury. Pathologists should strive not to overinterpret such changes as vasculitis when definitive evidence of vessel injury is lacking. For instance, leukocytoclasis also may result from necrosis of a neutrophilic infiltrate itself without fibrinoid necrosis of vessels. Similarly, fibrin thrombi may be present in noninflamed vessels in the setting of hypercoagulable states.

Secondary Vasculitis, Incidental Vasculitis, Vasculopathy, Pseudovasculitis

The development of terminology to describe whether vascular injury or vasculitis is primary or secondary (incidental), the degree of vascular injury present, or conditions or disorders mimicking vasculitis indicates the difficulty of interpreting signs of vascular injury and vasculitis (2–13). Primary vascular injury implies that the vascular insult is the predominant disease process. Secondary or incidental vascular injury indicates that another disease process outside the vessels is the primary pathologic process. An example of the latter is vascular alteration noted near cutaneous ulceration. In many instances, distinguishing clearly between a primary and a secondary vascular insult is not possible. However, secondary vascular injury is often variable, with sparing of some vessels within the zone of tissue injury. Other indications of secondary vascular injury include deposition of fibrinoid material at the periphery of the vessel wall and focal thrombosis without significant infiltration by inflammatory cells.

TABLE 8-1 Definitions of Vascular Injury

Primary vascular injury
Vasculopathy
Fibrinoid deposition, thrombosis with limited to no inflammation
Infiltration of vessel wall by inflammatory cells with otherwise minimal alteration
Leukocytoclasis of tissue infiltrate with minimal alteration of vessel, that is, swelling only, absence of fibrinoid necrosis
Vasculitis
Perivascular inflammatory cell infiltrate* (neutrophilic, eosinophilic, lymphocytic, histiocytic, or mixed)
Fibrinoid necrosis*: necrosis of vessel wall with deposition of fibrinoid material
Other changes often present but not essential: edema, extravasation of erythrocytes, leukocytoclasis, infiltration of vessel wall by inflammatory cells, swelling of endothelial cells, luminal thrombosis
Secondary vascular injury†
Vasculopathy or vasculitis
Secondary to another insult such as external trauma or ulceration
Variable vascular alterations with sparing of some vessels
Peripheral perivascular fibrinoid deposition

*Essential for diagnosis.
†Distinguishing between primary and secondary vasculitis is often not possible.

The term *vasculopathy* or *pseudovasculitis* may be used to describe certain degrees of vascular alteration and injury that fail to satisfy the criteria for vasculitis, may closely mimic vasculitis, or both (Table 8-1). Such histopathologic alterations might include hemorrhage, vascular thrombosis (hypercoagulable states), embolic phenomena with little additional evidence of vascular injury (Fig. 8-2), deposition of fibrinoid material with little or no inflammation, minimal infiltration of vessel walls with little or no leukocytoclasis, pathologic alterations of the vessel wall, vasospasm, and repetitive vascular trauma (2–13).

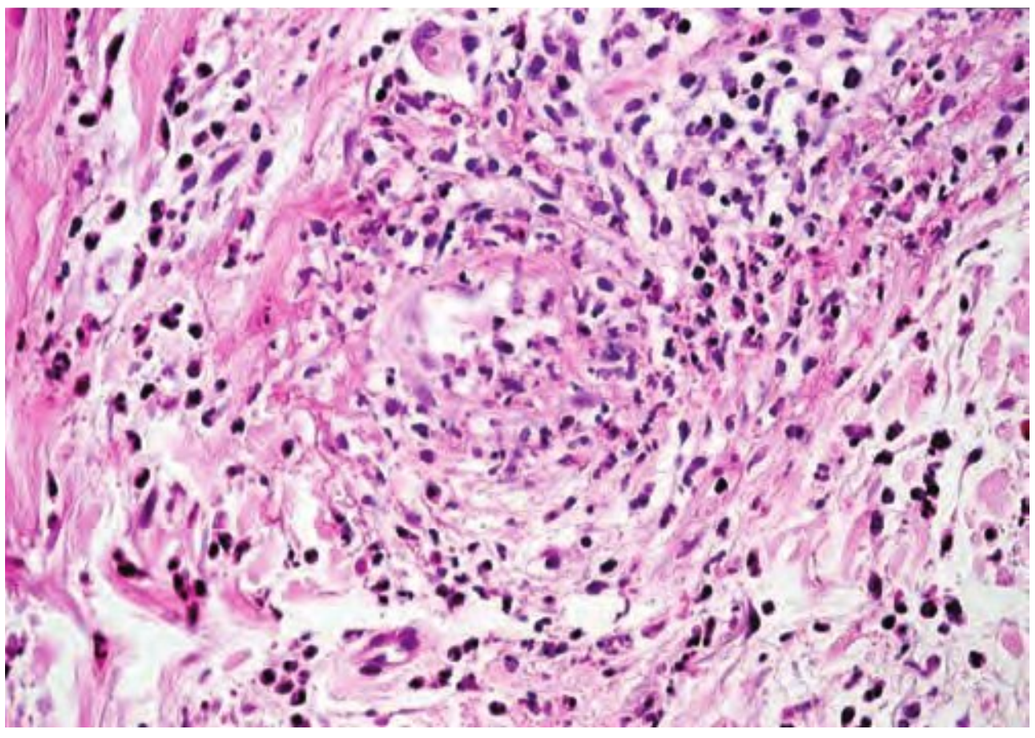


FIGURE 8-1. Hypersensitivity vasculitis showing an upper dermal small blood vessel with full-blown features of neutrophil-rich vasculitis. The specimen was obtained from a 2-day-old purpuric papule.

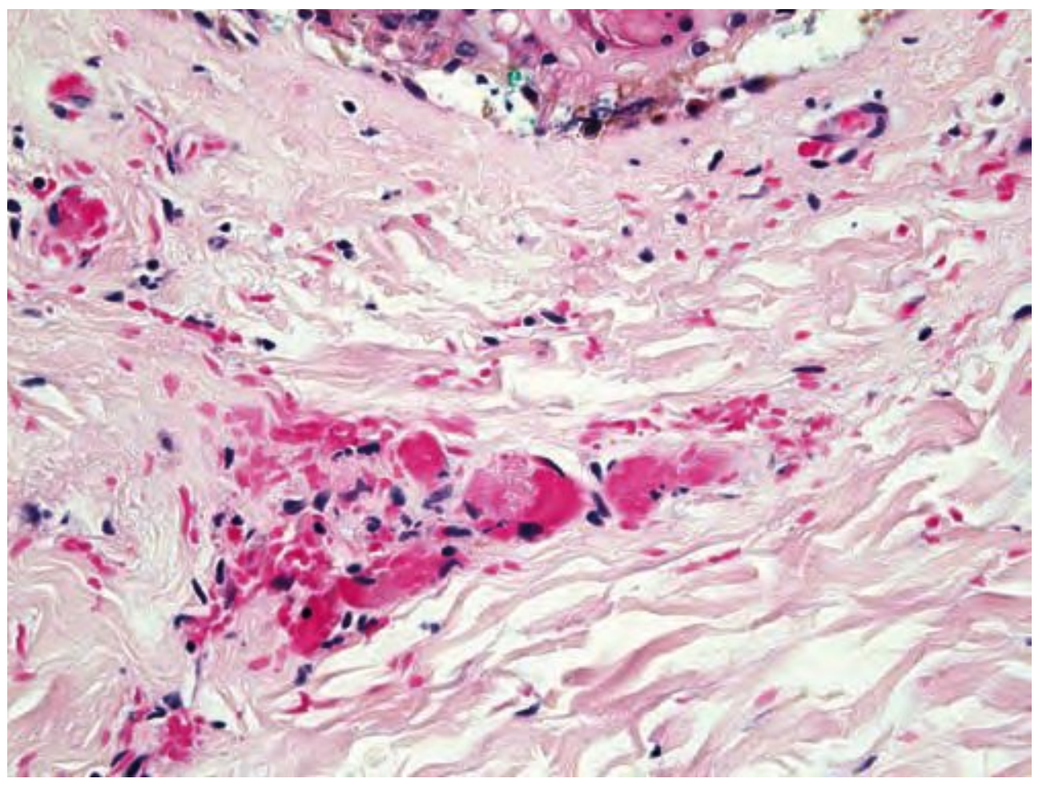


FIGURE 8-2. Vasculopathic reaction, disseminated intravascular coagulation. Pink fibrin thrombi are present within vessels that do not show evidence of damage or inflammation in their walls.

EVALUATION OF VASCULITIS

The classification of inflammatory vascular reactions—specifically that of vasculitides—is difficult for a variety of reasons (1–13). Clinically different entities lack histologic specificity, and the same disease process may show a spectrum of histologic changes depending on the stage of the disease, the level of activity, and the type of treatment that might have modified its course. In an attempt to standardize nomenclature for vasculitides, an international conference proposed a system primarily based on vessel size (3,4,14,15). Large vessels are considered to include the aorta and large named arteries and veins. Medium-sized vessels include the medium-sized and small arteries and veins. These vessels in dermatopathology specimens are located in the subcutis or near the dermal subcutis junction in the skin. Small vessels include arterioles, venules, and capillaries. Most of the vessels in the dermis belong to this group. Classification based on vessel size is helpful because there is some correlation with the clinical presentation. Purpura, palpable purpura, urticaria, vesicles and bullae, and splinter hemorrhages typically reflect small-vessel injury. Cutaneous nodules, ulcers, livedo reticularis, and digital gangrene suggest the involvement of medium-sized arteries. However, classification based on vessel size alone is of limited value in dermatopathology because most cutaneous vasculitides affect primarily small dermal vessels.

A practical approach (Table 8-2) for the histopathologist in evaluating small-vessel inflammatory reactions is first to decide whether clear-cut vascular damage is present and sufficient for a designation as vasculitis, then to assess the composition of

TABLE 8-2 Approach to Vasculitis

1. Determine whether vasculitis or vasculopathy is present or absent
2. Primary or secondary
3. Size of vessel and type
   a. Large
   b. Medium
   c. Small
4. Composition of infiltrate
   a. Neutrophilic/leukocytoclastic
   b. Eosinophilic
   c. Lymphocytic
   d. Histiocytic/granulomatous
5. Evaluation for infection
6. Serologic and immunopathologic evaluation
   a. Evaluation for antineutrophil cytoplasmic antibodies, antinuclear antibodies, rheumatoid factor, cryoglobulins
   b. Immunofluorescence and other studies for the detection of immune complexes, for example, immunoglobulin A-fibronectin aggregates
7. Clinical context
   a. Cutaneous involvement only
   b. Extent of systemic involvement

the inflammatory infiltrate (neutrophilic/leukocytoclastic vs. eosinophilic vs. lymphocytic vs. granulomatous), its distribution (superficial, superficial and deep, or deep only) and to look for associated findings, such as microorganisms, that might narrow the differential diagnosis. The context of the histologic findings is important—for example, vasculitic changes may merely be secondary events in the setting of nonvasculitic causes, such as adjacent to an ulcer, herpes virus infection, or trauma. Lesions also have life spans, and a leukocytoclastic vasculitis may evolve into a predominantly lymphocytic or even granulomatous process.

Histopathology alone is inadequate to classify a vasculitic disease process. Integration of data from other laboratory tests, clinical findings, and even arteriography may be critical to arrive at a diagnosis. In particular, clinical and radiographic findings are needed to assess the degree of systemic involvement and range in size of arteries involved. Infection must be excluded via special stains, cultures, and other laboratory studies. Specific systemic diseases that may be associated with vasculitis such as collagen vascular diseases must be excluded.

Antineutrophil cytoplasmic antibodies (ANCAs) are serologic markers that have allowed a new classification of certain vasculitides. These markers may reflect biologic relationships between disease processes (14–18). ANCAs are best demonstrated by a combination of indirect immunofluorescence of normal peripheral blood neutrophils followed by enzyme linked immunoasorbent assay (ELISA) to detect specific autoantibodies. Indirect immunofluorescence assays reveal two staining patterns: cytoplasmic (c-ANCA) and perinuclear (p-ANCA). ELISAs show that the majority of c-ANCAs are autoantibodies to proteinase 3, and most p-ANCAs are specific for myeloperoxidase (MPO).

TABLE 8-3 Antineutrophil Cytoplasmic Antibody (ANCA)–Positive Vasculitides

Disease Process	Antimyeloperoxidase (p-ANCA)	Antiserine Proteinase (c-ANCA)
Wegener's syndrome	Rare (5%)	Common (80%)
Microscopic polyangiitis (polyarteritis)	Common (50%–60%)	Common (45%)
Churg-Strauss syndrome	Common (70%)	Rare (7%)

c-ANCA, cytoplasmic ANCA; p-ANCA, perinuclear ANCA.

These antibodies are especially helpful, in combination with clinical features, in the differential diagnosis of three small-vessel vasculitides: Wegener's syndrome (WG), Churg-Strauss syndrome (CSS), and microscopic polyarteritis (MPA). WG is usually associated with c-ANCA, MPA with either p- or c-ANCA, and CSS with p-ANCA (see following discussion and Table 8-3). These three syndromes are termed "pauci-immune vasculitides" because vascular injury is not associated with immunoglobulin deposition in vessel walls, in contrast to the immune complex–mediated small-vessel injury seen in entities such as Henoch-Schönlein purpura. The role of ANCAs in these disease processes is unclear. ANCAs may induce vasculitis by activating circulating neutrophils and monocytes, making them adhere to vessels and degranulate, and releasing toxic metabolites, thereby causing vascular injury. On the other hand, ANCA may be an epiphenomenon unrelated to the pathogenesis of these diseases.

The following sections discuss the histologic features and clinical differential diagnoses of inflammatory vascular reactions affecting the skin. Vasculitides are categorized first by vessel size. Large-vessel vasculitides with cutaneous or subcutaneous findings include temporal (giant cell) arteritis and Takayasu's arteritis (19–22). Vasculitis affecting medium-sized and small arteries and, in particular, small-vessel vasculitides are discussed in more detail. Small-vessel vasculitides are classified according to the composition of the inflammatory infiltrate: neutrophilic/leukocytoclastic versus lymphocytic versus granulomatous vasculitis.

VASCULITIS OF LARGE AND MEDIUM-SIZED VESSELS: TEMPORAL (GIANT CELL) ARTERITIS

Giant cell arteritis of the elderly primarily affects large or medium-sized arteries in the temporal region. Although the etiology of temporal arteritis is unknown, in some cases actinic degeneration of the internal elastic lamina may provoke granulomatous inflammation in a reaction similar to actinic granuloma.

The arteritis may be unilateral or bilateral and associated with involvement of other cranial arteries—in particular, retinal arteries. The clinical presentation may include pain and

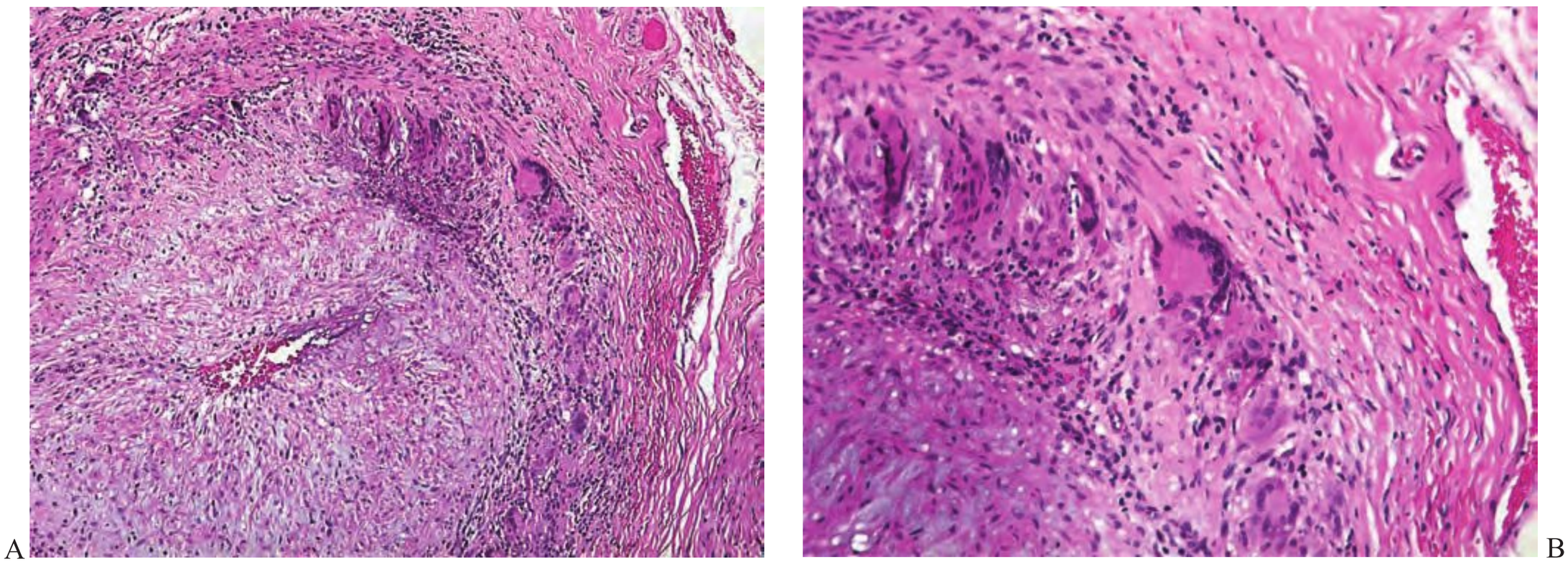


FIGURE 8-3. Giant cell arteritis. (A) and (B) Biopsy of the temporal artery shows a predominantly mononuclear cell infiltrate with a few giant cells in the region of the internal elastic lamina.

tenderness of the forehead and possible sudden visual impairment. Erythema and edema of the skin overlying the involved arteries are commonly seen, and occasionally the scalp may ulcerate (19). The involved artery may be palpable. Clinical laboratory data include a significantly elevated erythrocyte sedimentation rate.

Although the clinical presentation is strongly suggestive of the diagnosis, a biopsy is often performed for confirmation prior to the initiation of systemic steroid therapy. However, results of diagnostic tests are not always positive.

Histopathology. Involved arteries show an inflammatory process of mainly lymphocytes and macrophages that may extend throughout the entire arterial wall (Fig. 8-3). Classically, fragmentation of the lamina elastica and elastophagocytosis by multinucleated giant cells are seen. However, depending on the stage of the disease process, giant cells may not be present, and the inflammatory infiltrate is often unevenly distributed. Step sections may be needed to reveal diagnostic features. In some instances, neutrophils may be present, but this finding should not impede the diagnosis. An elastica van Gieson stain greatly facilitates the evaluation of elastic fibers. Disruption of the internal elastic lamina is not sufficient for diagnosis because this is nonspecific. In late stages, thickening of the intima by deposits of fibrin-like material and myofibroblastic proliferation with subsequent luminal narrowing may be the only findings.

Differential Diagnosis. Not all cases of arteritis involving the temporal artery represent examples of temporal arteritis. Infection-related vasculitis, connective tissue disease, and polyarteritis nodosa might enter into the differential diagnosis. The latter processes often show necrotizing neutrophilic vasculitides (depending on the stage), and diagnosis depends on serologic studies, the absence of infection, and clinical findings.

Takayasu's Arteritis

A large-vessel chronic and fibrosing vasculitis primarily involving the aorta, Takayasu's arteritis (TA) may rarely have cutaneous involvement (21,22). The principal clinical manifestations, usually in women younger than 40 years, include erythematous nodules often of the lower extremities, suggesting erythema nodosum or erythema induratum, or pyoderma gangrenosum–like ulcers (22).

Histopathology. Small and medium arteries of the subcutaneous fat usually show a necrotizing panarteritis with fibrinoid necrosis and sparse inflammatory infiltrates containing lymphocytes and neutrophils. Additional findings may include granulomatous vasculitis, fibrin thrombi without vasculitis, neutrophilic abscesses, and septal and lobular panniculitis.

Differential Diagnosis. Polyarteritis nodosa, pyoderma gangrenosum, and erythema nodosum may be histologically indistinguishable. Additional clinical findings and angiography should facilitate differentiation of TA from other entities.

VASCULITIS AFFECTING MEDIUM-SIZED AND SMALL VESSELS

Vasculitides affecting medium-sized vessels include Kawasaki's syndrome, Takayasu's arteritis, infections, Buerger's disease, polyarteritis nodosa, MPA, WG, CSS, rheumatoid and lupus vasculitis, and giant cell (temporal) arteritis. As noted earlier, there are several methods of classifying vasculitides. WG, MPA, and CSS can be categorized as ANCA-associated vasculitides. Temporal arteritis, WG, and CSS can also be classified as vasculitides associated with granulomatous inflammation.

Kawasaki's Disease (Mucocutaneous Lymph Node Syndrome)

Kawasaki's disease is a necrotizing arteritis that usually affects young children, with a peak age incidence at 1 year (20). Mucocutaneous findings are common and include a polymorphous exanthematous macular rash, conjunctival congestion, dry, reddened lips, "strawberry tongue," oropharyngeal reddening, and swelling of the hands and feet—especially the palms and soles.

Typically a nonpurulent cervical lymphadenopathy is associated. Desquamation of the skin of the fingers typically occurs after 1 to 2 weeks, often followed by thrombocytosis. The most serious clinical complications are related to arteritis and thrombosis of coronary arteries.

Histopathology. Cutaneous vasculitis is rare. The macular rash is usually accompanied by nonspecific histologic changes. Characteristic arteritis is typically found in visceral sites, such as the coronary arteries (see Chapter 7).

Superficial Thrombophlebitis

Superficial thrombophlebitis (STP) of small to medium-sized veins is a common condition usually involving the lower extremities and presents as a painful or tender erythematous cordlike structure or nodule (23). Affected individuals often have predisposing factors such as varicose veins, a hypercoagulable state, ingestion of oral contraceptives, or an underlying malignancy. Variants of STP include Mondor's disease and superficial septic thrombophlebitis (usually secondary to peripheral venous infusion).

Histopathology. Small and medium-sized veins of the lower dermis and subcutaneous fat are involved by an acute vasculitis and thrombosis that occludes the vessel lumina. Early lesions demonstrate dense inflammatory infiltrates primarily composed of neutrophils within the vessel wall. The venous wall is significantly thickened by this influx of leukocytes and edema fluid. In later stages one may observe other inflammatory cells, including lymphocytes, histiocytes, and multinucleate giant cells within the walls of veins. Recanalization of the affected veins ultimately occurs with resolution of the process. Gram stain is indicated for the assessment of septic STP.

Differential Diagnosis. Polyarteritis nodosa (PAN) is the principal entity to be distinguished. PAN affects medium-sized arteries rather than veins, is more inflammatory and less thrombogenic than STP, that is, thrombi are usually absent in PAN, and finally PAN shows conspicuous fibrinoid necrosis, whereas STP usually does not. An elastic tissue stain to demonstrate the presence of an internal elastic lamina in an arterial vessel versus its usual absence (not always) in a vein may facilitate the differentiation of PAN and STP.

Mondor's Disease

Mondor's disease is a thrombophlebitis of the subcutaneous veins of the chest region or dorsal vein of the penis (formerly termed sclerosing lymphangiitis) and is often manifested clinically by a cordlike induration (23,24). Generalized symptoms are usually not a feature, and resolution within weeks is the norm.

Histopathology. In early lesions, a polymorphonuclear infiltrate may be present. However, most biopsied lesions show subcutaneous veins with organizing thrombi and fibrous thickened walls that give them a cordlike appearance at scanning magnification.

Pathogenesis. In the majority of cases, the etiology is unknown; however, local interference with venous flow may be a factor. Trauma, connective tissue disease, breast carcinoma (in rare cases), and a variety of other conditions have been associated.

Thromboangiitis Obliterans (Buerger's Disease)

Buerger's disease is a distinctive condition characterized by a segmental, thrombosing inflammatory process affecting intermediate and small arteries and sometimes veins and may be closely related to STP (23). The vessels of the upper and lower extremities are most commonly involved. The condition almost exclusively affects smokers. Cutaneous findings are manifestations of ischemic injury.

Histopathology. Active lesions are characterized by luminal thrombotic occlusion and a mixed inflammatory cell infiltrate of the vessel wall, characteristically with microabscesses. Later, the thrombus is organized and its lumen may be recanalized (Fig. 8-4). A granulomatous reaction may be present as well.

Differential Diagnosis. The histologic findings in Buerger's disease have been believed to be characteristic. The prevalent current opinion is that these findings are nonspecific and probably occur in other processes, including nonspecific thrombosis and inflammation of intermediate-sized arteries and veins.

Polyarteritis Nodosa

In 1866, Kussmaul and Maier reported the case of a 27-year-old man with fever, abdominal pain, muscle weakness, peripheral neuropathy, and renal disease (25). They termed the fatal illness *periarteritis nodosa*, referring to nodular protuberances along the course of medium-sized muscular arteries, which histologically were characterized by inflammation predominantly at the periphery of the vessel walls, with vessel-wall destruction. Ferrari noted in 1903 the more characteristic presence of inflammatory cells within all levels of the affected vessels and suggested the term *polyarteritis* instead of *periarteritis* (26). The term PAN is believed to subsume three entities: (a) classic systemic PAN, (b) cutaneous PAN, and (c) MPA (27,28). Classic PAN is a multisystem disorder characterized by inflammatory vasculitis involving arterioles and small and medium-sized arteries. According to some authors, cutaneous PAN is the only variety of PAN consistently involving the deep dermis and subcutaneous fat with diagnostic features of arteritis. Some authors maintain that if there is no evidence of systemic involvement by (skin-limited) PAN at the time of initial diagnosis, then the condition will remain confined to the skin, despite a potentially prolonged clinical course with multiple recurrences (29).

Clinical Features. PAN is more common in men than women and usually occurs between the ages of 20 and 60 years. Clinical manifestations may be dramatic and protean. Fever, malaise, weight loss, weakness, myalgias, arthralgias, and anorexia are common symptoms, reflecting the systemic nature of the disease. Other findings may reflect infarction of specific organs. Renal involvement, present in about 75% of patients, is the most common cause of death. Hematuria, proteinuria, hypertension, and azotemia may result from both infarction owing to disease of renal arteries and sometimes focal, segmental necrotizing

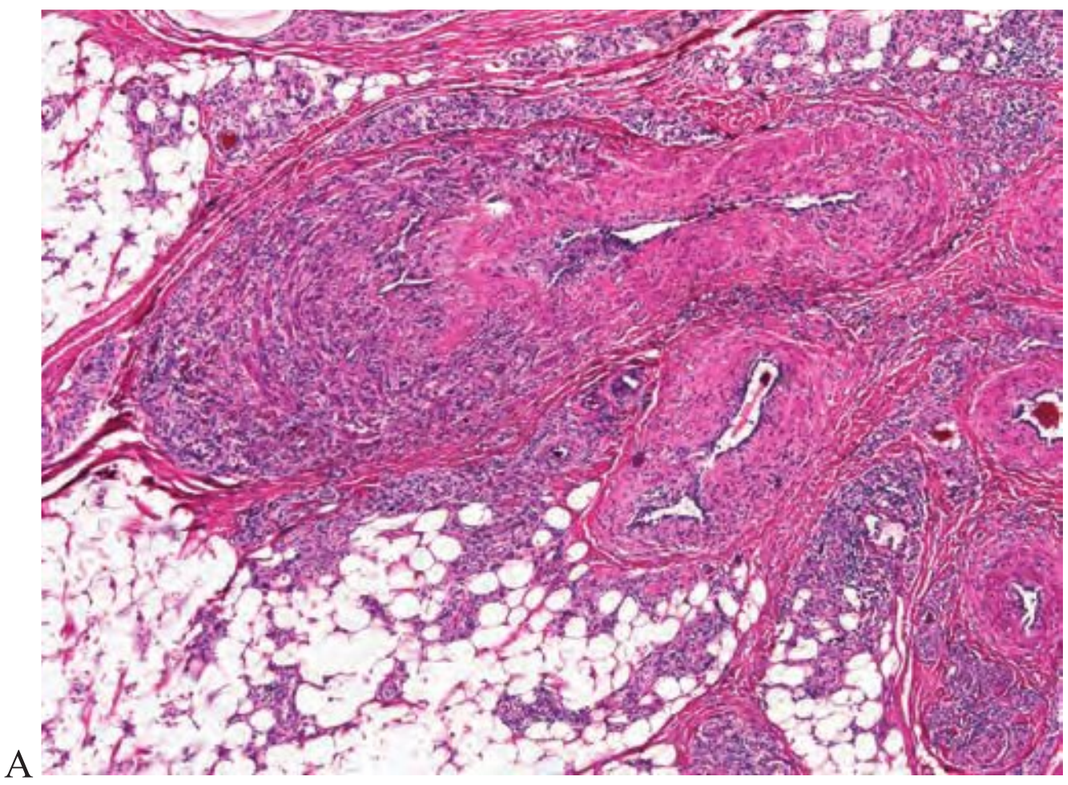


FIGURE 8-4. Thromboangiitis obliterans (Buerger's disease). A mixed inflammatory infiltrate is present in the wall of a large vein, and its lumen is recanalized in a 35-year-old man (A, B) with associated ischemic ulceration in the distal extremity (C).

glomerular lesions suggesting involvement of small vessels. Acute abdominal crises, strokes, myocardial infarction, and mononeuritis multiplex result from involvement of the relevant arteries. Arteriography of visceral arteries often shows multiple aneurysms that are highly suggestive of PAN. ANCAs are generally absent in patients with predominately medium-sized vessel involvement. Symptoms such as asthma, Löffler's syndrome, and rashes may be related to the hypereosinophilia sometimes seen in these patients. Cutaneous manifestations include subcutaneous nodules that may pulsate or ulcerate, ecchymoses, and gangrene of fingers and toes (Fig. 8-5A). Livedo reticularis, bullae, papules, scarlatiniform lesions, and urticaria occur in some patients. A limited form of PAN without visceral involvement may exist, but this concept is controversial (27–29). The so-called cutaneous polyarteritis nodosum may not be limited to the skin but may also affect muscle, peripheral nerve, and joints. The course of disease is described as benign but protracted with steroid dependence.

Histopathology. The characteristic lesion of classic PAN is a panarteritis involving medium-sized and small arteries (Fig. 8-5B, C). Even though in classic PAN the arteries show the characteristic changes in many visceral sites, affected skin often shows only small-vessel disease, and arterial involvement is typically focal. The changes affecting cutaneous small vessels are usually those of a necrotizing leukocytoclastic vasculitis. If there is a clinical presentation of cutaneous nodules, panarteritis similar to visceral lesions is usually detected. In classic PAN, the lesions typically are in different stages of development (i.e., fresh and old). Early lesions show degeneration of the arterial wall with deposition of fibrinoid material. There is partial to complete destruction of the external and internal elastic laminae. An infiltrate present within and around the arterial wall is composed largely of neutrophils, showing evidence of leukocytoclasis, although it often contains eosinophils. At a later stage, intimal proliferation and thrombosis lead to complete occlusion of the lumen with subsequent ischemia and possibly ulceration. The infiltrate also may contain a significant number of lymphocytes, histiocytes, and some plasma cells, which may extend far into the surrounding perivascular tissue and may be predominant at a certain stage. In the healing stage, there is fibroblastic proliferation extending into the perivascular area. The small vessels of the middle and upper dermis often exhibit a nonspecific lymphocytic perivascular infiltrate.

Differential Diagnosis. Vasculitis indistinguishable from PAN may be observed in infections (bacterial, e.g., pseudomonas;

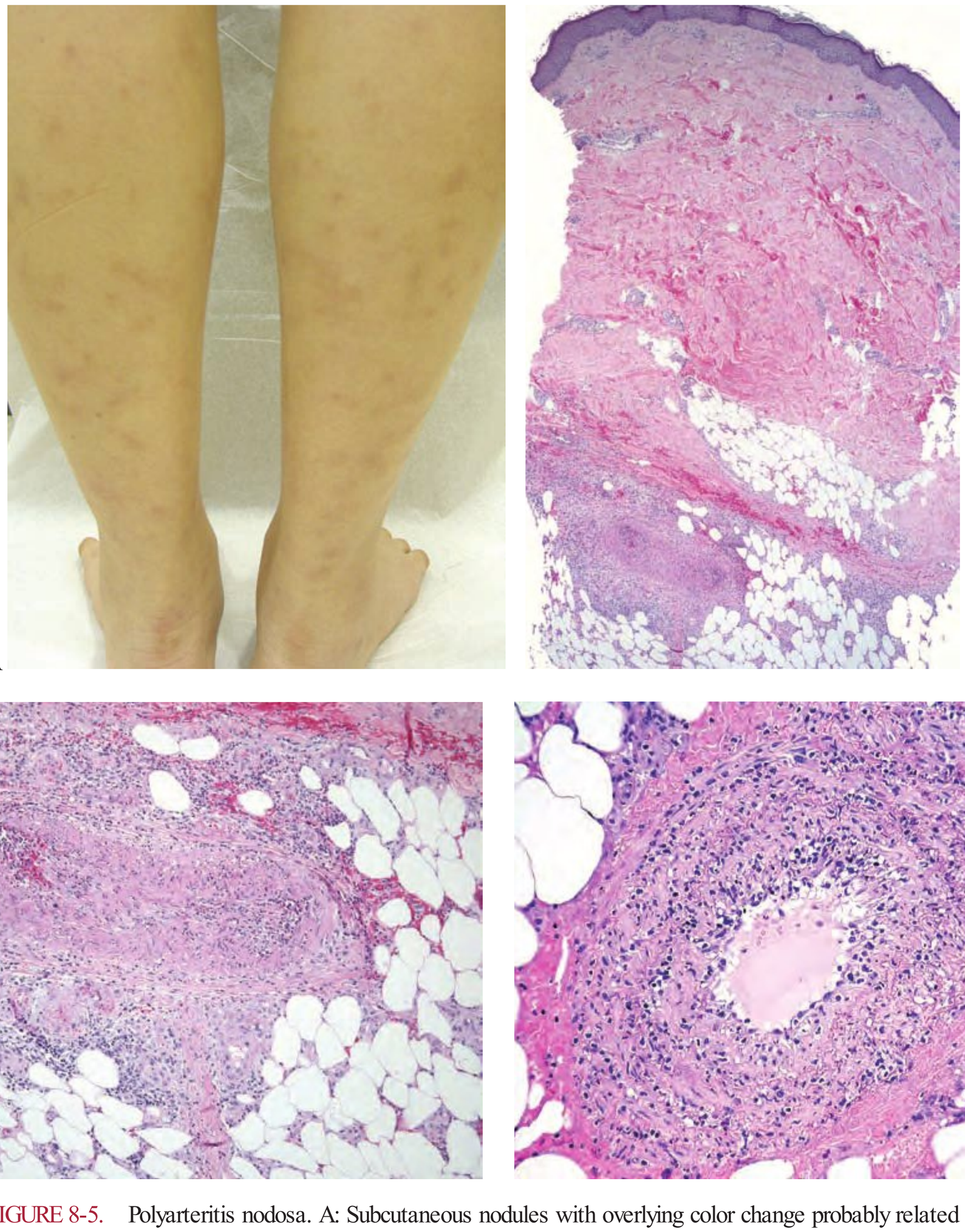


FIGURE 8-5. Polyarteritis nodosa. A: Subcutaneous nodules with overlying color change probably related to telangiectasias and/or hemorrhage. B: A small artery in the subcutis is surrounded and partially obliterated by a cellular inflammatory infiltrate. C: Necrotizing leukocytoclastic vasculitis, with eosinophilic change of the vessel wall, neutrophilic infiltration, and leukocytoclasia. D: Another example of neutrophil-rich, medium-sized vasculitis with focal necrotizing features in a subcutaneous vessel in a patient with polyarteritis nodosa.

viral, e.g., hepatitis B or HIV), in connective tissue diseases (lupus erythematosus, rheumatoid arthritis), in TA, WG, and CSS, and in other settings—for example, acute myelogenous leukemia—without explanation. MPA can overlap considerably with PAN, as discussed later.

Pathogenesis. The pathogenesis of classic PAN is poorly understood. Direct immunofluorescence testing of skin lesions of PAN shows some immune deposits in dermal vessels. However, they may reflect a secondary event after vascular injury from another cause. ANCAs are generally absent in patients with predominately medium-sized vessel involvement and thus are not involved in the pathogenesis of these cases of PAN.

Microscopic Polyangiitis

Davson et al. distinguished classic and microscopic polyarteritis nodosa (30). *Classic polyarteritis nodosa* is to a greater degree a disease of medium-sized vessels, so that ischemic glomerular

lesions are common but glomerulonephritis is rare. *Microscopic polyarteritis nodosa*, on the other hand, refers to a systemic small-vessel vasculitis primarily affecting arterioles and capillaries that is typically associated with focal necrotizing glomerulonephritis with crescents and serum myeloperoxidase-antineutrophil cytoplasmic autoantibodies. Involvement of the small vessels of the kidneys, lungs, and skin gives MPA a particular clinical picture and separates MPA from classic polyarteritis nodosum (30–36).

Clinical Features. The majority of patients with MPA are men and older than 50 years of age. Prodromal symptoms include fever, myalgias, arthralgias, and sore throat. The most common clinical feature is renal disease, manifesting as microhematuria, proteinuria, or acute oliguric renal failure. Although cutaneous involvement is rare in classic PAN, at least 30% to 40% of patients with MPA have skin changes. These include erythematous macules (100% in one study), livedo reticularis, palpable purpura, splinter hemorrhages, and ulcerations. Tender erythematous nodules are exceedingly rare in MPA. Pulmonary involvement without granulomatous tissue reaction occurs in approximately one third of patients. Other organ systems (e.g., gastrointestinal tract, central nervous system, serosal and articular surfaces) also may be affected, but this is less common. Serious clinical complications usually arise from renal and pulmonary disease.

Histopathologic Features. A leukocytoclastic vasculitis primarily affecting arterioles, venules, and capillaries is observed. Necrotizing vasculitis of medium-sized arteries typical of classic PAN is present on occasion. Cutaneous palisading granulomatous inflammation may be seen rarely.

Differential Diagnosis. MPA and classic PAN may not be distinguishable in every case, practically speaking. Glomerulonephritis, typical skin signs, ANCA positivity, and lack of arteriography findings (aneurysms and stenoses reflecting medium-sized vessel involvement) favor MPA over classic PAN (31). MPA also tends not to be associated with viral hepatitis, in contrast to some cases of classic PAN. Biopsy findings are less useful in distinguishing between these two syndromes because the size of diseased vessels detected is highly dependent on biopsy site, size of specimens, and number of tissue samples. Thus, lack of medium-size vessel involvement in a biopsy by no means excludes classic PAN. Conversely, detection of small-vessel involvement also does not exclude classic PAN, which may show small-vessel disease. A number of cases of vasculitis show overlapping features, leading to the introduction of the term "overlapping syndrome of vasculitis" to encompass vasculitis affecting both small and medium-sized arteries (31). The differential diagnosis also includes Wegener's vasculitis and other small-vessel vasculitides that are occasionally ANCA-positive, such as certain drug reactions. The granulomatous inflammation of WG should be lacking in MPA; however, these two entities share many features, and some researchers believe that the distinction of MPA from WG is largely artificial (33).

GRANULOMATOUS VASCULITIS AND GRANULOMATOUS VASCULAR REACTIONS

Over the life spans of many inflammatory reactions involving blood vessels, histiocytes may predominate at a certain stage and form granulomas (Fig. 8-6) (1,4). Granuloma formation

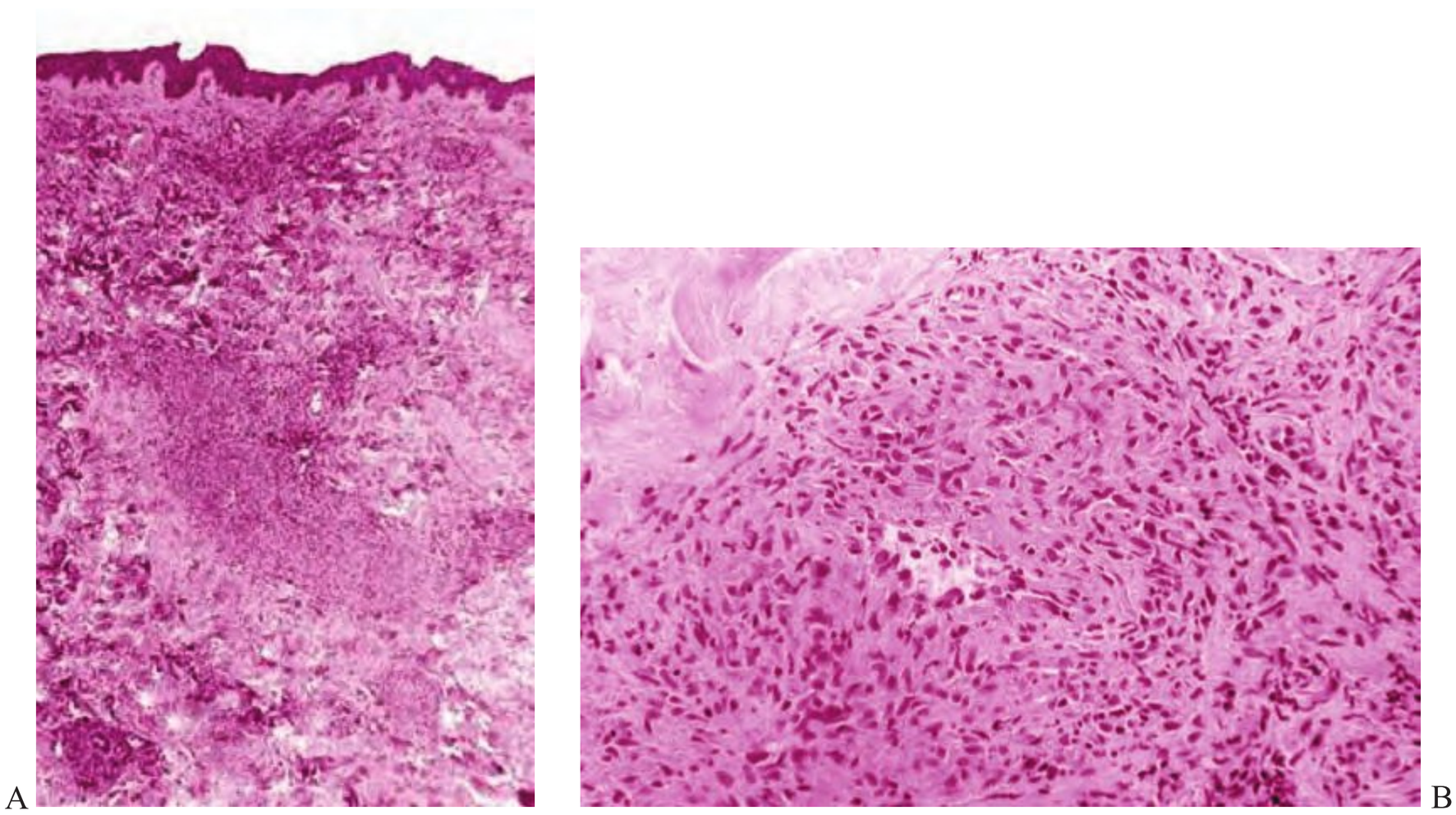


FIGURE 8-6. Granulomatous vasculitis. Note perivascular histiocytic/granulomatous infiltrate (A) and focal vascular damage (B).

TABLE 8-4 Differential Diagnosis of Granulomatous Vascular Reactions

Infection
Wegener's granulomatosis
Churg-Strauss syndrome
Polyarteritis nodosa
Cutaneous Crohn's disease
Drug reaction
Connective tissue disease
Granuloma annulare
Necrobiosis lipoidica
Paraneoplastic phenomena
Angiocentric T-cell lymphoma (lymphomatoid granulomatosis)
Erythema nodosum and erythema nodosum–like reactions

may occur with no or minimal vascular wall damage or may be associated with fibrinoid degeneration of the vessel wall. In the latter situation, a granulomatous vasculitis is present. The main disease processes that need to be considered in the differential diagnosis of a granulomatous vascular reaction are listed in Table 8-4.

The two main disease processes in which granulomatous vasculitis has been described as prominent and fairly characteristic, although nonspecific, are Wegener's granulomatosis and Churg-Strauss syndrome, which are discussed in more detail here. However, the most common cutaneous histologic finding in both diseases is leukocytoclastic vasculitis. The granulomatous inflammation seen in the skin usually is not angiodestructive. Other disease processes that enter the differential diagnosis are also mentioned.

Churg-Strauss Syndrome

The classic clinicopathologic syndrome of Churg-Strauss is characterized by asthma, fever, hypereosinophilia, eosinophilic tissue infiltrates, necrotizing vasculitis, and extravascular granuloma formation. Short of an autopsy, the classic pathologic triad of necrotizing vasculitis, eosinophilic tissue infiltration, and extravascular granulomas is extremely difficult to demonstrate because of the focality of the process (36). A broader definition of CSS requiring asthma, hypereosinophilia greater than 1.5×10^9/L, and systemic vasculitis involving two or more extrapulmonary organs has been suggested. Considerable overlap with other systemic vasculitides and with other inflammatory disorders associated with eosinophils, such as eosinophilic pneumonitis, has brought the legitimacy of the CSS into question.

Clinical Features. Despite multiple reports, CSS appears to be rare. Between 1950 and 1995, only 120 cases were identified at the Mayo clinic (37). The incidence of CSS is similar in males and females. It typically presents in the third or fourth decade of life. Patients tend to display several phases of disease development, from nonspecific symptoms of asthma and allergic rhinitis (prodromal phase) to a phase of hypereosinophilia with eosinophilic pneumonitis or gastroenteritis (second phase) and, finally, to systemic vasculitis (third phase). The internal organs most commonly involved are the lungs, the gastrointestinal tract, and, less commonly, the peripheral nerves and the heart. In contrast to PAN, renal failure is rare. The three disease phases do not always occur sequentially but may on occasion present simultaneously. There is also a limited form of allergic granulomatosis, in which, in addition to preexisting asthma, the lesions are confined to the conjunctiva, the skin, and subcutaneous tissue.

Two types of cutaneous lesions occur in about two thirds of all patients: (a) hemorrhagic lesions varying from petechiae to palpable purpura to extensive ecchymoses, sometimes accompanied by necrotic ulcers and often associated with areas of erythema (similar to Henoch-Schönlein purpura), and (2) cutaneous-subcutaneous nodules. The most common sites of skin lesions are the extremities, but the trunk may also show involvement. In some instances, the petechiae and ecchymoses are generalized. Other skin manifestations include urticaria, erythematous macules, and livedo reticularis.

Diagnostically helpful laboratory findings include an elevated peripheral eosinophil count. CSS is also associated with ANCA. Serum samples from patients with CSS obtained during an active phase of the disease contain anti-MPO (p-ANCA) in the majority of cases (approximately 70%). The levels of anti-MPO have been found to correlate with disease activity. Anti-MPO is found less often in patients with limited forms of the disease. Antiserine proteinase antibodies (c-ANCA) may infrequently be found in patients with CSS (approximately 7%).

Histopathology. The areas of cutaneous hemorrhage typically show leukocytoclastic vasculitis (LCV). However, eosinophils may be conspicuous. In some instances, the dermis shows a granulomatous reaction called palisading necrotizing granuloma composed predominantly of radially arranged histiocytes and, frequently, multinucleated giant cells centered around degenerated collagen fibers (Fig. 8-7). The central portions of the granulomas contain degenerated collagen fibers and disintegrated cells, particularly eosinophils, in great numbers—the so-called "red" palisading granulomas. These palisading granulomas can be embedded in a diffuse inflammatory exudate rich in eosinophils. In the subcutaneous tissue, the granulomas may attain considerable size through expansion and confluence, giving rise to the clinically apparent cutaneous-subcutaneous nodules. Initially believed to be characteristic histologic features, these granulomas were referred to as Churg-Strauss granulomas. However, they are not always present and are not a prerequisite for the diagnosis. Moreover, more recent studies have shown that similar findings can also be observed in other disease processes, such as connective tissue diseases (rheumatoid arthritis and lupus erythematosus), Wegener's granulomatosis, PAN, lymphoproliferative disorders, subacute bacterial endocarditis, chronic active hepatitis, and inflammatory bowel disease (Crohn's disease and ulcerative colitis) (38). Despite the

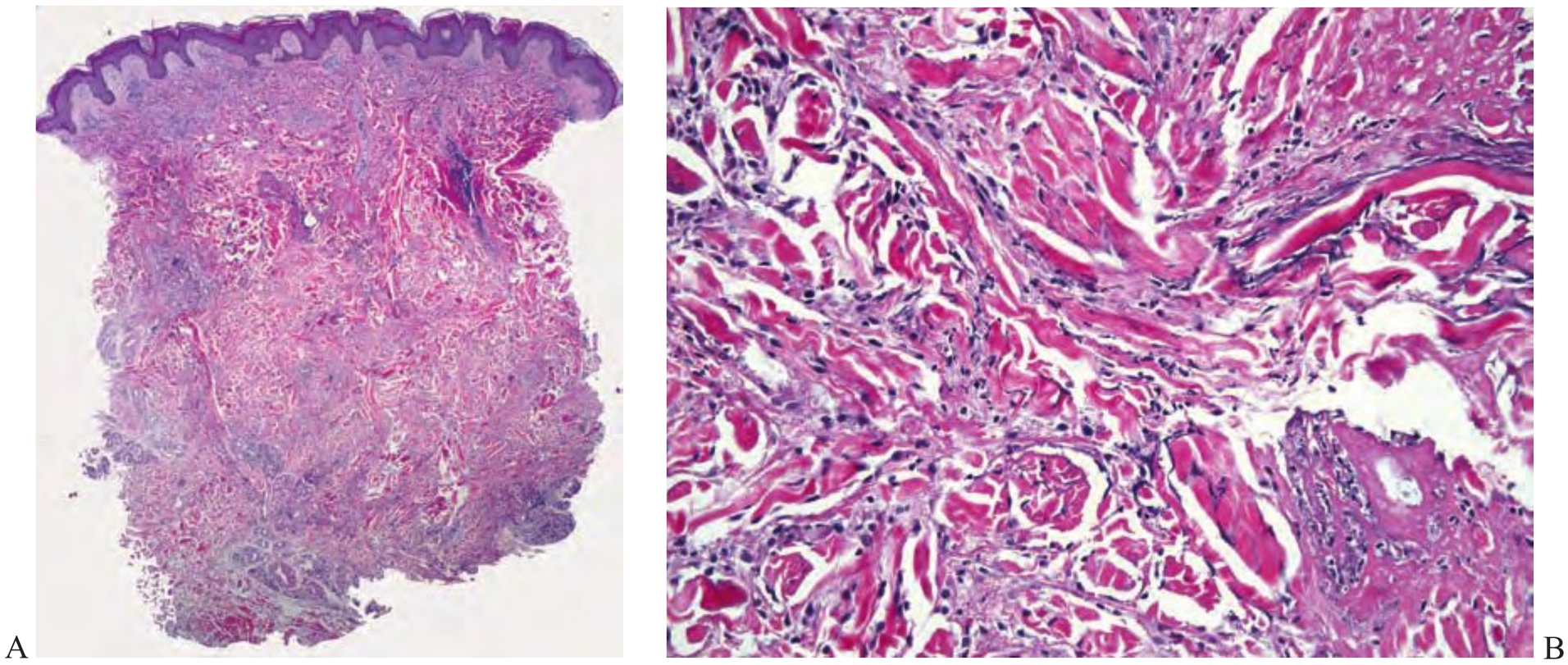


FIGURE 8-7. Palisading necrotizing granuloma. A: Scanning magnification shows a moderately dense cellular infiltrate with an ill-defined palisading pattern around areas of collagen degeneration. B: The infiltrate comprises mainly histiocytes, and collagen degeneration is prominent. C: Degenerating cells including eosinophils are present in some foci. This lesion, formerly called Churg-Strauss granuloma, is not diagnostic of any particular entity, and, in addition to Wegener's syndrome, may also be seen in connective tissue diseases, polyarteritis nodosa, lymphoproliferative disorders, subacute bacterial endocarditis, chronic active hepatitis, and inflammatory bowel disease (see text).

common occurrence of LCV and CS granulomas in CSS, granulomatous arteritis may also be observed (39).

Differential Diagnosis. CSS is a clinicopathologic entity. As such, a diagnosis of CSS depends on the clinical picture of respiratory disease, particularly a history of asthma, p-ANCA positivity, and histology compatible and supportive of this diagnosis, especially granulomatous inflammation, necrotizing angiitis, and eosinophilia. The principal differential diagnosis is from PAN, MPA, WG, and the conditions mentioned previously that may show extravascular necrotizing granulomas. There appears to be significant overlap with WG and PAN. Particular patients may shift from one disease category to another over time.

Wegener's Granulomatosis

Wegener's granulomatosis was first recognized as a distinct clinicopathologic disease process in 1936, when Wegener reported three patients with a "peculiar rhinogenic granulomatosis." Goodman and Churg summarized postmortem studies in 1954, from which evolved the classic triad of this clinicopathologic complex characterized by (a) necrotizing and granulomatous inflammation of the upper and lower respiratory tracts, (b) glomerulonephritis, and (c) systemic vasculitis (40). Liebow and Carrington (36) and later Deremee et al. (41) described limited variants of the disease involving the respiratory tract only.

With the recognition of an association between ANCAs and WG, the concept of WG has been modified and the necessity of demonstrating granulomatous inflammation as a prerequisite for the diagnosis of WG has been challenged. A less restrictive definition was proposed in the Third International Workshop on ANCA in 1991 (3) as *Wegener's vasculitis*. Subsumed under this less restrictive category are ANCA-positive patients with clinical presentations of WG, such as sinusitis, pulmonary infiltrates, and nephritis, and documented necrotizing vasculitis, but without biopsy-proven granulomatous inflammation. Both classic WG and Wegener's vasculitis are considered different manifestations of *Wegener's syndrome*, a more generic term.

Two thirds of patients with WG are male, and the mean age of diagnosis is 35 to 54 years. The vast majority of patients

are white. The clinical presentation is extremely variable, ranging from an insidious course with a prolonged period of nonspecific constitutional symptoms and upper respiratory tract findings to abrupt onset of severe pulmonary and renal disease. The most commonly involved anatomic sites include upper respiratory tract, lower respiratory tract, and kidneys. Other organ systems that are commonly affected include joints and skin. Migratory, polyarticular arthralgia of large and small joints is found in up to 85% of patients with WG. Cutaneous involvement is extremely variable in different series, ranging from about 10% to more than 50% of patients. Skin involvement presents most commonly as palpable purpura. Other cutaneous manifestations include macular erythematous eruptions, papules, papulonecrotic lesions, subcutaneous nodules with and without ulceration, and pyoderma gangrenosum–like ulcerations. Occasionally cutaneous lesions are the first manifestation of WG. However, because of their nonspecific appearance, they are infrequently recognized as presentations of WG.

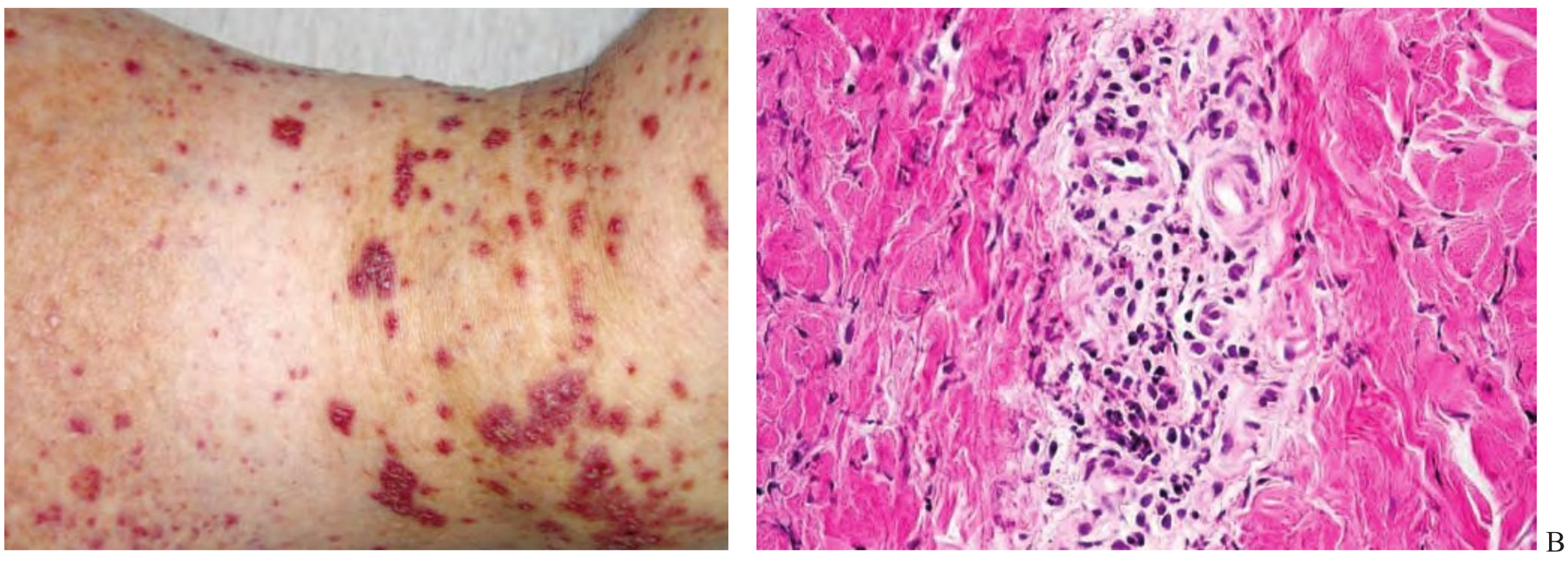
The development of assays for ANCA has greatly facilitated the diagnosis of WG and the monitoring of disease activity. In a series of 106 patients with WG, sera from 88% of the patients with active disease and 43% of the patients in remission were positive for antiserine proteinase (c-ANCA) (41).

Histopathology. The majority of skin biopsies in patients with WG show nonspecific histopathology, and not all of them are directly related to the pathophysiology of WG (42–44). Such nonspecific reaction patterns include perivascular lymphocytic infiltrates. However, in about 25% to 50% of patients, cutaneous lesions have fairly characteristic histopathologic findings. The more frequent distinct reaction patterns include necrotizing/leukocytoclastic small-vessel vasculitis and granulomatous inflammation. Minute foci of tissue necrosis are surrounded by histiocytes and are similar to lesions described in open lung biopsies from WG patients. The palisading granulomas resembling those of Churg-Strauss syndrome may occur, except that the center of the WG granuloma contains necrobiotic collagen and basophilic fibrillar necrotic debris admixed with neutrophils (the "blue" palisading granulomas) (Fig. 8-7). True granulomatous vasculitis appears to be rare.

Differential Diagnosis. Other conditions causing LCV and granulomatous reactions include CSS, metastatic Crohn's disease, rheumatoid arthritis, and sarcoidosis. Granulomatous vascular reactions may also be a manifestation of T-cell lymphomas such as angiocentric T-cell lymphoma or panniculitic T-cell lymphoma. The distinction between CSS and WG relies primarily on the clinical findings. In contrast to WG, CSS is associated with asthma, lacks lesions in the upper respiratory tract, rarely shows severe renal involvement, and typically is accompanied by eosinophilia or eosinophilic infiltrates and p-ANCA positivity. The distinction between MPA and WG may be difficult clinically; however, MPA should lack granulomatous inflammation.

SMALL-VESSEL NEUTROPHILIC/ LEUKOCYTOCLASTIC VASCULITIS

A large number of different disease processes can be accompanied by small-vessel vasculitis with predominantly neutrophilic infiltrates. The clinical and histologic manifestations are thus fairly nonspecific (Fig. 8-8). The main diseases to be considered are listed in Table 8-5 (3–14,45,46).



A B

FIGURE 8-8. A: Palpable purpura associated with leukocytoclastic vasculitis. There is a suggestion of vesiculation (bullous and/or pustular vasculitis). (Courtesy of Rahat S. Azfur, MD.) B: Hypersensitivity vasculitis showing an upper dermal small blood vessel with neutrophil-rich vasculitis and other adjacent postcapillary venules with a perivascular mononuclear cell infiltrate without features of vasculitis. The specimen was obtained from a 6-day-old purpuric macule.

TABLE 8-5 Differential Diagnosis of Cutaneous Neutrophilic Small-Vessel Vasculitis, Categorized on the Basis of Proposed Pathogenic Mechanisms

- Infection
  - Bacterial (gram-positive/gram-negative organisms, mycobacteria, spirochetes)
  - Rickettsial
  - Fungal
  - Viral
- Immunologic injury
  - Immune complex mediated
    - Henoch-Schönlein purpura
    - Urticarial vasculitis
    - Cryoglobulinemia
    - Serum sickness
    - Connective tissue diseases
  - Autoimmune diseases
    - Infection-induced immunologic injury (e.g., hepatitis B or C, streptococcal)
  - Drug induced
  - Paraneoplastic processes
  - Behçet's disease
    - Erythema elevatum diutinum
  - Antineutrophil antibody associated
    - Wegener's granulomatosis
    - Microscopic polyangiitis
    - Churg-Strauss syndrome
    - Some drug-induced vasculitis
  - Unknown
    - Polyarteritis nodosa

Histopathology of Neutrophilic Small-Vessel Vasculitis. Neutrophilic small-vessel vasculitis is a reaction pattern of small dermal vessels, almost exclusively postcapillary venules, characterized by a combination of vascular damage and an infiltrate composed largely of neutrophils (Fig. 8-8). Because there is often fragmentation of nuclei (karyorrhexis or leukocytoclasis), the term *leukocytoclastic vasculitis* is frequently used. Depending on its severity, this process may be subtle and limited to the superficial dermis or be pandermal and florid and associated with necrosis and ulceration. If edema is prominent, a subepidermal blister may form. If the neutrophilic infiltrate is dense and there is pustule formation, the term *pustular vasculitis* may be applied (Fig. 8-9). In a typical case of LCV, the dermal vessels show swelling of the endothelial cells and deposits of strongly eosinophilic strands of fibrin within and around their walls. The deposits of fibrin and the marked edema together give the vessel walls a "smudgy" appearance referred to as *fibrinoid degeneration*. Actual necrosis of the perivascular collagen, however, is seen only rarely in conjunction with ulcerative lesions. If the vascular changes are severe, luminal occlusion of vessels may be observed. The cellular infiltrate is present predominantly around the dermal blood vessels or within the vascular walls, so that the outline of the blood vessels may appear indistinct. The infiltrate consists mainly of neutrophils and of varying numbers of eosinophils and mononuclear cells. The infiltrate also is scattered throughout the upper dermis in association with fibrin deposits between and within collagen bundles. Extravasation of erythrocytes is commonly present.

As with any inflammatory process, the appearance of the reaction pattern depends on the stage at which the biopsy is taken. In older lesions, the number of neutrophils may be decreased and the number of mononuclear cells increased so that mononuclear cells may predominate, and a designation of a lymphocytic or even granulomatous vasculitis or vascular reaction might be made.

Pathogenesis. Many disease processes may exhibit LCV. The major causes of vasculitis are infection and immune-mediated inflammation. Table 8-5 categorizes vasculitides on the basis of suggested pathogenetic mechanisms. Although T-cell–mediated inflammation has been implicated in large-vessel vasculitides, antibody-mediated inflammation seems to play a prominent role in small-vessel vasculitis. Its final common pathway typically involves neutrophil and monocyte activation with adherence to endothelial cells, infiltration of the vessel wall, and release of lytic enzymes and toxic metabolites. This final pathway of vascular injury may be initiated by (a) the deposition of immune complexes, (b) direct binding of antibodies to antigens in vessel walls, and (c) activation of leukocytes by antibodies with specificity for leukocyte antigens (ANCAs).

For example, hepatitis C virus (HCV) is directly linked to a subset of mixed cryoglobulinemia, which is an immune complex–mediated vasculitis (46). HCV particles and nonenveloped nucleocapsid protein participate in the formation of immune complexes. Clonal expansion of rheumatoid factor–synthesizing B lymphocytes is fundamental to the development of mixed cryoglobulinemia. Such B-cell clonal expansion primarily takes place in the liver and correlates directly with intrahepatic HCV viral load, indicating the critical role of HCV in the pathogenesis of such B-cell clonality.

However, it must be stressed that an immune complex etiology has been invoked much too often to explain all forms of vasculitis and particularly small-vessel vasculitis. In many instances, immune complexes are not the primary events in vascular injury but are simply epiphenomena.

Diagnostic Approach to Neutrophilic Small-Vessel Vasculitis. As already mentioned, the clinical and histologic manifestations are fairly nonspecific for this category of vasculitis. For example, palpable purpura may be the clinical appearance of dermal leukocytoclastic small-vessel vasculitis secondary to infection (e.g., gonococcal sepsis), immune complex–mediated vasculitis (e.g., cryoglobulinemia or Henoch-Schönlein purpura), ANCA-associated vasculitis (e.g., WG), allergic vasculitis (e.g., reaction to a drug), vasculitis associated with connective tissue, or a paraneoplastic phenomenon. It is important, therefore, to interpret the histologic findings only in the context of clinical

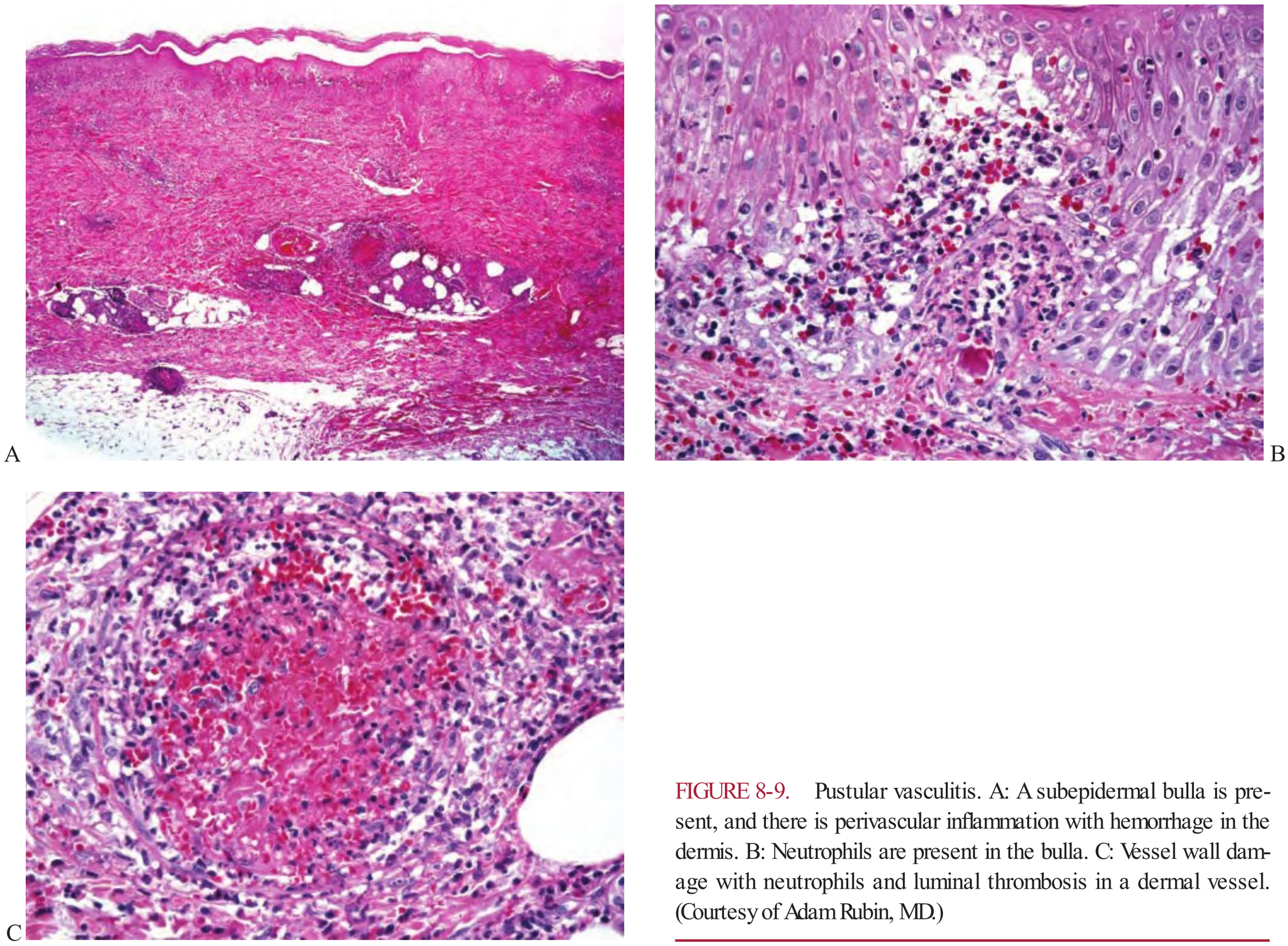


FIGURE 8-9. Pustular vasculitis. A: A subepidermal bulla is present, and there is perivascular inflammation with hemorrhage in the dermis. B: Neutrophils are present in the bulla. C: Vessel wall damage with neutrophils and luminal thrombosis in a dermal vessel. (Courtesy of Adam Rubin, MD.)

information to reach an appropriate diagnosis. Often, additional laboratory data, such as from microbiologic cultures, special stains for organisms, or immunofluorescence or serologic studies, are needed. Because the treatment for infectious vasculitides is so radically different from the treatment for immune-mediated diseases, the most important diagnostic step in the evaluation of a vasculitis is to rule out an infectious process. If noninfectious vasculitis is suspected, evidence for systemic vasculitis must be sought. Clinical findings—such as hematuria, arthritis, myalgia, enzymatic assays for muscle or liver enzymes, and serologic analysis for ANCAs, antinuclear antibodies, cryoglobulins, hepatitis B and C antibodies, IgA-fibronectin aggregates, and complement levels—are important to further delineate the disease process. Exposure to a potential allergen, such as a drug, that might have elicited a hypersensitivity reaction should be sought. Evidence of an allergic pathogenesis is reassuring because it suggests that the vasculitic process may be self-limited and not associated with systemic vasculitis. As mentioned previously, it is also important to address the possibility that the histologic findings of vasculitis may be a secondary phenomenon, for example, in ulceration from localized trauma.

The following subsections discuss the main clinical settings in which LCV occurs.

Infectious Vasculitis

An infectious process needs to be ruled out early in the evaluation of an LCV (1,4). Microorganisms may invade vessels directly or damage them by an immune-mediated mechanism (47). *Neisseria meningitides* is a common cause of infectious cutaneous leukocytoclastic vasculitis. Meningococci may be found within endothelial cells and neutrophils at sites of vascular inflammation. However, other gram-positive or gram-negative bacteria and fungi also may cause cutaneous small-vessel vasculitis (Fig. 8-10). Staphylococcal sepsis can lead to neutrophilic vasculitis with purpura or nodular lesions, which may contain microabscesses. Rickettsial infections, such as Rocky Mountain spotted fever (RMSF), are characterized by invasion of endothelial cells by organisms causing vascular damage. Inflammation, however, is often minimal in RMSF. Direct immunofluorescence microscopy may demonstrate the organism. Clinically, the spectrum of changes ranges from small macules to papules and purpura. Acid-fast organisms can also cause vasculitis. Lucio's

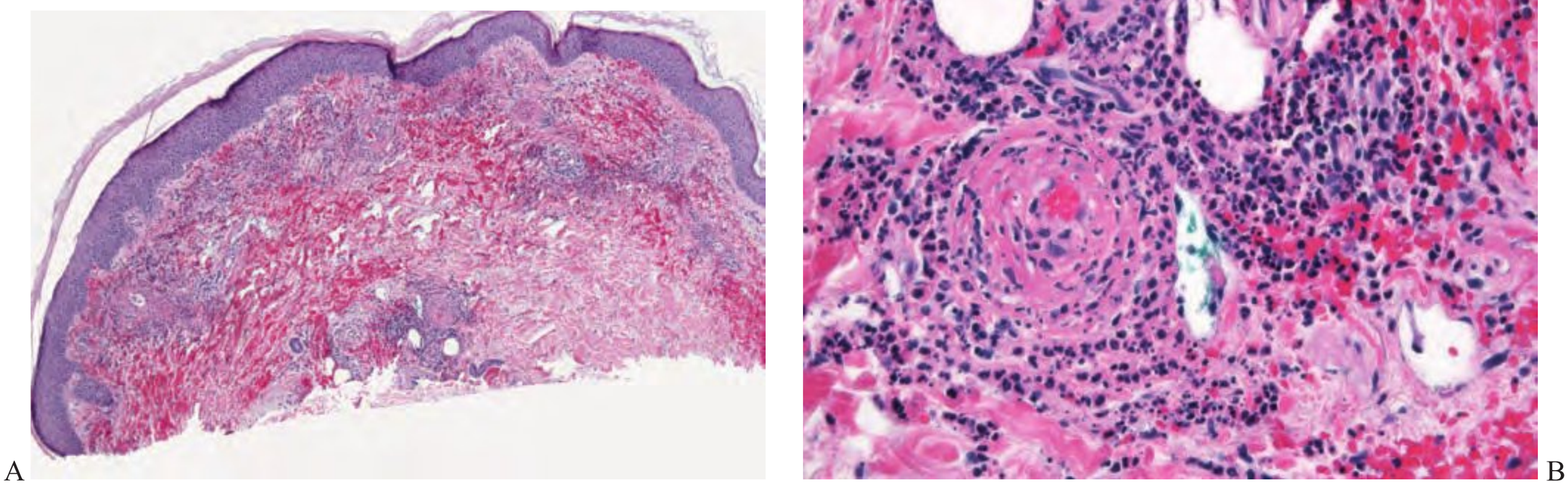


FIGURE 8-10. Septic vasculitis. A: Multiple vessels are surrounded by a dense inflammatory infiltrate and/or contain eosinophilic thrombotic material. It is associated with marked purpuric hemorrhage. B: A small vessel contains fibrin in its lumen and shows fibrinoid change of its wall, with a prominent neutrophilic infiltrate in the wall and in the adjacent tissue. Culture was positive for Pseudomonas. Organisms are difficult to appreciate in the figure.

phenomenon (erythema necroticans) and erythema nodosum leprosum are syndromes that may arise during the course of lepromatous leprosy. In both cases, biopsies show vascular damage, including LCV. Histologically, Lucio's phenomenon shows necrotizing small-vessel vasculitis, and Fite-Faraco staining reveals large aggregates of acid-fast bacilli within the vascular walls and endothelium and throughout the dermis. Ischemia and necrosis of the epidermis, dermis, and adnexal structures often with ulceration are seen. Some researchers have suggested that the massive endothelial mycobacterial burden in Lucio's phenomenon may directly lead to vascular damage (47,48).

Many viral organisms, such as hepatitis C, herpesvirus, and parvovirus B19 (49), may result in LCV on occasion.

Henoch-Schönlein Purpura

Henoch-Schönlein purpura (H-SP) is clinically characterized by palpable purpura of the buttocks and lower extremities, abdominal pain, and hematuria (50) (Fig. 8-11A). Retiform or patterned purpura is considered characteristic of H-SP. It typically affects children after streptococcal upper respiratory tract infections and is usually self-limited, with a resolution expected

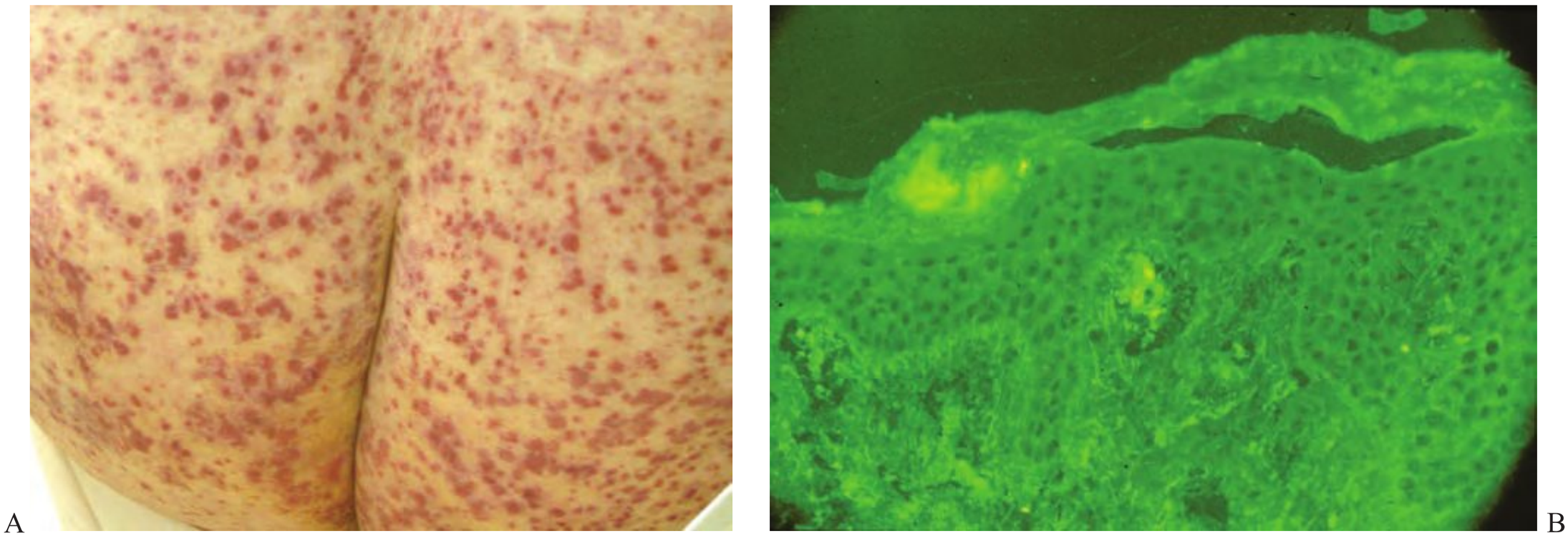


FIGURE 8-11. A: Palpable purpura of sudden onset affecting the buttocks and lower extremities. (Courtesy of Rahat S. Azfur, MD.) B: Direct immunofluorescence showing granular immunoglobulin A (IgA) deposits in very superficial dermal vessels. This immunofluorescence finding is diagnostic for IgA vasculitis (Henoch-Schönlein purpura). Other immunoreactants were negative or significantly weaker.

6 to 16 weeks after the onset of symptomatology. Complications generally arise from renal involvement that may even necessitate kidney transplantation. IgA myeloma has also resulted in HSP-like manifestations (51,52).

Acute infantile hemorrhagic edema (AHE) is an uncommon benign form of cutaneous vasculitis occurring in children younger than 2 years of age and is considered by some to be a variant of HS-P. AHE often presents with striking inflammatory edema and ecchymotic purpura with a targetoid or cockade appearance. Recently, rotavirus infection has been implicated in one case (53).

Histopathology. Henoch-Schönlein purpura cannot be distinguished histologically from other forms of LCV, although the degree of vascular damage is often not as great as that usually observed in typical LCV. Immunofluorescence studies typically demonstrate the deposition of IgA in capillaries (Fig. 8-11). Such a limited extent of vascular damage is also commonly observed in urticarial vasculitis (see text following), and clinical findings may be necessary for distinction of H-SP from urticarial vasculitis. IgA-associated vasculitis may occur outside of the symptom complex of H-SP (52). However, serologic detection of IgA-fibronectin aggregates may be associated with greater likelihood of renal or systemic disease in patients with cutaneous LCV (54).

Urticarial Vasculitis

Persistent wheals (lasting more than 24 hours by convention) with faint purpura are a typical clinical finding of urticarial vasculitis (55–57). Residual purpura is often seen after resolution of the urticarial lesions. Urticarial vasculitis (UV) is not a specific disease but rather a manifestation of a vasculitis that is associated with increased vascular permeability. The course of UV is generally benign and episodic, lasting several months. However, urticarial vasculitis sometimes occurs in lupus erythematosus and may be the initial clinical manifestation of that disease. Approximately one third of all patients with vasculitic urticaria have decreased complement levels (hypocomplementemic vasculitis) (Fig. 8-12). They may have systemic findings, such as arthralgias and adenopathy, and may be more likely to have underlying systemic lupus erythematosus (56). Low complement levels and positive anti-C1q antibodies may indicate greater likelihood of more severe systemic disease.

Histopathology. The histology of urticarial vasculitis is characterized by scant perivascular and interstitial neutrophilic infiltrates and ranges from mild to fully developed LCV (Fig. 8-13). The minimal essential criteria for UV include nuclear debris or fibrinoid alteration of microvessels, with or without extravasation of erythrocytes.

Cryoglobulinemias and Other Small-Vessel Vasculitides Associated with Paraproteins

Small-vessel vasculitis may be associated with paraproteins—that is, abnormal serum proteins (1,58,59). Such paraproteins include cryoglobulins, cryofibrinogens, macroglobulins, and

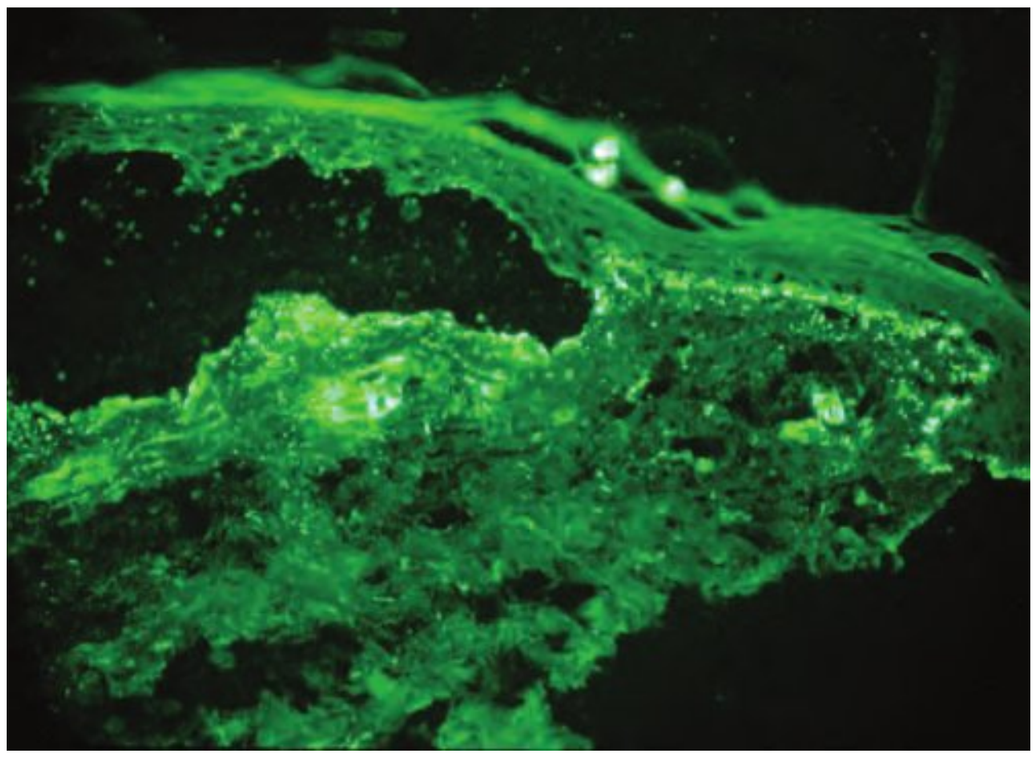


FIGURE 8-12. Direct immunofluorescence showing granular immunoglobulin G deposits in superficial dermal vessels and along the basement membrane zone. This combined vasculitic and lupus type of immunofluorescence finding is characteristic of hypocomplementemic urticarial vasculitis.

gamma heavy chains. Cryoglobulins are serum immunoglobulins that precipitate when the serum is cooled and redissolve on rewarming. There are three major types of cryoglobulinemia: In type I cryoglobulinemia, monoclonal IgG or IgM cryoglobulins are found, often associated with lymphoma, leukemia, Waldenström's macroglobulinemia, or multiple myeloma, or without known underlying disease. In type II cryoglobulinemia, the cryoprecipitate consists of both monoclonal and polyclonal cryoglobulins, with one cryoglobulin acting as an antibody against the other. These cryoglobulins are circulating immune complexes. The most common combination is IgG-IgM (Fig. 8-14). In type III cryoglobulinemia, the immunoglobulins are polyclonal. Type II and III or mixed

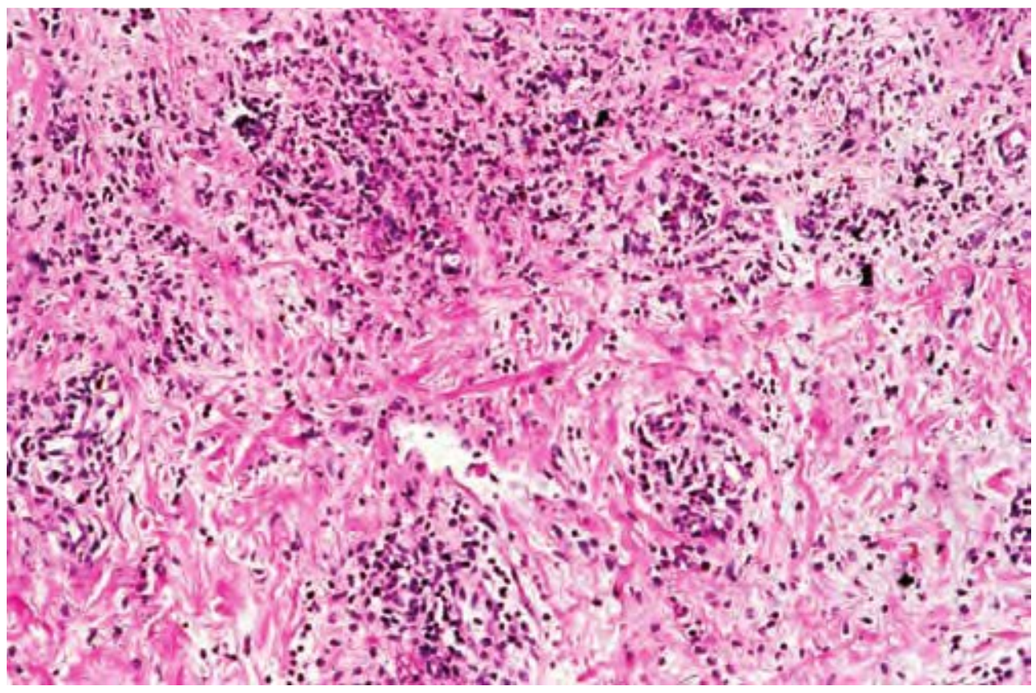


FIGURE 8-13. Neutrophil-rich small-vessel vasculitis of upper and middermal vessels associated with interstitial spillage of neutrophils from a patient with hypocomplementemic urticarial vasculitis.

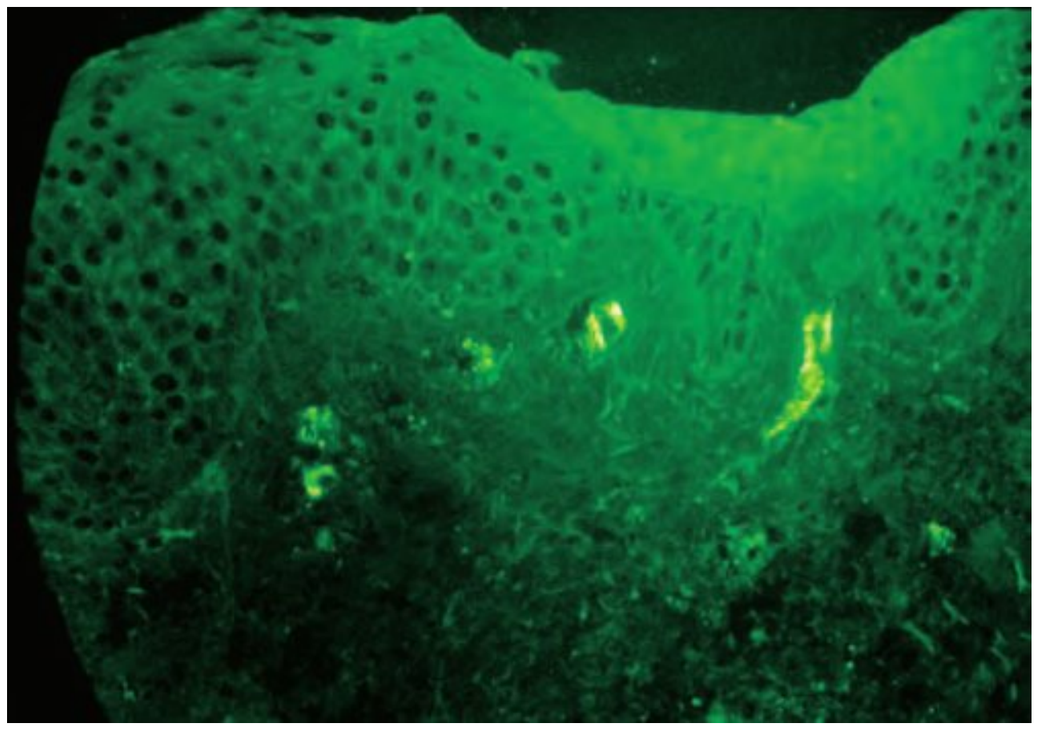


FIGURE 8-14. Direct immunofluorescence showing dense granular immunoglobulin M deposits in superficial small vessels in a patient with cryoglobulinemia type 2. This specimen also showed concomitant dense granular C3 in the same blood vessels.

cryoglobulinemias are frequently associated with hepatitis C infection or connective tissue disorders, such as lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome, or may be related to infection—in particular, hepatitis C infection. Idiopathic forms of type II and III cryoglobulinemias are also termed essential mixed cryoglobulinemia.

Clinically, cutaneous lesions in patients with cryoglobulinemia may manifest as chronic palpable purpura, urticaria-like lesions, livedo reticularis, PAN-like lesions, leg ulcers, splinter hemorrhages, palmar erythema, acrocyanosis, and digital gangrene. Raynaud's phenomenon is common. Systemic manifestations may include arthralgia, hepatosplenomegaly, lymphadenopathy, and glomerulonephritis.

Histopathology. In type I cryoglobulinemia, amorphous material (precipitated cryoglobulins) is deposited subjacent to endothelium and throughout the vessel wall as well as within the vessel lumen, resulting in a thrombus-like appearance (Fig. 8-15). These precipitates stain pink with hematoxylin and eosin and bright red with PAS stain, as opposed to less intense staining of fibrinoid material. Some capillaries are filled with red blood cells, and extensive extravasation of erythrocytes may be present. An inflammatory infiltrate is usually lacking, in contrast to mixed cryoglobulinemia, which typically shows an LCV (Fig. 8-16). PAS-positive intramural and intravascular cryoprecipitates may be found also in mixed cryoglobulinemia, although less frequently than in type I cryoglobulinemia.

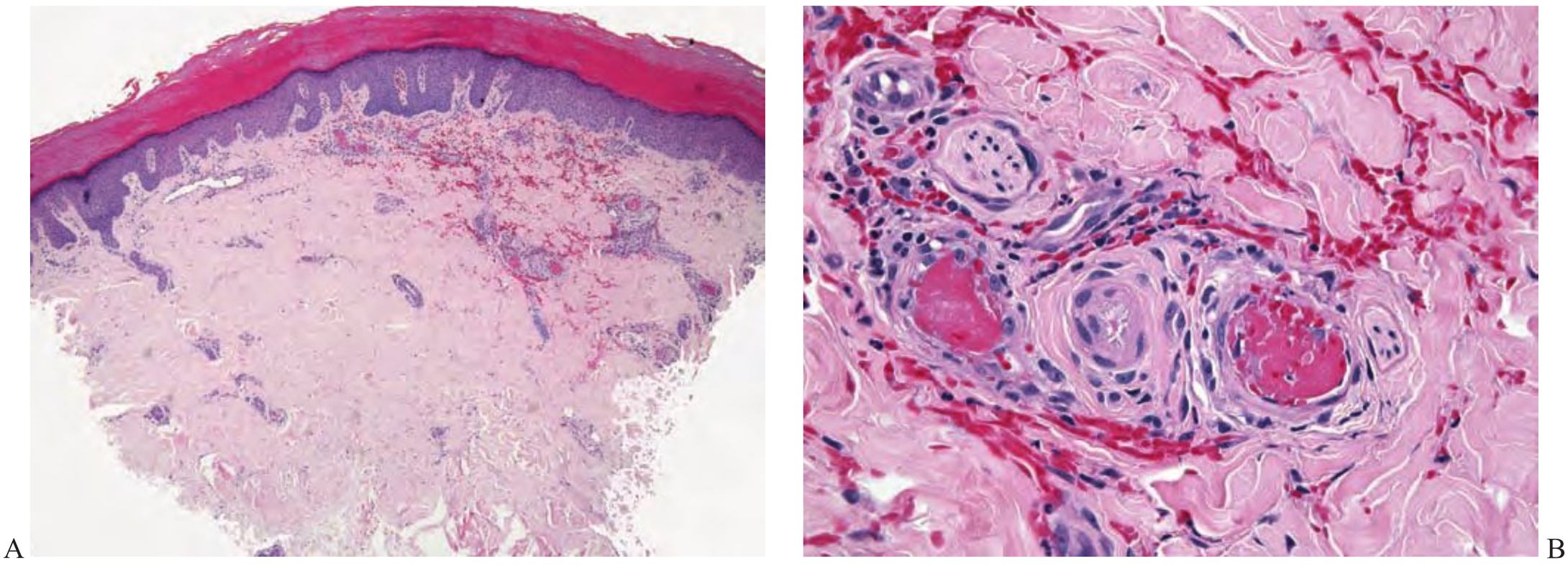
Other small-vessel vasculitides with the histologic pattern of an LCV may be found in association with Waldenström's hyperglobulinemia (hyperglobulinemic purpura) and in Schnitzler's syndrome, which manifests as chronic urticaria with macroglobulinemia (usually monoclonal IgM) and other paraproteinemias.

Serum Sickness

This syndrome of a morbilliform urticarial eruption, fever, and lymphadenopathy occurs 7 to 10 days after a primary antigen exposure or 2 to 4 days after a repeat exposure. The antigen may be a drug, from an arthropod sting or a previous infection, or therapeutic serum globulins (60). Serum sickness is usually a self-limited condition. The LCV of serum sickness has no distinctive histologic features.

Connective Tissue Disease

Rheumatoid arthritis, lupus erythematosus, and other diseases in the spectrum of connective tissue disease may develop LCV (61–64). Leukocytoclastic vasculitis may also occur in patients with antiphospholipid antibody syndrome (65). Clinical and



A B

FIGURE 8-15. A: Cryoglobulinemia. Vessels in the reticular dermis contain brightly eosinophilic material. B: The deposition is associated with little or no damage to the vessel walls in this case.

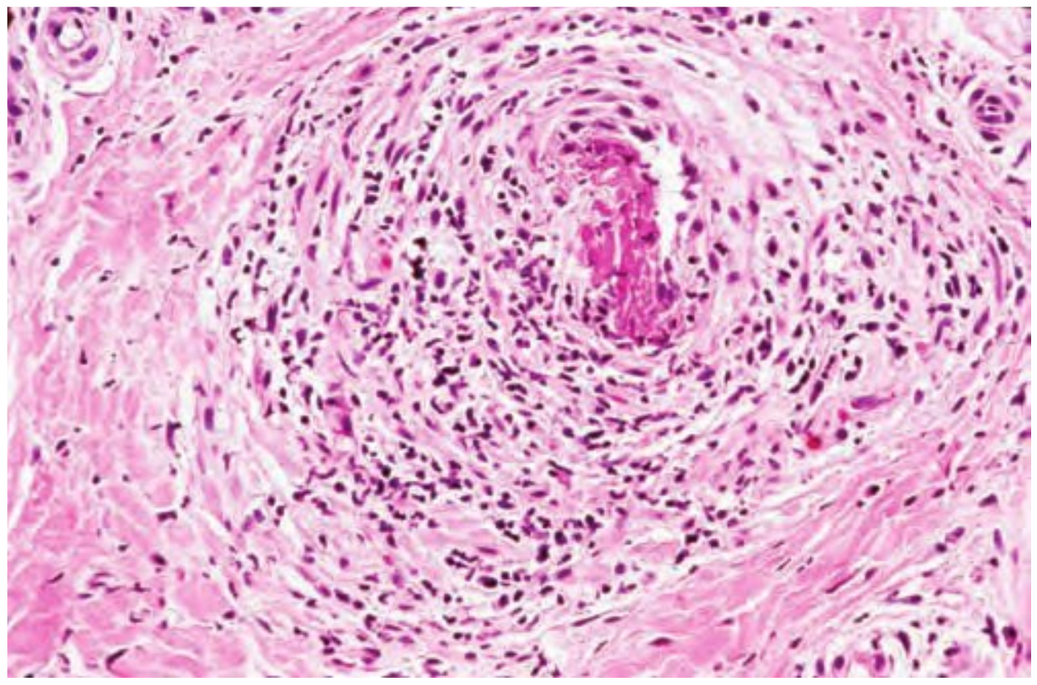


FIGURE 8-16. Cryoglobulinemia. A small middermal artery showing neutrophil-rich vasculitis secondary to hepatitis C–associated cryoglobulinemia type 2.

serologic information is critical to the correct interpretation of the cutaneous findings in these clinical settings.

Autoimmune Diseases

Primary Sjögren's syndrome is not associated with connective tissue disease but may present with purpura in addition to ocular and glandular involvement (1). The histologic reaction pattern is often an LCV or lymphocytic vasculitis.

ANCA-Associated Vasculitis

The pauci-immune vasculitides associated with ANCA were discussed in more detail earlier. MPA, WG, and Churg-Strauss syndrome may all be associated with cutaneous LCV.

Drug-Induced Vasculitis

A hypersensitivity reaction to a drug may result in an LCV (1,4). Penicillin, thiazides, and sulfonamides are the most common drugs used to induce LCV. Drugs also may induce the pattern of pustular vasculitis. Increased tissue eosinophil counts (5.2 vs. 1.05 per 10 high-power fields) have recently been shown to correlate with drug-induced versus non–drug-induced LCV (66).

Paraneoplastic Vasculitis

A wide spectrum of vasculitic processes has been associated with neoplastic disorders (67,68). Sixty patients with cancer-related vasculitis demonstrated the following vasculitic patterns: 45% LCV, 36.7% PAN, 6.7% WG, 5% MPA, and 5% H-SP. The distribution of malignancies among these patients was as follows: 63.1% with hematologic (including 32.3% with myelodysplastic syndromes and with 29.2% lymphoid neoplasms) and 36.9% with solid malignancies. Common associations include polyarteritis nodosa with hairy cell leukemia and cutaneous small-vessel vasculitis with lymphoproliferative disorders and some carcinomas.

Behçet's Disease

Behçet's disease is a multisystem disease characterized by oral aphthous lesions and at least two of the following criteria: genital aphthae, synovitis, posterior uveitis, cutaneous pustular vasculitis, and meningoencephalitis (69,70). This HLA-B51–associated disease is common in the Middle East and Japan but rare in northern Europe and the United States. The clinical presentation is extremely variable and so is the vascular involvement, which can range from active inflammatory lesions to aneurysms, arterial or venous occlusions, or varices.

Histopathology. The histopathologic spectrum of mucocutaneous inflammatory vascular lesions includes, depending on the stage and activity of the lesion, neutrophilic, lymphocytic, and granulomatous vascular reactions. Biopsy specimens of early lesions typically show a neutrophilic vascular reaction, and Behçet's disease is sometimes classified as a neutrophilic dermatosis/neutrophilic vascular reaction. However, fully developed necrotizing leukocytoclastic vasculitis may develop. If the neutrophilic infiltrate is very dense, the pattern of pustular vasculitis may be found (see Fig. 8-9).

Pathogenesis. The etiology of Behçet's disease is unknown. The vascular injury is presumably immune mediated because immune complex deposition has been demonstrated in vessel walls. Disorders of neutrophils are also being discussed with regard to the etiology of this disease. However, the occurrence of cutaneous vasculitis together with the vascular injury seen in other organ systems suggests that Behçet's disease is best classified as a systemic vasculitis (70).

Localized Fibrosing Small-Vessel Vasculitis

Erythema elevatum diutinum (EED), granuloma faciale (GF), and some examples of cutaneous inflammatory pseudotumor are very similar chronic fibrosing conditions that show evidence of vascular damage (71,72). Sometimes, they may be classified with the neutrophilic dermatoses. These entities are hypothesized to be reactions to localized persistent immune complex deposition or hypersensitivities to a persistent antigen. EED- and GF-like reactions may occasionally be seen in clinical settings atypical for either entity (71).

Erythema Elevatum Diutinum

This rare condition is characterized by persistent, initially red to violaceous and later brown to yellow papules, nodules, and plaques (73–75). The lesions, typically distributed symmetrically on the extensor surfaces of the extremities, are initially soft and then evolve into fibrous nodules.

Histopathologic Features. In the early stage of EED, nonspecific LCV is observed. In later stages, granulation tissue and fibrosis form with a diffuse mixed-cell infiltrate showing a predominance of neutrophils. The capillaries may still show deposits of fibrinoid material or merely fibrous thickening. Fully developed lesions of EED may be indistinguishable from neutrophilic dermatoses discussed later, Behçet's disease, or neutrophilic drug reaction. Granuloma faciale may also resemble

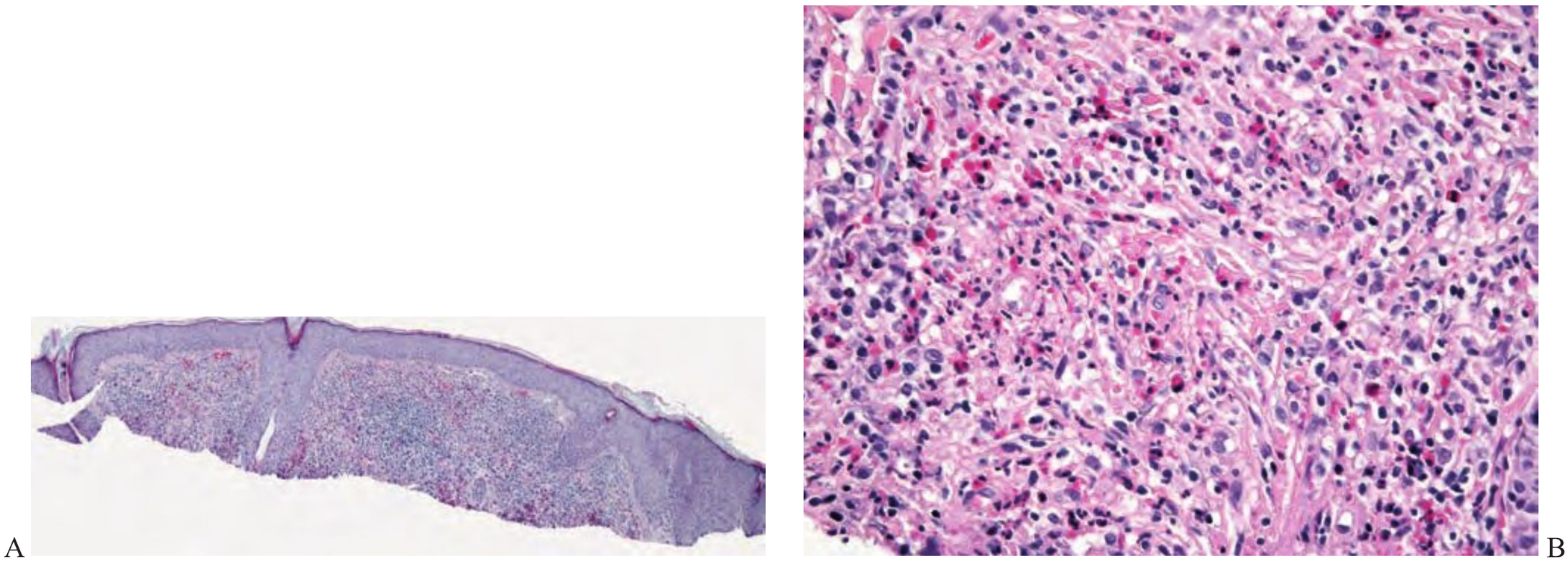


FIGURE 8-17. Granuloma faciale. A: There is a cellular infiltrate in the dermis, separated from the epidermis by an uninvolved or grenz zone. B: The infiltrate contains numerous neutrophils and eosinophils. Vascular damage is minimal.

EED but is distinguished by clinical localization to the face, sparing of the superficial papillary dermis (a grenz zone), and prominence of eosinophils and plasma cells in addition to neutrophils. Occasional cases show neutrophilic microabscesses in the tips of dermal papillae that might suggest dermatitis herpetiformis (74). In old, fibrotic lesions of EED there is an orderly array of spindle cells and collagen bundles often parallel to the skin surface with vertically arranged capillaries similar to a scar. Lipid material also may be present as cholesterol clefts. Serial sections may be required to demonstrate vascular damage in late lesions. These older lesions of EED must be differentiated from Kaposi's sarcoma, dermatofibroma, or granuloma annulare. Neutrophils, nuclear dust, and fibrin owing to persistent vascular damage may be present, helping to distinguish these lesions from dermatofibromas or scars. The irregularly arranged, jagged vascular spaces of Kaposi's sarcoma are absent, and many of the spindle cells have the immunohistochemical and electron microscopic features of macrophages. Focal areas of basophilic collagen caused by nuclear dust in EED can resemble the mucin seen in granuloma annulare but do not stain with Alcian blue.

Pathogenesis. EED probably is not a distinct disease entity but rather a clinicopathologic reaction pattern, most often developing in either a monoclonal or polyclonal gammopathy, in particular IgA hyperglobulinemia. Inflammatory bowel disease, rheumatoid arthritis, and systemic lupus erythematosus may also be associated with EED. HIV-infected patients also develop EED, which can clinically mimic Kaposi's sarcoma (75).

Granuloma Faciale

Clinically, granuloma faciale presents as one or several asymptomatic, soft, brown-red, slowly enlarging papules or plaques, almost always on the face of older individuals. Rare upper respiratory tract forms have been described (76).

Histopathologic Features

A dense polymorphous infiltrate is present mainly in the upper half of the dermis but may extend into the lower dermis and occasionally even into the subcutaneous tissue. Quite characteristically, the infiltrate does not invade the epidermis or the pilosebaceous appendages but is separated from them by a narrow grenz zone of normal collagen (Fig. 8-17). The pilosebaceous structures tend to remain intact. The polymorphous infiltrate consists primarily of neutrophils and eosinophils, but mononuclear cells, plasma cells, and mast cells also are present. Vascular damage in GF is seen but often is limited, and thus perhaps GF is best termed a neutrophilic vascular reaction (78). Frequently, the nuclei of some of the neutrophils are fragmented, especially in the vicinity of the capillaries, thus forming nuclear dust. Often, there is some evidence of vasculitis with deposition of fibrinoid material within and around vessel walls. Occasionally, some hemorrhage is noted. Foam cells and fibrosis frequently are observed in older lesions.

Differential Diagnosis. Granuloma faciale can appear similar to erythema elevatum diutinum, although a grenz zone and prevalence of eosinophils and plasma cells favors granuloma faciale. Other neutrophilic dermatoses can be distinguished from granuloma faciale by the lack of a grenz zone and clinical features. Frank leukocytoclastic vasculitis should not be seen in granuloma faciale. In acneiform lesions and folliculitides, pilosebaceous units are invaded by inflammatory cells and may be destroyed or disrupted.

Pathogenesis. Vascular damage may be important to the pathogenesis of this lesion because direct immunofluorescence data suggest an immune complex–mediated event with deposition of mainly IgG in and around vessels.

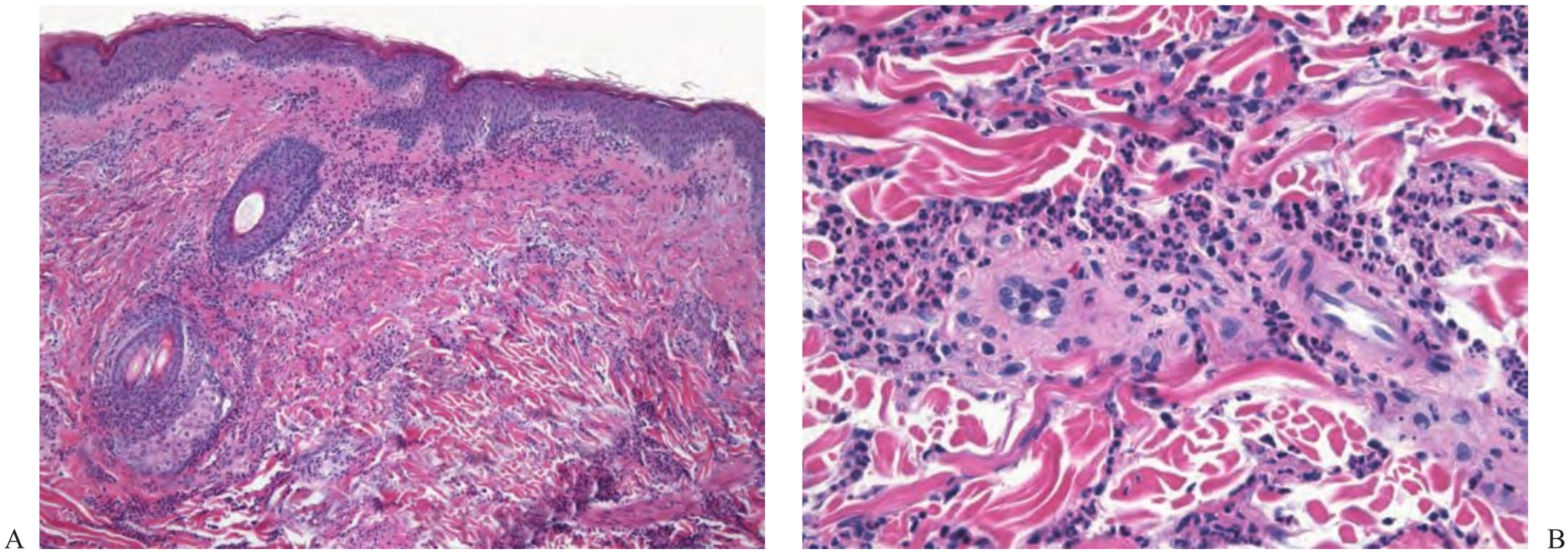


FIGURE 8-18. Sweet's syndrome. A: There is a dense infiltrate in the upper dermis, consisting mainly of neutrophils, without leukocytoclasia. B: Vascular damage is slight.

NEUTROPHILIC DERMATOSES

The histopathologist occasionally encounters lesions consisting of a neutrophilic infiltrate, sometimes even with leukocytoclasis, and some degree of vascular damage in up to one third of cases (69). Microvascular injury is most likely secondary to the dense neutrophilic infiltrates; the extent of vascular damage is insufficient for necrotizing vasculitis—that is, fibrinoid necrosis is lacking. Occasionally such a histologic picture may be seen in an early lesion of vasculitis. However, several clinical conditions characterized by neutrophilic infiltrates rarely develop necrotizing vasculitis and need to be distinguished from vasculitis. These entities are categorized as neutrophilic dermatoses and are characterized by (a) a neutrophilic infiltrate histologically, (b) a lack of microorganisms on special stains and cultures, and (c) clinical improvement on systemic steroid treatment (78). Vascular damage has been observed in these conditions, but it remains unclear whether the vascular injury plays an etiologic role or is merely an epiphenomenon. A relationship between these entities may be indicated by their occasional cooccurrence in patients with predisposing conditions.

Acute Febrile Neutrophilic Dermatosis (Classic Sweet's Syndrome and Sweet's-Like Neutrophilic Dermatosis)

Dr. R. D. Sweet described in 1964 a disease process, which he termed "acute febrile neutrophilic dermatosis," that was characterized by abrupt onset of fever, leukocytosis, and erythematous plaques infiltrated by neutrophils (78,79). This condition typically occurs in middle-aged women after nonspecific infections of the respiratory or gastrointestinal tract. The lesions tend to be found on the face or extremities and only rarely involve the trunk and respond to steroid treatment. Despite the numerous neutrophils, the lesions are sterile. Vesicles and pustules may also arise. Involvement of noncutaneous sites, such as eyes, joints, oral mucosa, and visceral sites (lungs, liver, kidneys), has been reported. A variety of disorders have been associated with neutrophilic dermatoses similar to those seen in Sweet's syndrome (Sweet's-like neutrophilic dermatosis). About 20% of cases are associated with malignancy. Cutaneous eruptions with inflammatory vascular reactions, which on occasion simulate the lesions of Sweet's syndrome, may also occur in association with hereditary periodic fever, which comprises several syndromes including familial Mediterranean fever, the hyper-IgD syndrome, and the tumor necrosis factor receptor–associated periodic syndrome (80).

Histopathology. Typically, a dense perivascular infiltrate composed largely of neutrophils is seen assuming a bandlike distribution throughout the papillary dermis (Fig. 8-18). Some of the neutrophils may show nuclear fragmentation (leukocytoclasis). In addition, the infiltrate may contain scattered lymphocytes and histiocytes and occasional eosinophils. The density of the infiltrate varies and may be limited in a small proportion of cases. Vasodilation and swelling of endothelium with moderate erythrocyte extravasation and prominent edema of the upper dermis are characteristic. In some instances, subepidermal blister formation may result. Extensive vascular damage is not a feature of Sweet's syndrome. The histologic appearance varies depending on the stage of the process. In later stages, lymphocytes and histiocytes may predominate. Sweet's-like neutrophilic dermatoses often show a similar histologic picture. However, the reaction pattern may on occasion be quite different, for instance, manifesting as deep subcutaneous localized suppurative panniculitis. The infiltrate of Sweet's syndrome is not characteristic enough to exclude infection on histologic findings alone. As always, to arrive at the correct interpretation of a neutrophilic infiltrate, cultures need to be obtained and special stains need to be performed to exclude an infectious etiology.

Pathogenesis. Sweet's syndrome's etiology is unknown but is thought to be a hypersensitivity reaction. The three major concepts that have been discussed are immune complex vasculitis, altered T-cell activation, and altered function of neutrophils. All lack, however, sufficient experimental support. The vascular alterations seen in Sweet's syndrome may be secondary to the massive extravasation of activated neutrophils. Direct immunofluorescence studies are generally negative in Sweet's syndrome (78).

Bowel-Associated Dermatosis-Arthritis Syndrome

This syndrome was initially described in patients after jejunoileal bypass surgery. Subsequently, however, the spectrum of the syndrome has expanded to include other disease processes with typical cutaneous findings and associated bowel disease (1). Patients may have inflammatory bowel disease or a blind loop after peptic ulcer surgery. The cutaneous lesions are characterized by initial small macules that develop through a papular phase into pustules on a purpuric base. The evolution usually occurs within a 2-day period. The lesions typically reach a size of 0.5 to 1.5 cm. They are typically distributed on the upper part of the body, especially the arms, rather than on the dependent sites of the legs. Cutaneous lesions often occur in crops and are episodic (1 to 2 weeks), with a tendency to recur within months. Fever, myalgias, and arthralgias may accompany the disease process.

Histopathology. The histopathologic changes are usually those of neutrophilic vascular reactions with little or none of the vascular damage observed in Sweet's syndrome and other neutrophilic dermatoses. However, frank necrotizing small-vessel vasculitis may occasionally be noted. In fully developed lesions, the neutrophilic infiltrate and papillary dermal edema may be florid, and subepidermal pustule formation is seen. If vascular damage is observed in such a context, the term "pustular vasculitis" is applied.

Pathogenesis. One suggested etiology involves antigens derived from intestinal bacteria triggering an immune complex–mediated reaction with vascular insults (81).

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is included in this chapter as well as in Chapter 16 because in these and other authors' opinions, it represents a clinicopathologic manifestation that falls within the spectrum of neutrophilic dermatoses (1). As with other neutrophilic dermatoses, infection must be excluded to arrive at the correct diagnosis.

Several clinical types have been described: ulcerative PG with an undermined border; pustular PG with discrete, painful pustules; painful bullae with progression to a superficial ulceration; and vegetative PG with a painless ulcer and a nonundermined exophytic border (Fig. 8-19A). (82). Classically, lesions begin as tender papulopustules or folliculitis that eventually may ulcerate. In the fully developed stage, the lesions have a distinctive raised, undermined border with a dusky purple hue. Again, as with neutrophilic dermatoses in general, pyoderma gangrenosum may occur as an isolated cutaneous phenomenon or may be a cutaneous manifestation associated with various systemic disease processes, such as inflammatory bowel disease, connective tissue diseases, and lymphoproliferative lesions.

Histopathology. The histologic findings are nonspecific, and the diagnosis is primarily clinical. Most authors studying early lesions have reported a primarily neutrophilic infiltrate, which frequently involves follicular structures (83). Others, however, have stated that the lesions begin with a lymphocytic reaction (84). Degree of vessel involvement ranges from none to fibrinoid necrosis. In the majority of biopsied lesions, a neutrophilic infiltrate is present with some, but limited, vascular damage. Outright vasculitis has been reported and has led to speculations about its possible role in the etiology of pyoderma gangrenosum. Focal vasculitis is often observed in fully developed lesions but appears secondary to the inflammatory process. The infiltrate tends to be deeper and more extensive than that in classic Sweet's syndrome. The pattern of pustular vasculitis may be present. Fully developed lesions exhibit ulceration, necrosis, and a mixed inflammatory cell infiltrate (Fig. 8-19). Involvement of the deep reticular dermis and subcutis may exhibit primarily mononuclear cell and granulomatous inflammatory reactions.

LYMPHOCYTIC SMALL-VESSEL VASCULITIS

A histologic diagnosis of a lymphocytic vasculitis may be made if there is sufficient evidence of vascular damage and the inflammatory infiltrate is predominantly lymphocytic (Fig. 8-20). Often, the vascular damage is subtle, and in many cases there may be disagreement among dermatopathologists on whether the term "vasculitis" is warranted (85). Clear-cut evidence of vasculitis is indisputable if an inflammatory infiltrate is present together with fibrinoid necrosis of the vascular wall. However, these findings are rarely or only focally present in the majority of conditions that have been said to manifest lymphocytic vasculitis.

The disease processes in which lymphocytic vasculitis is commonly observed are listed in Table 8-6. Lymphocytic vasculitis may also be seen in a stage of an otherwise leukocytoclastic or granulomatous vasculitis or in a process that at other times may even be noninflammatory and manifested perhaps as a vasculopathy (e.g., atrophie blanche).

Lymphomatoid Vasculitis and Vascular Reactions

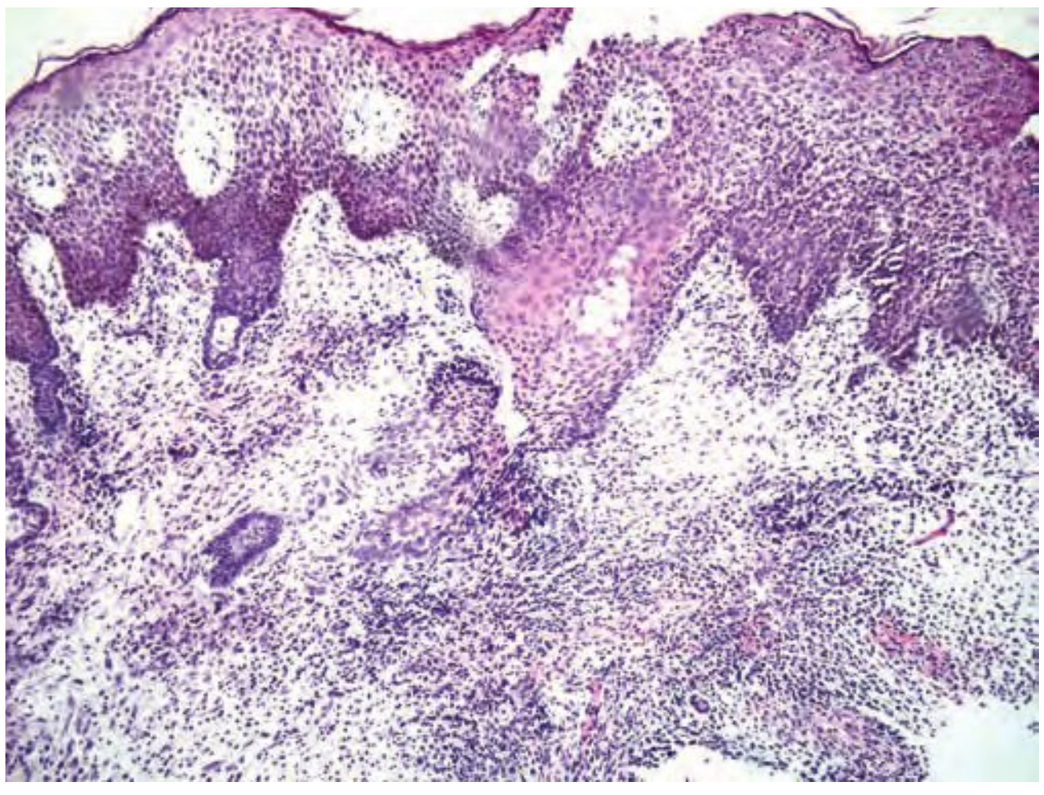
The terms "lymphomatoid vasculitis" and "lymphomatoid vascular reaction" may be used if there is a lymphocytic vasculitis or lymphocytic vascular reaction with significant cytologic atypia of the lymphoid cells (Table 8-7). Although lymphoid nuclear irregularities of some degree may be present in many lymphocytic vascular reactions, probably as a reflection of an activated state of the lymphocytes, lymphoid atypia tends to be particularly well developed in lymphomatoid papulosis and some viral processes. The differential diagnosis includes vascular



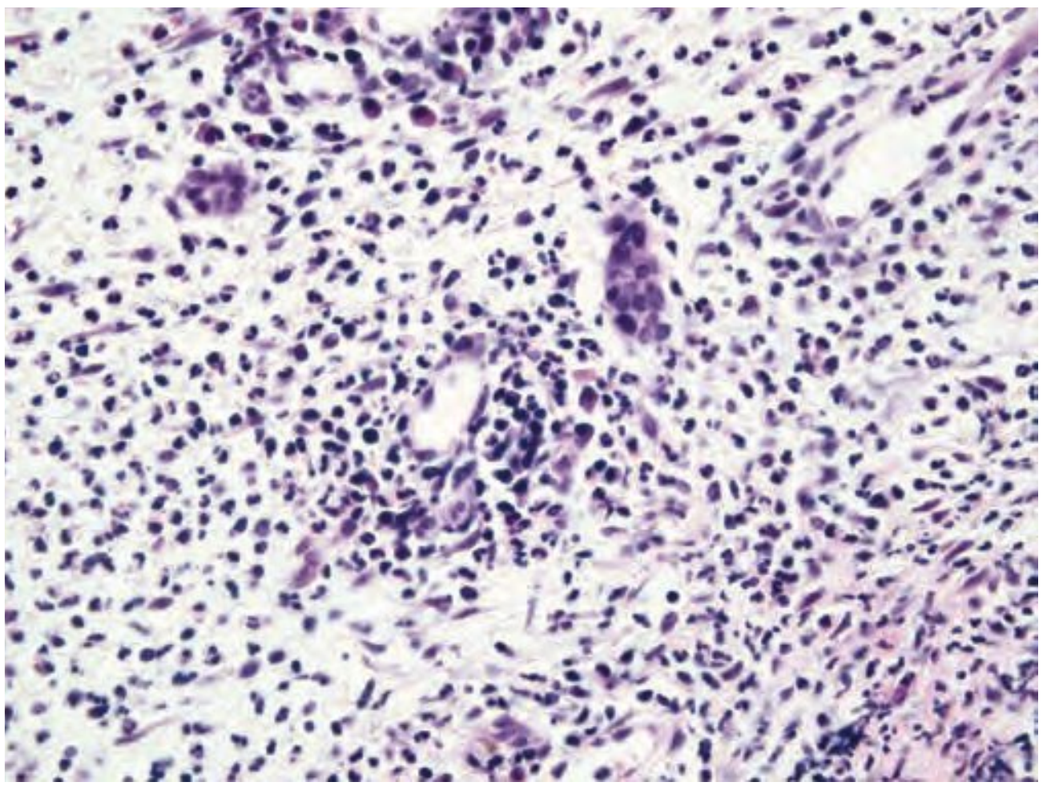
A



B



C



D

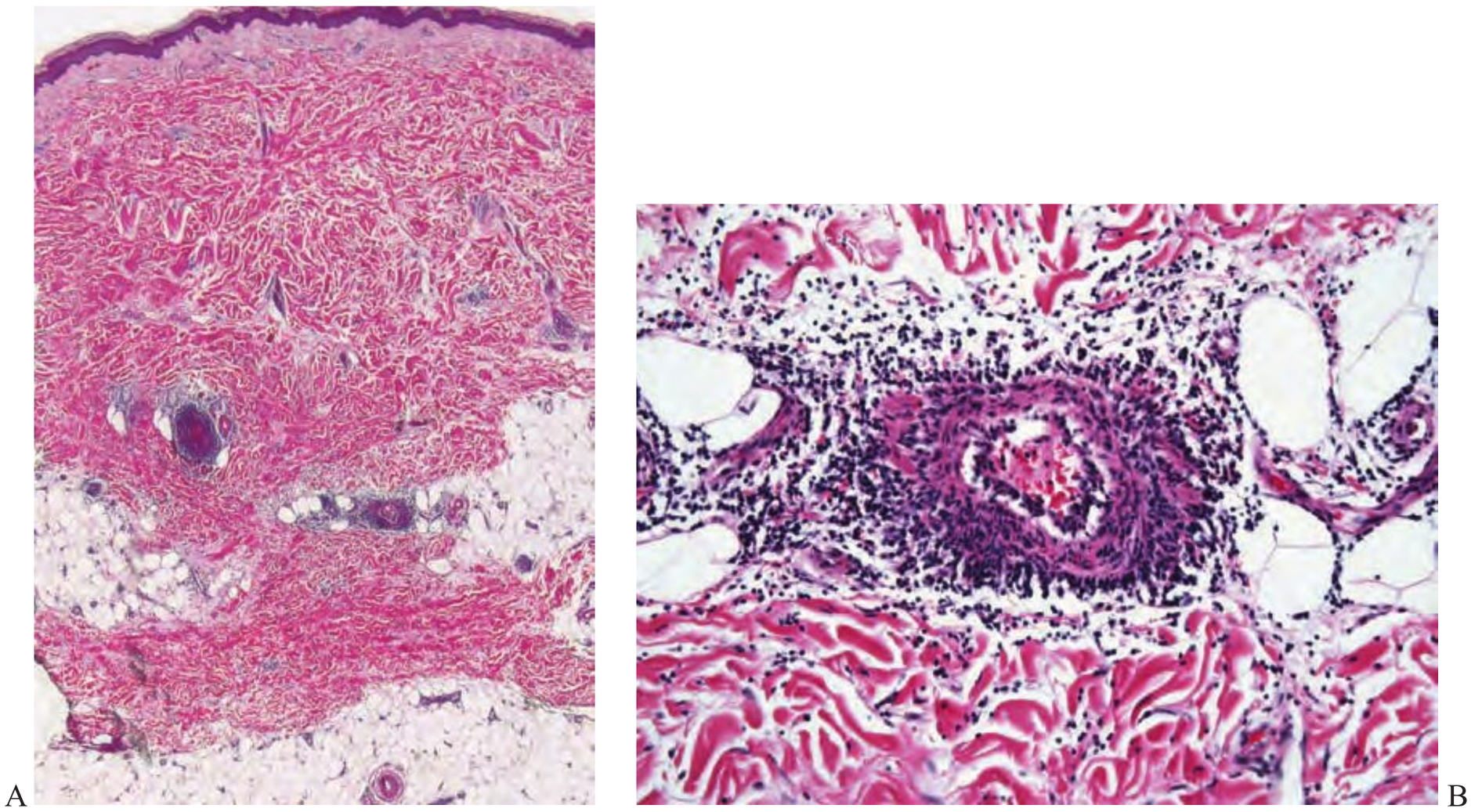
FIGURE 8-19. Pyoderma gangrenosum. A: Superficial ulcers with central suppurative exudate and a peripheral raised and slightly undermined border. (Courtesy of Adam Rubin, MD.) B: Punch biopsy from the edge of an ulcer shows a mixed inflammatory infiltrate spanning the dermis and the panniculus. The infiltrate is deeper and more extensive than that in classic Sweet's syndrome. C: A mixed inflammatory infiltrate in the dermis with spongiosis of the epidermis at the edge of the ulcer. D: Neutrophils and lymphocytes surround a vessel, but there is no frank vasculitis.

damage in the context of cutaneous lymphoma, such as angiocentric T-cell lymphoma and other lymphomas (86).

Pigmented Purpuric Dermatitis

Historically, four variants of purpura pigmentosa chronica have been described: purpura annularis telangiectoides of Majocchi, progressive pigmentary dermatosis of Schamberg, pigmented purpuric dermatitis of Gougerot and Blum, and eczematoid-like purpura of Doucas and Kapetanakis. These entities are all closely related and often cannot be reliably distinguished on clinical and histologic grounds (87). In practice, subclassification may not be necessary. Lichen aureus is a closely related localized variant. The general terms "pigmented purpuric dermatitis," "chronic purpuric dermatitis," and "purpura pigmentosa chronica" appear suitable for this disease spectrum.

Clinically, the primary lesion consists of discrete puncta. Gradually, telangiectatic puncta may appear as a result of capillary dilation, with pigmentation as a result of hemosiderin deposits. In some cases, telangiectasia (Majocchi's disease) predominates; in others, pigmentation (Schamberg's disease) predominates. In Majocchi's disease, the lesions are usually irregular in shape and occur predominantly on the lower legs.



A B

FIGURE 8-20. Lymphocytic vasculitis. A: A small vessel in the reticular dermis is surrounded by an inflammatory infiltrate. B: The infiltrate is composed of lymphocytes. There is damage to the vessel wall.

In some cases, the findings may mimic those of stasis. Not infrequently, clinical signs of inflammation are present, such as erythema, papules, and scaling (Gougerot-Blum disease) or papules, scaling, and lichenification (eczematoid-like purpura). The disorder is often limited to the lower extremities, but it may be extensive. Mild pruritus may be present. There are no systemic symptoms related to this disease process. A localized variant of pigmented purpuric dermatitis (PPD) is lichen aureus, in which one or a few patches are present, most commonly on the legs (88). The patches are composed of closely set, flat papules of a rust, copper, or orange color. In some cases, petechiae are present within the patches. Lichen aureus shows a male predilection and a peak incidence in the fourth decade. The lesions of lichen aureus tend to persist. They typically occur on the lower legs but may affect many other sites.

Histopathology. The basic process is a lymphocytic perivascular infiltrate limited to the papillary dermis (Fig. 8-21). Epidermal alterations may include slight acanthosis and basal layer

TABLE 8-6 Differential Diagnosis of Lymphocytic Vasculitis and Lymphocytic Vascular Reactions

Arthropod bites
Drug-induced and other hypersensitivity reactions
Infection-associated reactions (e.g., viral)
Connective tissue diseases
Behçet's disease
Purpuric dermatitides
PLEVA/PLC/LYP
Cutaneous lymphoma
Autoimmune diseases
Pernio
Polymorphous light eruption
Atrophie blanche
Infestations (e.g., scabies)

LYP, lymphomatoid papulosis; PLC, pityriasis lichenoides chronica; PLEVA, pityriasis lichenoides et varioliformis acuta.

TABLE 8-7 Differential Diagnosis of Lymphomatoid Vasculitis and Vascular Reaction

T-cell lymphoproliferative disorders
Peripheral T-cell lymphoma
Angiocentric T-cell lymphoma
Lymphomatoid papulosis
Lymphomatoid granulomatosis
Angioimmunoblastic lymphadenopathy
Pigmented purpuric dermatitis–like eruptions
Lymphomatoid drug eruptions
Lymphomatoid contact dermatitis
Connective tissue disease
Viral processes
Florid hypersensitivity reactions
Arthropod bites
Scabies infestations

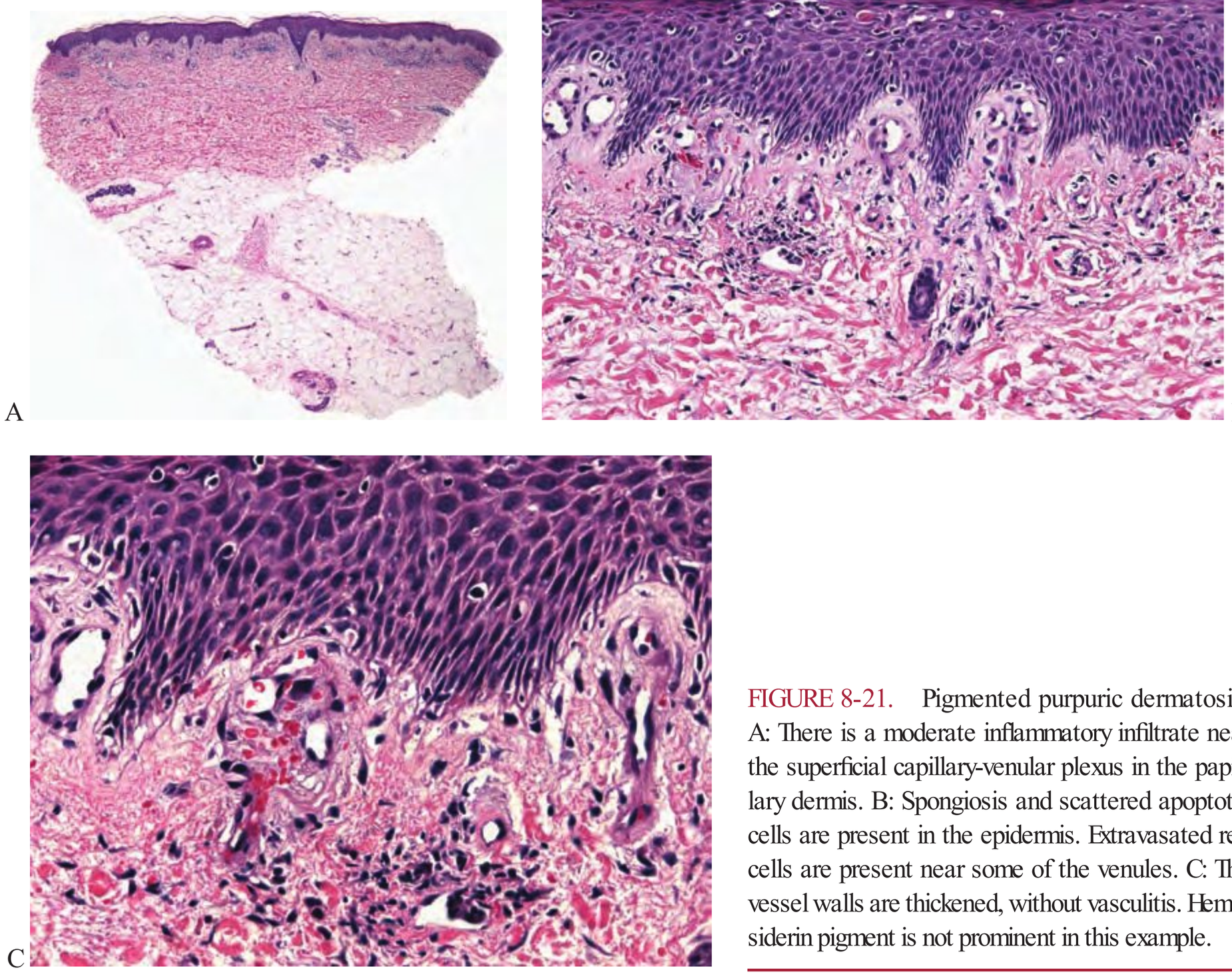


FIGURE 8-21. Pigmented purpuric dermatosis. A: There is a moderate inflammatory infiltrate near the superficial capillary-venular plexus in the papillary dermis. B: Spongiosis and scattered apoptotic cells are present in the epidermis. Extravasated red cells are present near some of the venules. C: The vessel walls are thickened, without vasculitis. Hemosiderin pigment is not prominent in this example.

vacuolopathy. There is also some variability in the pattern of the dermal infiltrate. In some instances, the infiltrate may assume a bandlike or lichenoid pattern, particularly in the lichenoid variant of Gougerot-Blum disease, and may involve the reticular dermis in a perivascular distribution. Evidence of vascular damage may be present, and the reaction pattern may then be termed lymphocytic vasculopathy, vasculitis, or capillaritis. However, the extent of vascular injury is usually mild and often insufficient to justify the term "vasculitis." Vascular damage commonly consists only of endothelial cell swelling and dermal hemorrhage. Extravasated red blood cells and subtle deposits of hemosiderin are usually found in the vicinity of the capillaries. However, less commonly fibrinoid material is deposited in vessel walls. In some instances, the infiltrate involves the epidermis and may be associated with mild spongiosis and patchy parakeratosis, particularly in some cases of pigmented purpuric lichenoid dermatitis of Gougerot and Blum and eczematoid-like purpura of Doucas and Kapetanakis. The pattern of the infiltrate often is both perivascular and interstitial, infiltrating the papillary dermis between vessels.

In old lesions, the capillaries often show dilation of their lumen and proliferation of their endothelium. Extravasated red blood cells may no longer be present, but one frequently finds hemosiderin, although in varying amounts. The inflammatory infiltrate is less pronounced than in the early stage.

In lichen aureus, a dense lymphohistiocytic infiltrate is present in the superficial dermis, typically distributed in a bandlike fashion and often associated with an increase in dermal capillaries. Exocytosis of mononuclear cells into the epidermis may be seen. Scattered within the infiltrate are hemosiderin-laden macrophages (Fig. 8-22). The absence or near absence of Civatte bodies or basal layer vasculopathy facilitates the differential diagnosis from lichenoid dermatitides, such as lichen planus or lichen striatus.

Differential Diagnosis. PPD may resemble stasis dermatitis because inflammation, dilation of capillaries, extravasation of erythrocytes, and deposits of hemosiderin occur in both. However, in stasis dermatitis, the process extends much deeper into the dermis, and more pronounced epidermal changes and fibrosis of the dermis are usually present. Changes of intravascular red blood cell sludge and some fibrin deposits also may be seen in stasis, indicating a low flow state. As mentioned earlier, the histologic pattern of PPD may resemble or possibly be

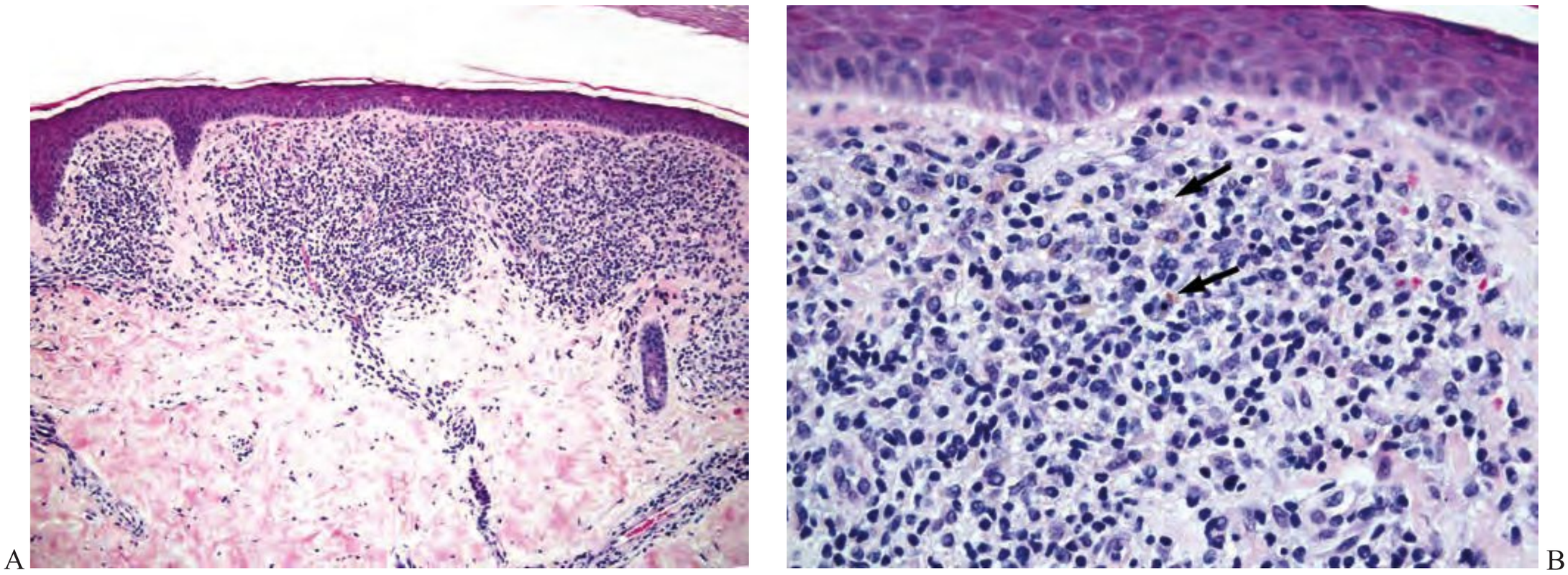


FIGURE 8-22. Lichen aureus. A dense lichenoid infiltrate in the papillary dermis (A), with hemosiderin-laden macrophages (B) (arrows), accounting for the golden clinical color of these lesions.

an abnormal T-cell process. Evidence of T-cell clonality may even be demonstrated in some examples of PPD that otherwise lack sufficient criteria for T-cell lymphoma. Careful evaluation of the lesion for epidermotropism and lymphoid atypia and (of particular importance) good clinicopathologic correlation are needed to arrive at the correct diagnosis. However, suspicious or equivocal lesions require monitoring and possibly further evaluation for possible progression to cutaneous T-cell lymphoma.

Pathogenesis. The etiology of PPD is essentially unknown, and there are probably several different factors involved. Some cases of chronic purpuric dermatitis may be related to a hypersensitivity reaction to drugs. However, in the majority of cases, the etiology of this process is unclear. Stasis changes are seen in some individuals with PPD, suggesting that venous insufficiency may be a contributing factor (84). Eruptions with the clinical and histologic appearance of a pigmented purpuric dermatitis have also been associated with subsequent development of a T-cell lymphoproliferative disorder in some patients. Thus, it is possible that some PPD may be the initial manifestation of T-cell lymphoproliferative disease (88,89).

VASCULOPATHIC REACTIONS AND PSEUDOVASCULITIS

Vasculopathic processes, as defined in Table 8-8, refer to the histologic finding of vascular damage in the absence of vasculitis. As already mentioned, the term pseudovasculitis has been used to describe a closely related group of conditions that mimic or exhibit some attributes of vasculitis. Vasculopathic reactions (and pseudovascultis) may be associated with (a) coagulopathies, (b) pathologic alterations of the vessel wall, (c) embolic phenomena, (d) structural deficiencies of the perivascular connective tissue, or (e) miscellaneous other disease processes, including drug-induced vasospasm and repetitive vascular injury.

Coagulopathies and Vascular Thrombosis

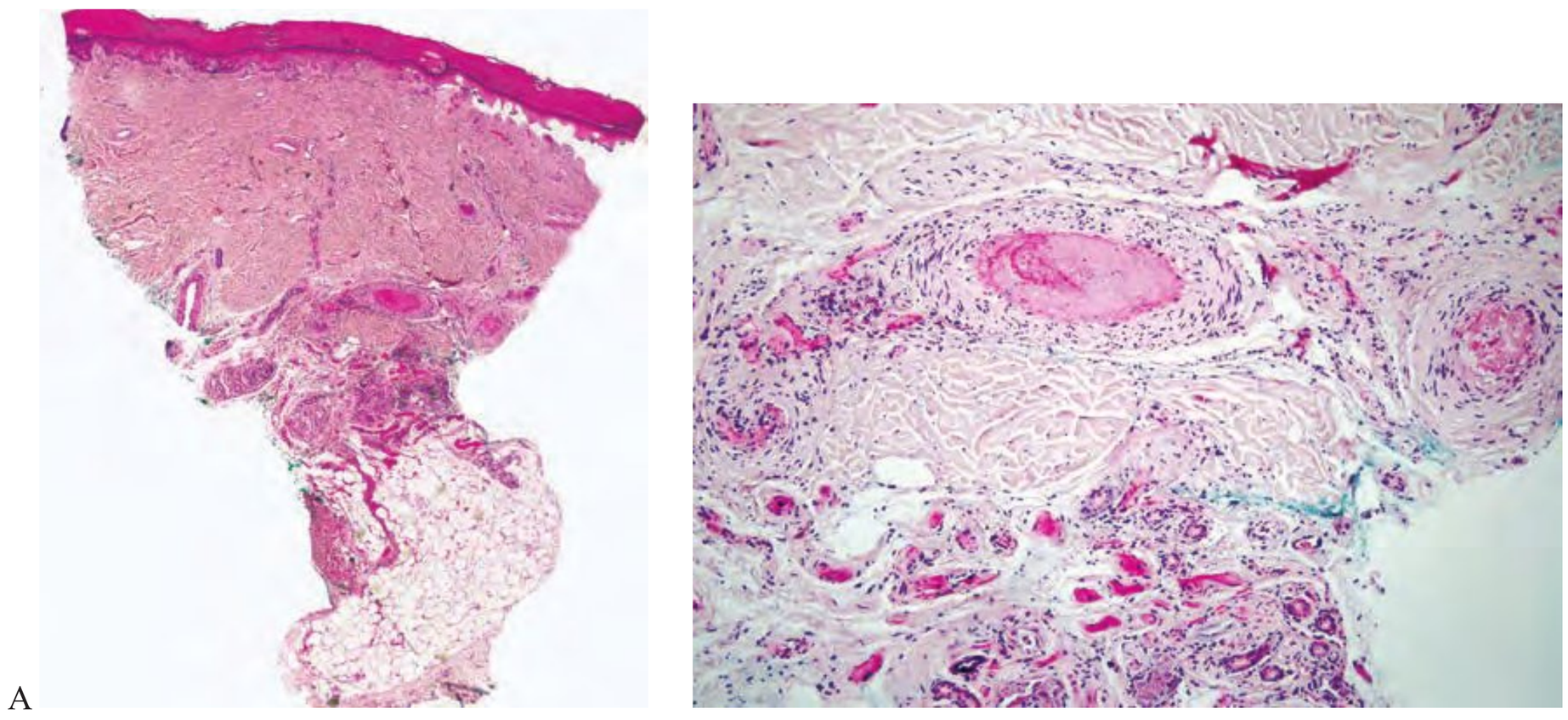
Any coagulopathy may be accompanied by vasculopathic changes. The extent of vascular damage is variable. Vascular damage may occur in the setting of altered platelet counts, such as in idiopathic thrombocytopenic purpura, in coagulation factor deficiencies (e.g., inherited or acquired protein C and S deficiencies), coagulopathies associated with connective tissue disease (e.g., lupus anticoagulant, antiphospholipid antibody syndrome; Fig. 8-23) and platelet thrombosis in heparin-induced skin necrosis. Extensive vascular damage with luminal occlusion by thrombotic material may develop in coumarin/warfarin-induced skin necrosis, in thrombotic thrombocytopenic purpura, and in disseminated intravascular coagulation—specifically in the setting of purpura fulminans (90).

In mild forms, the clinical manifestations may be subtle and limited to petechiae. In severe forms of coagulopathies, large areas of ecchymosis may be present, typically located on the extremities. Large hemorrhagic bullae may overlie the ecchymoses, and some of the ecchymotic areas may undergo necrosis. Retiform purpura (a livedoid pattern of cutaneous hemorrhage) in palpable plaques is characteristic of antiphospholipid antibody syndrome, heparin-induced skin necrosis, Coumadin/warfarin-induced skin necrosis, and calciphylaxis (91).

Histopathology. The histologic features are nonspecific for any particular disorder. In mild forms of coagulopathies, the only histologic manifestation may be dermal hemorrhage—that is, extravasation of red blood cells into perivascular connective tissue. With increasing severity of the disease process, intravascular fibrin thrombi may be found (Fig. 8-2). In severe forms (e.g., thrombotic thrombocytopenic purpura, coumarin necrosis, and

TABLE 8-8 Vasculopathic Reactions and Pseudovasculitis

Mechanism	Condition
Coagulopathies	Idiopathic thrombocytopenic purpura Coagulation factor deficiencies (e.g., protein C and S deficiencies) Antiphospholipid antibody syndrome Thrombotic thrombocytopenic purpura Coumadin/warfarin-induced skin necrosis Heparin-induced skin necrosis Calciphylaxis Purpura fulminans Disseminated intravascular coagulation Monoclonal gammopathy Sickle cell disease Livedo vasculopathy
Pathologic alterations of the vessel wall	Calciphylaxis Primary hyperoxaluria Diabetes mellitus Amyloidosis Porphyria Radiation vasculopathy
Embolic phenomena	Cholesterol embolism Atrial myxoma
Structural deficiencies of the perivascular connective tissue	Solar/senile purpura Scurvy
Vasospasm	Ergot derivatives Cocaine Methamphetamines
Repetitive vascular trauma	Hypothenar hammer syndrome



A B

FIGURE 8-23. Antiphospholipid syndrome. A: A vessel in the deep dermis contains an eosinophilic fibrin thrombus. The affected vessels are commonly more superficial in this condition. B: The thrombus is not associated with inflammation of the vessel wall. Other small vessels in the vicinity are also affected.

purpura fulminans), thrombotic vascular occlusion may lead to hemorrhagic infarcts, epidermal and dermal necrosis, or subepidermal bulla formation. In severe systemic intravascular coagulation, internal organs may also show widespread thrombosis of small vessels and hemorrhagic necrosis.

Calciphylaxis

Calciphylaxis is an uncommon complication of renal failure usually in combination with secondary or tertiary hyperparathyroidism. Obesity, female gender, and poor nutritional status are putative risk factors. Painful violaceous lesions that may be indurated often develop in areas of livedo reticularis on the trunk and extremities and can rapidly progress to form bullae, ulcers, eschars, and gangrene. The prognosis is extremely poor, especially for proximal disease, even with aggressive treatment by parathyroidectomy (92). Fulminant sepsis may develop from infection of necrotic or gangrenous tissue.

Histopathologic Features. The principal histologic findings include (a) calcification of soft tissue and small vessels, (b) nonspecific intimal proliferation of small vessels, often resulting in luminal narrowing, (c) variable fibrin thrombi, and (d) frequent ischemic necrosis of skin and subcutis (Fig. 8-24). The small vessels involved by this process cannot be identified as either arterial or venous. Foreign body giant cell reaction to calcium and mixed inflammatory cell infiltrates that are neutrophil-rich may be seen.

Cutaneous calcium deposits may be seen in a number of other conditions, especially cutaneous calcinosis and metastatic calcifications. Calcinosis usually lacks prominent vascular involvement. Other crystal-induced inflammatory diseases such as gout, pseudogout, or oxalosis that are associated with a giant cell reaction to crystal deposits and surrounding fibrosis may resemble calciphylaxis. Histopathologically, pancreatic panniculitis may suggest calciphylaxis. However, the polymorphous infiltrate and ghostlike cells seen in panniculitis are absent in calciphylaxis (93). If a biopsy of calciphylaxis lacks significant calcium deposits due to sampling error, the findings may be limited to ischemic damage or mimic a coagulopathy.

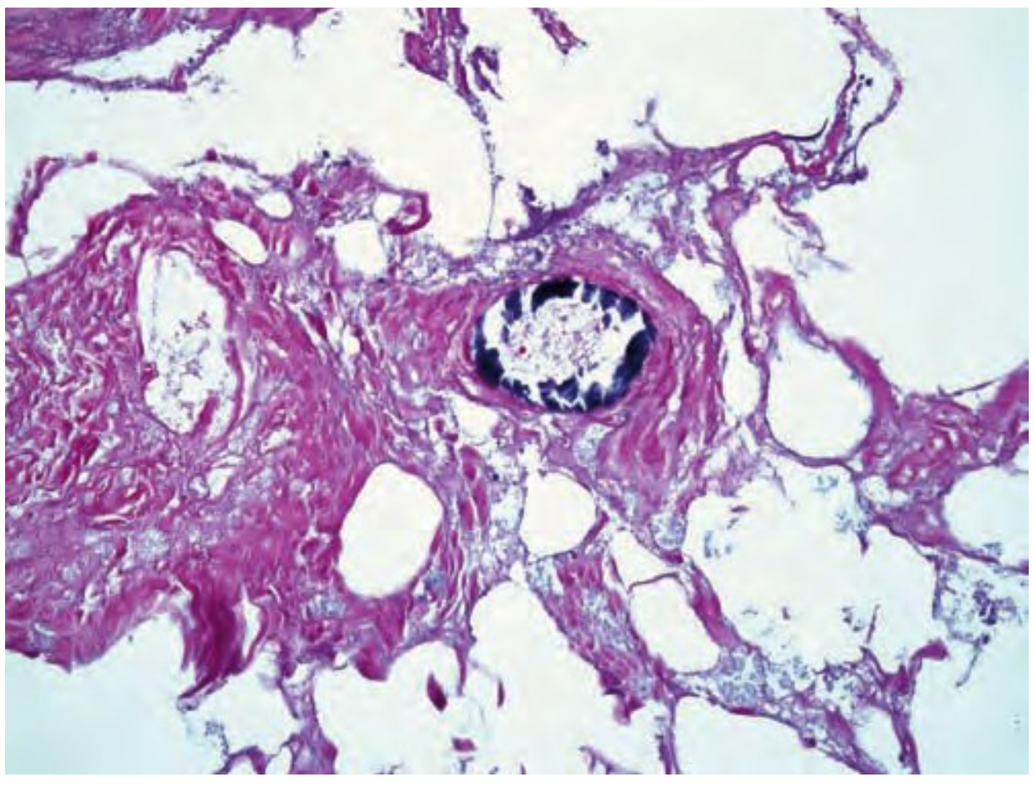


FIGURE 8-24. Calciphylaxis. There is calcification of the media of a small vessel in the panniculus, with delicate fibroplasia of the intima. There may be interstitial deposition of calcium as well.

Pathogenesis. The relationships among the calcification, thrombosis, and ischemic necrosis in calciphylaxis are unclear. Although vascular calcification is common in uremic patients, calciphylaxis is rare. Elevation of the calcium and phosphorous product along with a poorly defined precipitating or challenging event or agent is hypothesized to be necessary for calcium deposition in cutaneous tissues. However, the list of putative sensitizing agents is long, and the calcium and phosphorus product may be within normal limits. The development of a hypercoagulable state may be an additional important element in the pathogenesis of this entity but is not present in all cases (94). Finally, calciphylaxis may mimic vasculitis clinically (95,96).

Pathologic Alterations of the Vessel Wall Including Metabolic Vasculopathies

Vasculopathies may arise also from metabolic disorders. Deposition of endogenously produced material, as in diabetes mellitus, amyloidosis, or porphyria, may lead to vessel fragility. Hemorrhage and ischemic damage to the area of skin supplied by the affected vessels is seen. The basic histologic vascular alteration in the aforementioned disorders is the deposition of amorphous material in the walls of dermal capillaries. The details of the histopathology of these disorders are discussed in more detail in other chapters of this book.

Atherosclerosis is by far the most common form of vasculopathy. However, atherosclerosis is primarily a disease of large vessels supplying visceral organs, and thus it is not discussed here in detail. Cutaneous changes are usually rare and are secondary manifestations of peripheral ischemia. Luminal occlusion may result from intimal thickening and lipid deposition, superimposed thrombosis, or, less frequently, cholesterol emboli. Because cholesterol microemboli can cause cutaneous findings mimicking vasculitis, this phenomenon is discussed in more detail in the next subsection.

Embolic Phenomena

Cutaneous Cholesterol Embolism

Cholesterol crystal embolization is usually a disease of the elderly with significant atherosclerosis (97,98). Atheromatous plaque material may erupt or detach spontaneously. However, more commonly, plaque material is dislodged by an invasive procedure, such as arterial catheterization. Microemboli or cholesterol crystals typically lead to ischemic changes. Cutaneous manifestations are common, often affect the lower extremities, and include livedo reticularis, purple discoloration, gangrene of toes, and small, painful ulcerations on the legs. Occasionally, a few nodules or indurated plaques may occur. A typical clinical sign is adequate distal pulsation, indicating that the ischemia is arteriolar rather than arterial.

Histopathology. Cholesterol emboli may be found as needle-shaped clefts within the lumina of small vessels. The intravascular clefts, which are in effect dissolved cholesterol crystals, may be single or multiple and are commonly associated with amorphous eosinophilic material, macrophages, or foreign body giant cell reactions. Vascular walls exhibit intimal fibrosis and often obliteration of lumina in older lesions. In many instances, only fibrin thrombi are observed. Often a deep biopsy and multiple sections of biopsy material are needed to reveal such emboli, which are distributed focally and therefore are difficult to find.

Vasculopathies Resulting from Deficiencies in Connective Tissue

Finally, structural deficiencies in the perivascular connective tissue may cause vascular fragility and lead to dermal hemorrhage. Such alterations underlie the hemorrhages that accompany senile purpura and scurvy.

Histopathology. In senile purpura, extravasation of red blood cells is encountered in atrophic skin with solar elastosis and normal-appearing capillaries. In scurvy, dermal hemorrhage is found predominantly in the vicinity of hair follicles without evidence of capillary changes. Hemosiderin-laden macrophages are usually noted (99). Other findings associated with scurvy include intrafollicular keratotic plugs and coiled hair.

Other Clinical Presentations Associated with Vasculopathic Reactions

Livedo Reticularis

Livedo reticularis is persistent red-blue mottling of the skin in a netlike pattern and differs from cutis marmorata by not subsiding with warming of the skin. This condition is a nonspecific sign of sluggish blood flow from any cause. Associations include vasculitis or vasculopathy in the context of several different systemic or localized disease processes, such as infection, atrophie blanche, cholesterol emboli, and connective tissue disease. Frequently, however, the condition is idiopathic and limited to the lower extremities. Generalized livedo reticularis has also been described as part of a potentially severe arterio-occlusive syndrome (Sneddon's syndrome) that is often complicated by cerebrovascular disease (100).

Histopathology. A biopsy specimen taken from an erythematous area may be normal, whereas a biopsy specimen from a white area may show a vessel with a thickened wall and the lumen occluded by a thrombus. In other cases, deeply situated dermal arterioles have shown obliterative changes. Other changes observed in livedo reticularis are intravascular aggregates of red blood cells, suggesting a low flow state.

Atrophie Blanche

Atrophie blanche is a common condition that usually affects middle-aged or elderly women (101). Synonymous terms are *livedoid vasculitis*, *livedo reticularis with seasonal ulceration*, and *segmental hyalinizing vasculitis*. Typically located on the lower portions of the legs, particularly on the ankles and the dorsa of the feet, this condition begins as purpuric macules and papules, which develop into small, painful ulcers with a tendency to recur. Healing of the ulcers results in the white atrophic areas that have given the disease its name. A fully developed case of atrophie blanche shows irregularly outlined, whitish atrophic areas with peripheral hyperpigmentation and telangiectasia. Many of the patients have associated livedo reticularis. The condition also may be seasonal, with the greatest disease activity in the summer and winter months.

Histopathology. The histologic findings are nonspecific and vary with the stage of the lesion. However, in all stages, vascular changes are present. In early lesions, fibrinoid material may be noted in the vessel wall or vessel lumen (Fig. 8-25). Infarction

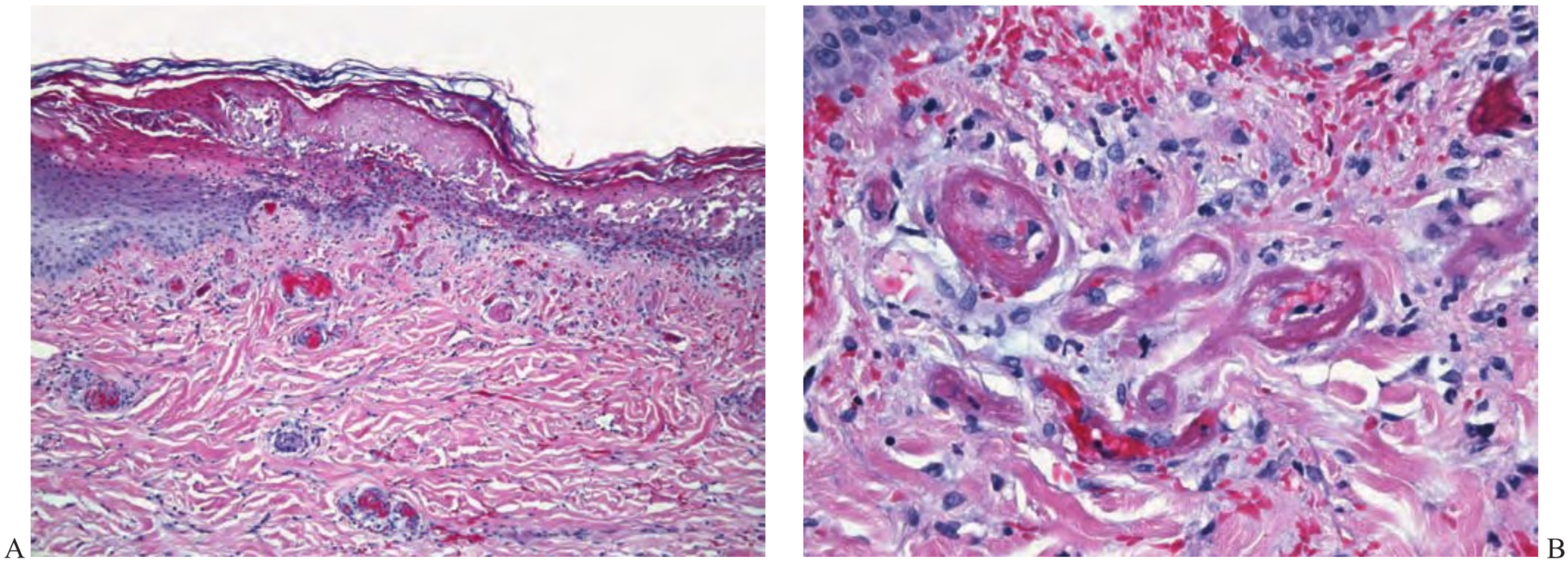


FIGURE 8-25. Atrophie blanche. A: An early lesion characterized by an area of epidermal necrosis with underlying vasculopathy. B: The superficial portion of the epidermis is necrotic. Vessel walls are thickened and contain fibrinoid/thrombotic material.

with hemorrhage and an inflammatory infiltrate may be present as well. In late atrophic lesions, the epithelium is thinned and the dermis is sclerotic, with little if any cellular infiltrate. The walls of the dermal vessels may show thickening and hyalinization of the intima. Luminal occlusion by intimal proliferation and/or fibrinoid material and sometimes recanalized thrombotic vessels may be seen. In some cases, the vessels in the superficial dermis are predominantly affected; in others, the vessels in the middle and even deep dermis are mostly affected.

Pathogenesis. The etiology of atrophie blanche is unknown. Immune complex deposits that have been observed in late lesions are likely secondary changes (102). A primary disturbance of fibrinolysis in the endothelium of affected microvessels has been postulated (103).

Degos' Syndrome

Degos had initially described a cutaneointestinal syndrome in which distinct skin findings ("drops of porcelain") were associated with recurrent attacks of abdominal pain that often ended in death from intestinal perforations (104). The skin lesions of this syndrome arise in crops of asymptomatic, slightly raised, yellowish red papules that gradually develop an atrophic porcelain-white center. These papules tend to affect the trunk and proximal extremities. Degos chose the name *malignant atrophic papulosis* (MAP) for these lesions to emphasize the serious clinical course of the cutaneointestinal disease he was describing. At that time, the cutaneous lesions were then thought to be specific and pathognomonic for this unique disease entity (Degos' disease). However, skin-limited forms of Degos' disease have been described (105–107), and currently such skin lesions are considered to be a clinicopathologic reaction pattern that can be associated with a number of conditions (108). Lesions similar if not identical to MAP have been noted in connective tissue diseases such as lupus erythematosus, dermatomyositis, and progressive systemic sclerosis, in atrophie blanche, and in Creutzfeldt-Jakob disease (109).

Histopathology. The classic lesion shows a wedge-shaped area of altered dermis covered by atrophic epidermis with slight hyperkeratosis. Dermal alterations may include frank necrosis. More common, however, are edema, extensive mucin deposition, and slight sclerosis (Fig. 8-26). A sparse perivascular lymphocytic

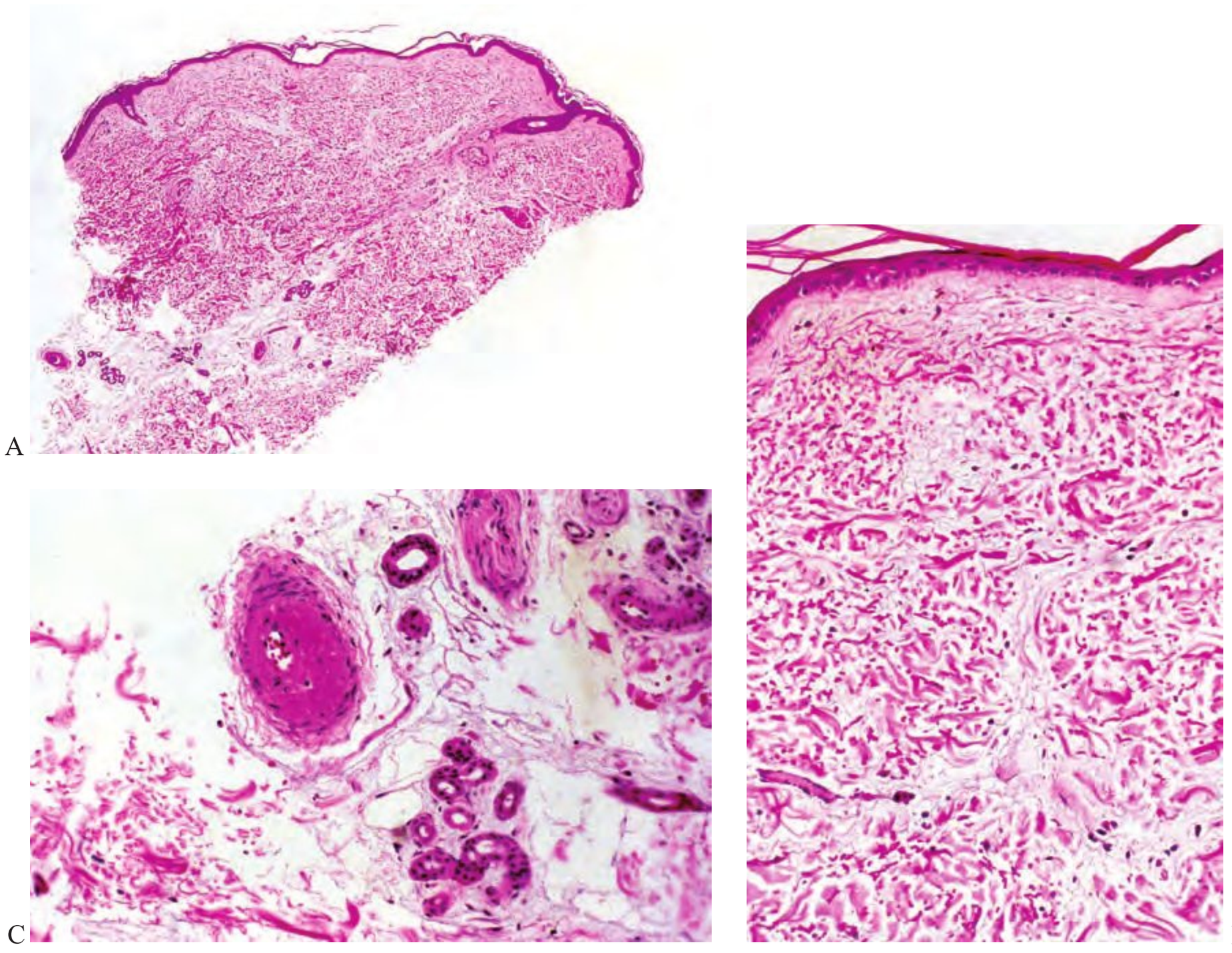


FIGURE 8-26. Degos' lesion. Atrophic epidermis overlies a wedge-shaped area of dermis (A) with mucin deposition (B) and a thrombosed vessel at the base (C). This Degos' lesion was observed in a patient with dermatomyositis.

infiltrate may be seen, although the dermis is largely acellular. Typically, vascular damage is noted in the vessels at the base of the "cone of necrobiosis." Vascular alterations may be subtle and manifest as endothelial swelling or demonstrate lymphocytic vasculitis. However, more characteristically, intravascular fibrin thrombi may be noted, suggesting that the dermal and epidermal changes result from ischemia. Altered vessels may lack an inflammatory infiltrate. The histopathology observed may vary with the evolution of the lesions. Early lesions may be more mucinous and mimic tumid lupus, whereas more evolved lesions are more sclerotic and suggest lichen sclerosus et atrophicus (105).

Pathogenesis. The etiology of Degos' syndrome is unclear. The findings have been ascribed to a coagulopathy, vasculitis, or mucinosis. However, convincing evidence to support any single causal factor is lacking.

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CHAPTER 9

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Noninfectious Vesiculobullous and Vesiculopustular Diseases

CLASSIFICATION OF BLISTERS

Definition

A blister is a fluid-filled cavity formed within or beneath the epidermis. The fluid consists of tissue fluid and plasma. A variable component of inflammatory cells may also be present. Blisters may occur in many dermatoses. At first glance, this observation seems to imply that blistering is too general or nonspecific for use in clinical gross evaluation. However, the character of blisters in a given disorder tends to be uniform and to have reproducible characteristics. One useful distinction is the categorization of blisters into *vesicles* (blisters $<$0.5 cm in diameter) and *bullae* (blisters $>$0.5 cm in diameter). For example, vesicles characteristically occur in dermatitis herpetiformis as opposed to pemphigoid, in which bullae are most commonly observed.

Mechanisms of Blister Formation

The mechanisms observable in routine sections for some diseases are shown in Table 9-1. *Spongiosis* is the accumulation of extracellular fluid within the epidermis with resultant separation of the keratinocytes. Pronounced spongiosis gives the keratinocytes a stellate appearance and subsequently leads to disruption of desmosomes and blister formation. Thus, the epidermis has a "spongy" appearance microscopically, and the increasing accumulation of fluid leads to a vesicle and, in some instances, to a bulla. Marked spongiosis may terminate in reticular degeneration (see below). Spongiosis is almost always associated with an infiltrate of lymphocytes within the epidermis and around superficial vessels. However, spongiosis is a passive event associated with increased permeability of the superficial vascular plexus, particularly the postcapillary venules. Spongiotic keratinocytes are viable cells.

Acantholysis results from the loss of appropriate keratinocyte cell-cell contact. Histologic evidence of acantholysis includes the presence of rounded keratinocytes with condensed cytoplasm and large nuclei with peripheral condensation of chromatin and prominent nucleoli. Acantholytic keratinocytes are viable. The rounded keratinocytes of acantholysis differ strikingly from the stellate keratinocytes of spongiotic dermatitis.

Reticular degeneration results from ballooning degeneration (intracellular edema) with secondary rupture and death of the keratinocytes. The remaining desmosomal attachments often connect strands of ruptured keratinocytic membranes and cytoplasm to intact keratinocytes, giving the epidermis an irregular meshwork appearance.

Cytolysis is the disruption of keratinocytes. It occurs in the normal epidermis when the structural (keratin) matrix and desmosomal plaques of the keratinocyte are overwhelmed by high levels of physical agents such as friction and heat. Friction (mechanical energy applied parallel to the epidermis) leads to the shearing of keratinocytes one from another and of the keratinocytes themselves, giving the characteristic clear fluid-filled blisters. Minimal friction may lead to cytolysis in subjects whose keratinocytes do not have normal structural matrix and desmosomes, such as in epidermolysis bullosa (EB) simplex and EB of the Cockayne-Weber type.

Basement membrane zone disruption or destruction results from primary structural deficiencies as well as from both humoral and cellular immunologically mediated damage. When blisters arise at the epidermal basement membrane zone, any of the specific subanatomic compartments can be affected: (a) the basal keratinocytes, in particular their lower portions; (b) the lamina lucida, an electron lucid area immediately subjacent to the plasma membrane; (c) the lamina densa, composed principally of type IV collagen; and (d) the sublamina densa zone.

Pathologic Evaluation

When blisters are encountered microscopically, systematic analysis can lead to diagnosis in most cases. The critical interpretive assessments to be approached in sequence are as follows: (a) the blister separation plane (Table 9-2); (b) the mechanism(s) of blister formation (Table 9-1); and (c) the character of the inflammatory infiltrate, including its presence or absence, its pattern, and the specific cell types involved (Table 9-3).

Six principal problems are encountered when using this algorithm. The first is that the separation plane may change as blisters age. Spongiotic microvesicles may move into the stratum corneum as crust. The epidermal blister roofs may become necrotic, not allowing assessment of the original blister plane. However, the basal keratinocytes may retain their columnar appearance in the blister roof (or base), allowing for

TABLE 9-1 Diseases and Their Mechanisms of Blister Formation

Spongiosis:	Eczematous dermatitis Miliaria Pemphigus (early) Transient acantholytic dermatosis (one pattern)
Acantholysis:	Pemphigus Transient acantholytic dermatosis (some patterns) Hailey-Hailey disease Darier's disease Irritant dermatitis (some)
Reticular degeneration:	Viral infections Eczematous dermatitis (late stage)
Cytolysis:	EB simplex Epidermolytic hyperkeratosis Friction blister EM (in part) Irritant dermatitis (some)
Basement membrane zone destruction:	Bullous pemphigoid Cicatricial pemphigoid LAD Dermatitis herpetiformis EBA Junctional EB EB dystrophica

EB, epidermolysis bullosa; LAD, linear IgA dermatosis; EBA, epidermolysis bullosa acquisita; EM, erythema multiforme.

separation into either suprabasal or subbasal blister formation. Also, basal keratinocytes are the most melanized cells in the epidermis. Search for the melanized basal keratinocytes (i.e., the basal unit), even if they are necrotic, may allow assessment of the original blister plane. Immunohistochemical stain for type IV collagen is sometimes useful in sublamina densa blistering disorder because type IV collagen may be detectable on the base of subepidermal blister roofs even when the blister roof is necrotic. Some blister roof may be viable for a week or so; in this case, the viable keratinocytes may become elongated and line the base of the blister roof. Similarly, the re-epithelialized subepidermal or suprabasal blister bases are initially lined by flat squamous keratinocytes rather than columnar or cuboidal keratinocytes. When re-epithelialization first occurs, there is no normal rete and the flat squamous keratinocytes migrate on a matrix of fibrinogen, not normal papillary dermis. Second, microscopic slitlike spaces occur within the epidermis in the group of clefting diseases—Darier's disease, Hailey-Hailey disease, and Grover's disease—mimicking true blisters. However, these clefts are small and do not contain fibrin and tissue fluid. Furthermore, this group of disorders only rarely presents clinically with blisters. Third, evaluation of routine histologic preparations may not allow accurate assessment of the specific mechanism of blister formation. This is particularly true in the subepidermal vesiculobullous disorders. Fourth, the cell types infiltrating the lesions in the vesiculobullous diseases change as the lesions age. Fifth, the histologic descriptions of many of the subepidermal blistering disorders are not accompanied by the rigorous immunologic evaluation required today. For example, many cases originally reported as bullous pemphigoid and cicatricial pemphigoid are now known to be better classified as epidermolysis bullosa acquisita (EBA) and linear IgA bullous dermatosis. Many of the subepidermal blistering disorders may strikingly mimic each other clinically, leading to inappropriate diagnosis and making the histologic descriptions in the literature suspect. Finally, in order to rapidly improve the rash and symptomology of the patient, clinicians often embark on therapeutic regimens for the presumed clinical diagnosis. The therapy often consists of topical or systemic steroids and inhibitors of inflammation. Histopathologic examination of a biopsy is only pursued when the therapeutic response is nil or partial, calling into question the clinical diagnosis. Many submit biopsies without notifying the dermatopathologist of the therapy. Such therapy often suppresses the inflammatory infiltrate, the epidermal response, the "triple response of Lewis," and other histopathologic changes. The evolution and temporal relationship of histologic changes of dermatitides under various therapies are NOT sufficiently

TABLE 9-2 Some Diseases With Their Specific Separation Planes

INTRAEPIDERMAL
Subcorneal/granular:
Miliaria crystallina
SSSS
Pemphigus foliaceus and variants
Bullous impetigo
IgA pemphigus
SPD
Erythema toxicum neonatorum
Transient neonatal pustular melanosis
Acropustulosis of infancy
Spinous:
Spongiotic dermatitis
Friction blister (may extend into dermis)
Miliaria rubra
Incontinentia pigmenti
IgA pemphigus
Epidermolytic hyperkeratosis
Hailey-Hailey disease
Suprabasal:
Pemphigus vulgaris and variants
Paraneoplastic pemphigus
Darier's disease

SUBEPIDERMAL
Basal keratinocyte necrosis, cytolysis, or damage:
EB simplex
Thermal injury (some)
EM
Herpes gestationis
Epidermal basement membrane zone destruction or disruption:
Lamina lucida
Bullous pemphigoid
Cicatricial pemphigoid
Herpes gestationis
Dermatitis herpetiformis
LAD
Junctional EB
Suction blister
Thermal injury (some)
Sublamina densa
Bullous SLE
EBA
LAD (IgA-mediated EBA)
EB dystrophica
Porphyria cutanea tarda/Pseudoporphyria

DERMAL
Penicillamine-induced blisters (iatrogenic)
Bullous amyloidosis (primary systemic)

SSSS, staphylococcal scalded skin syndrome; SPD, subcorneal pustular dermatosis; EB, epidermolysis bullosa; LAD, linear IgA dermatosis; SLE, systemic lupus erythematosus; EM, erythema multiforme.

documented to allow optimal or perhaps even accurate diagnostic study. Biopsies should be taken of virgin disease and not of therapeutically altered skin if at all possible. If therapy has been instituted, it should be stopped, if possible, at least a week before biopsy.

With these points in mind, the specific disorders and groups of disorders will be discussed.

SPONGIOTIC DERMATITIS

Definition and Evaluation

Spongiotic dermatitis may be acute, subacute, or chronic. The process is dynamic, and each specific type of dermatitis may progress from the acute to the chronic phase. Although the term *spongiotic dermatitis* is occasionally used interchangeably with *eczema*, the word *eczema* lacks specific meaning. *Spongiosis* refers to the accumulation of edema fluid between keratinocytes, in some cases progressing to vesicle or even bulla formation.

In *acute spongiotic dermatitis*, the stratum corneum is normal and the epidermis is of normal thickness. The degree of spongiosis is variable, extending from slight to marked, with intraepidermal vesiculation in the latter instance. The surrounding keratinocytes may be stellate, surrounded by clear spaces representing the site of fluid collection (Fig. 9-1). Papillary dermal edema is present, correlating with the degree of spongiosis. A lymphohistiocytic infiltrate is present around the superficial plexus, with exocytosis of lymphocytes into spongiotic foci.

In *subacute spongiotic dermatitis*, there is usually mild to moderate spongiosis, occasionally with microvesiculation. The epidermis is moderately acanthotic. The parakeratotic stratum corneum may contain aggregates of coagulated plasma and scattered lymphocytes and neutrophils, forming a crust (Fig. 9-2). There is a superficial perivascular lymphohistiocytic infiltrate, which is less prominent than in the acute phase. Impetiginization by gram-positive cocci (Staphylococci and Streptococci) may lead to neutrophilic crust.

In *chronic dermatitis*, there is hyperkeratosis with areas of parakeratosis, often wedge-shaped hypergranulosis, and moderate to marked acanthosis. Spongiosis may be present focally, often minimal in degree. The inflammatory infiltrate is often sparse, and papillary dermal fibrosis may be a prominent feature. The degree of spongiosis and quantity of the infiltrate reflect the present activity of the underlying dermatitis. The other changes reflect lichen simplex chronicus (Fig. 9-3) with its vertical streaking of thick papillary dermal collagen.

Specific Types of Spongiotic Dermatitis

Allergic Contact Dermatitis

The prototype of acute spongiotic dermatitis is allergic contact dermatitis, secondary to exposure to poison ivy. Usually between 24 and 72 hours after exposure to the antigen, the

TABLE 9-3 Principal Infiltrating Inflammatory Cells in Some Vesiculobullous Dermatoses*

Dermatosis	Principal cell type	Infiltrate
Porphyria Variegate Cutanea tarda	—	Absent
EBA (classic)	—	Absent
Bullous pemphigoid (cell poor)	Eosinophils	Minimal
Spongiotic dermatitis	Lymphocytes	Present
EM	Lymphocytes	Present
Bullous pemphigoid (cell rich)	Eosinophils	Present
Herpes gestationis	Eosinophils	Present
Dermatitis herpetiformis	Neutrophils	Present
LAD	Neutrophils	Present
EBA (inflammatory)	Neutrophils or Mixed neutrophils and eosinophils	Present
Anti-p200 pemphigoid	Neutrophils or Mixed neutrophils and eosinophils	Present
Bullous SLE	Neutrophils Interface dermatitis	Present
Cicatricial pemphigoid	Mixed neutrophils and eosinophils Lymphocytic, bandlike (mucosa only) Eosinophils	Present
Paraneoplastic pemphigus	Lymphocytes—interface dermatitis (lichen planus or EM-like)	Present

EBA, epidermolysis bullosa acquisita; EM, erythema multiforme; LAD, linear IgA dermatosis; SLE, systemic lupus erythematosus.
*These descriptions are accurate in the vast majority of the cases in each dermatosis; however, occasionally the cell types may differ, rendering IF testing mandatory. Other inflammatory cells may be present as a minor component but on occasion are of significant number. The inflammatory cells in old or healing lesions often are not cells that are characteristic of the specific primary disease but represent the inflammatory cells present in healing or responding to secondary effects of the vesiculobullous disorder.

patient develops pruritic, edematous, erythematous papules and plaques and, in some cases, vesicles. Linear papules and vesicles are common in allergic contact dermatitis to poison ivy, reflecting the points of contact between the plants or the antigen-contaminated hands and the skin. Other common causes of allergic contact dermatitis (Fig. 9-1A) include nickel, paraphenylenediamine, rubber compounds, fragrances, and preservatives in cosmetics. The degree of histologic alterations to these antigens may be less striking than that secondary to poison ivy.

Histopathology. Early lesions are acute spongiotic dermatitis. If vesicles develop, they may contain clusters of Langerhans cells, some flask-shaped. There is a superficial dermal infiltrate of lymphocytes, macrophages, and Langerhans cells with accentuation around the small vessels. Eosinophils may be present in the dermal infiltrate as well as within areas of spongiosis (Fig. 9-1B, C). In patients with continued exposure to the antigen, the biopsy may show a subacute or, later, a chronic spongiotic dermatitis, often with lichen simplex chronicus due to rubbing.

Pathogenesis. Allergic contact dermatitis represents a type IV cell-mediated delayed hypersensitivity reaction. The immunologic reaction consists of an afferent limb, the sensitization or induction phase, and an efferent limb, the elicitation phase. The allergen is usually of low molecular weight (a hapten) and lipid soluble. After penetrating the skin, the hapten binds to a carrier protein to form a complete antigen, which is processed by antigen-presenting cells, principally the epidermal Langerhans cells, and possibly other cutaneous dendritic cells. These cells then migrate to the draining lymph nodes, where they present the antigen to T lymphocytes. The process triggers antigen-specific commitment and production of memory and effector T cells. Following subsequent exposure of the sensitized subject to the same allergen, an accelerated and more aggressive secondary immune response will be elicited. Both $CD4^+$ and $CD8^+$ subtypes of T lymphocytes participate in

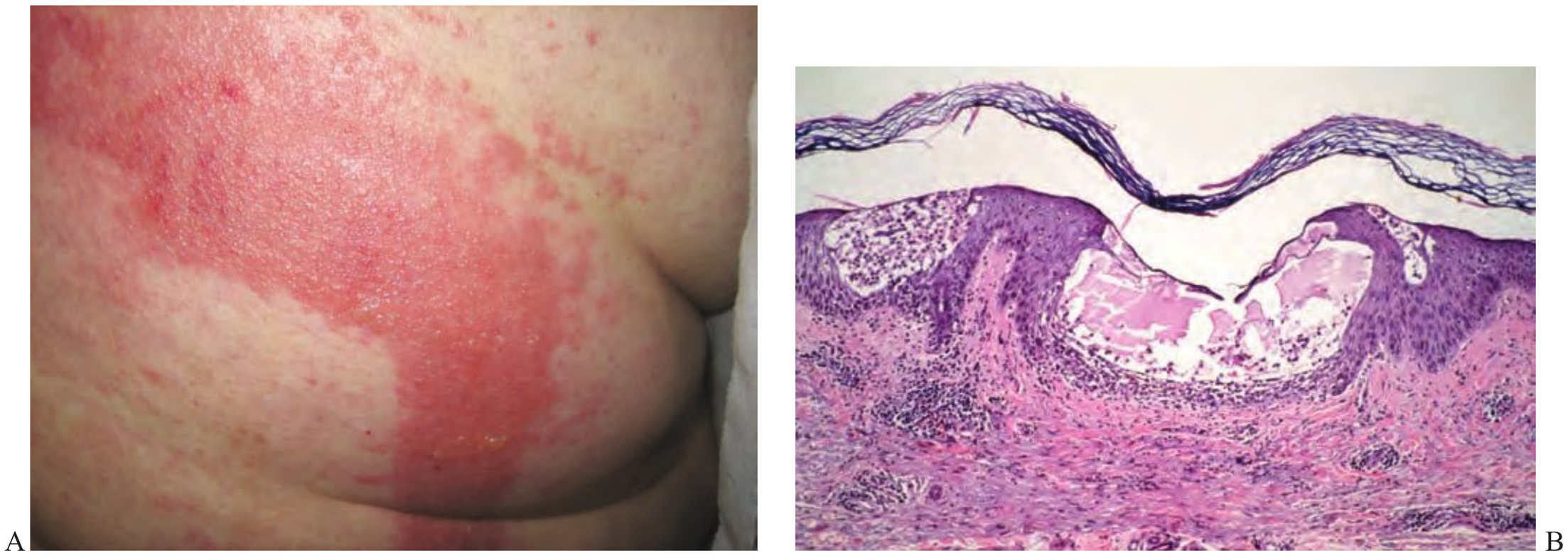


FIGURE 9-1. Acute dermatitis: allergic contact dermatitis. A: Geometric erythematous plaque with overlying vesicles on the back of a patient with allergic contact dermatitis to adhesive tape. B: Spongiosis with vesicles containing fluid and inflammatory cells. C: Exocytosis of lymphocytes and eosinophils into the spongiotic epidermis.

contact hypersensitivity reactions (1). The homing of lymphocytes to the antigen in exposed skin requires various cell adhesion molecules, such as lymphocyte function–associated antigen-1 (LFA-1) (2). Lymphocytes liberate various cytokines in the affected area of skin, including interleukins (ILs), IFN-γ and TNF-α, leading to a further influx of inflammatory cells, particularly nonsensitized lymphocytes and eosinophils. Chemokines appear to be crucial regulators of both induction and expression of allergic contact dermatitis.

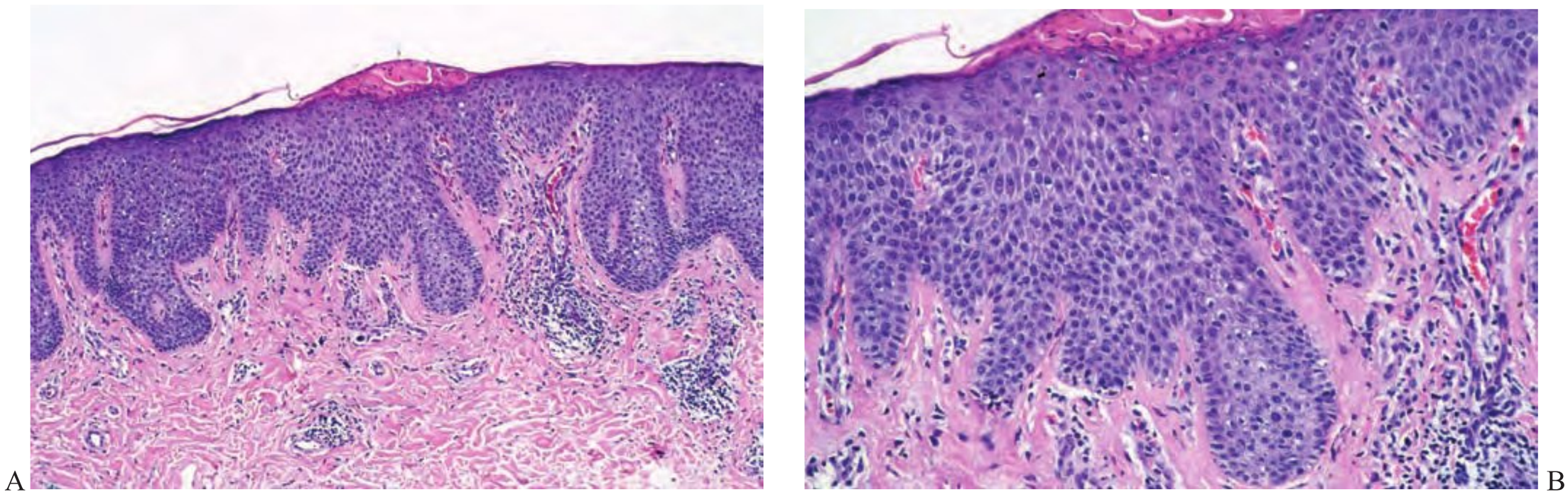


FIGURE 9-2. Subacute spongiotic dermatitis: nummular dermatitis. A: There is irregular acanthosis, spongiosis, and superficial perivascular inflammatory infiltrate. Parakeratosis containing plasma is also present. B: Spongiosis is accompanied by exocytosis of inflammatory cells.

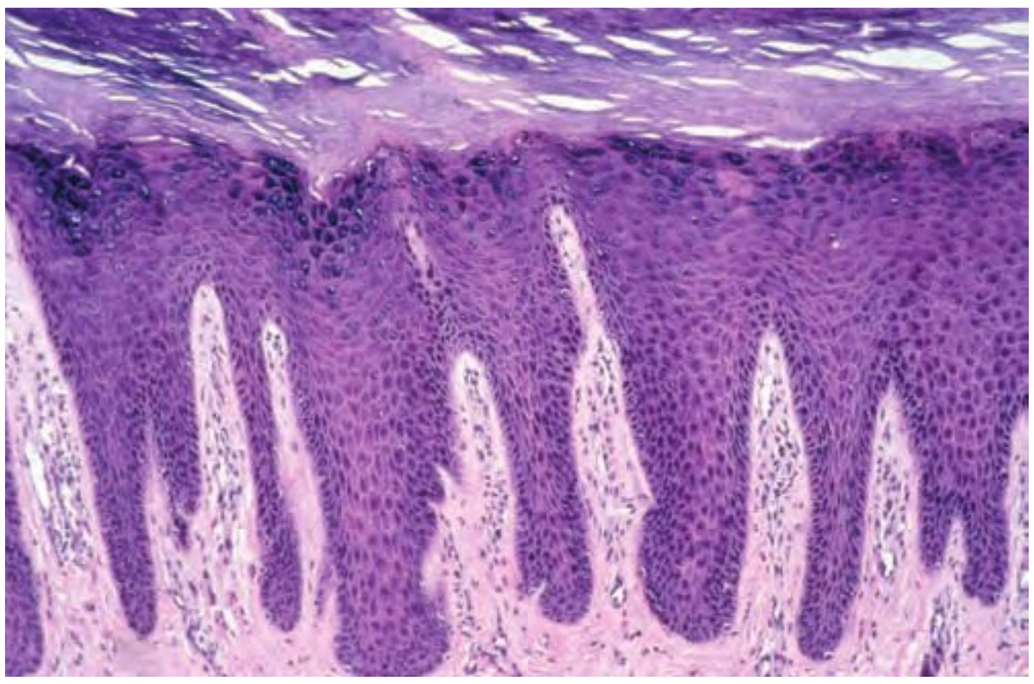


FIGURE 9-3. Lichen simplex chronicus. There is hyperkeratosis, hypergranulosis, and irregular psoriasiform acanthosis with minimal spongiosis. Vertically oriented collagen in the papillary dermis is characteristic.

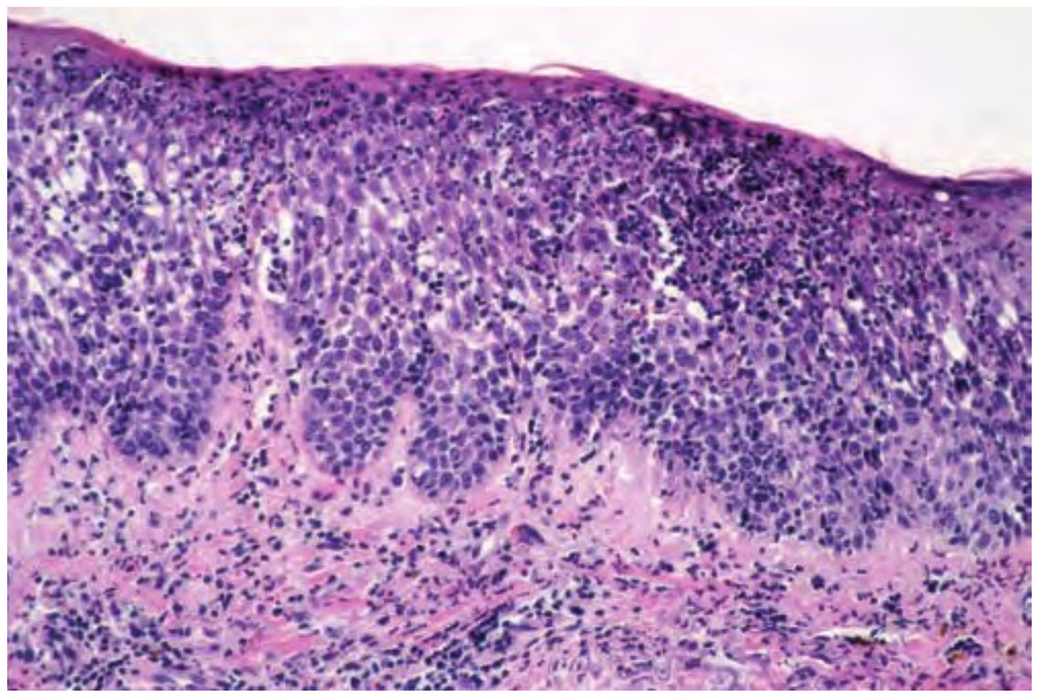


FIGURE 9-4. Irritant dermatitis. There is superficial epidermal necrosis together with spongiosis and infiltrate of neutrophils.

Irritant Contact Dermatitis

This inflammatory reaction occurs after exposure to an irritant, a toxic compound that causes a reaction in most individuals who come into contact with it. Common irritants include alkalis, such as soaps, detergents, lye, and ammonia-containing compounds. The irritant response is determined by the type of chemical, its concentration, the mode of exposure, the body site, the barrier function locally, and the age of the patient. Atopy is a predisposing factor. The clinical morphology varies. Sometimes it is indistinguishable from allergic contact dermatitis.

Chemical burns, usually caused by strong alkalis and acids, lead to immediate painful erythema progressing to vesiculation, necrosis, and, if severe, ulceration. Acute irritant reactions produce a monomorphic picture with scaling, redness, vesicles, pustules, or erosions and are caused by such mild irritants as detergents and water with additives. Agents producing this pattern include tretinoin, benzalkonium chloride, dithranol, adhesive tapes, and cosmetics. Dryness, chapping, and absence of vesicles characterize chronic irritant contact dermatitis. This reaction pattern is produced by repetitive contact to water, detergent, and solvents.

Histopathology. The histologic picture varies from extensive ulceration to simply diffuse hyperkeratosis or parakeratosis with congestion and ectasia to a spongiotic pattern essentially identical to allergic contact dermatitis. The variable features reflect the protean factors discussed above. Some correlations are worthy of note. In some instances, there is significant necrosis with nuclear karyorrhexis and cytoplasmic pallor. In severe reactions, the necrosis may extend into the dermis. Some irritants such as cantharidin and trichloroethylene produce acantholysis and neutrophilic infiltration in the epidermis (3) (Fig. 9-4). Other contactants may specifically target vascular endothelium. However, some reactions may be entirely spongiotic, such as those due to weak irritants, strong irritants in low concentration, and those in the "irritable skin syndrome." Because of these observations and those made in positive patch test sites, routine histopathologic changes do not reliably separate irritant from allergic contact reactions, although necrosis, neutrophilic infiltration, and acantholysis are more frequent in the former. In the recovery phase of irritant dermatitis, mild epidermal hyperplasia, sometimes psoriasiform, is often present. Psoriasiform hyperplasia may develop in chronic irritant reactions. In other words, most common irritants lead to subacute and chronic spongiotic dermatitis—histologic features that are identical to those of allergic contact reactions. Some contact reactions may manifest as only hypekeratosis and minimal spongiosis.

Pathogenesis. The pathogenesis at the cellular and molecular level of irritant contact dermatitis is not completely understood. Mechanisms of damage are variable with different irritants; these include keratin denaturation, damage of the permeability barrier through removal of surface lipid and water-holding substances, disruption of cell membranes, and direct cytotoxic effects. Recent studies indicate that very complex reaction patterns involving immunologic components occur in the irritant response. There are surprisingly more similarities than differences between irritant contact dermatitis and allergic contact dermatitis in morphology, clinical manifestation, chemokine expression, and involvement of T cells (4–6).

Dyshidrotic Dermatitis

Dyshidrotic dermatitis is characterized by recurrent, severely pruritic, deep-seated vesicles that classically involve the lateral aspects of the fingers and, in some cases, the toes. Episodes may be precipitated by infections, "id" reactions, contact reactions, and emotional stress. In chronic cases, there may be more extensive involvement of the palms and soles. Although the eruption develops acutely, it may become chronic with erythema, lichenification, and fissuring. Secondary impetiginization is common.

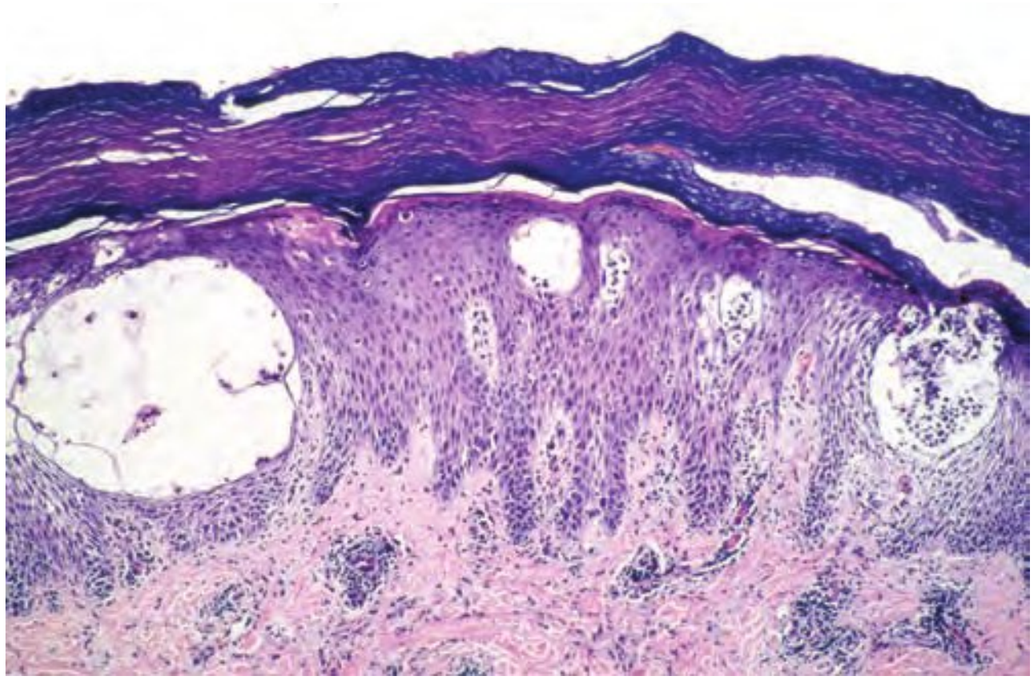


FIGURE 9-5. Dyshidrotic dermatitis. In acral skin, large intraepidermal vesicles are held intact by the thick stratum corneum.

Histopathology. Spongiosis and intraepidermal vesiculation occur in acute lesions (Fig. 9-5). There is a superficial perivascular lymphohistiocytic infiltrate with exocytosis of lymphocytes into spongiotic zones. The infiltration is usually mild. In acute lesions, the compact, thickened stratum corneum of acral skin remains intact, and the epidermal thickness is normal. With chronicity, spongiosis diminishes; acanthosis and parakeratosis predominate with variable crusting. Difficulty in differential diagnosis with pustular psoriasis may occur because of the formation of vesiculopustules in older lesions. A periodic acid-Schiff (PAS) stain should always be performed on vesicular lesions of the palms and soles, because tinea manus/pedis may mimic dyshidrotic dermatitis histologically.

Autoeczematization or Id Reaction

A sudden generalized or localized vesicular dermatitis developing in association with a defined local dermatitis or infection is known as an *id reaction*. The lesions are pinhead-sized, acuminate or flat-topped, papules. The patient most often has bullous tinea pedis or kerion, thus the name, *dermatophytid*. In some cases, patients have a severe localized dermatitis, such as stasis dermatitis, with subsequent development of widespread papulovesicular lesions (7). Other forms of id reaction exist.

Histopathology. The features are those of acute spongiotic dermatitis, often with micro- or macrovesiculation. Eosinophils may be present. There is often some edema of the superficial papillary dermis with some large lymphocytes (presumably activated) in the upper dermis (8). The infiltrating cells are T cells—those within the epidermis are principally $CD8^+$, and those within the dermis are principally $CD4^+$.

Pathogenesis. Id reactions have been postulated to represent hypersensitivity dermatitis to an autoantigen; however, this has never been proven. Several other possibilities exist. First, the reaction may represent a conditioned hyperirritability or responsiveness precipitated by the local infection or dermatitis. Acute local chemical irritation may lower the threshold for an irritant reaction to the same chemical at remote sites. Second, localized dermatitis leads to local production of cytokines by keratinocytes. If the cytokines are hematogenously disseminated, they may lead to distant skin hyperirritability. Circulating activated T lymphocytes may play a role in id reaction associated with allergic contact dermatitis. Lastly, dissemination of antigen (but not of whole infectious agents) from the local site may occur with a secondary response developing at a site of distant deposition. Microbial antigens have been identified in an id reaction in a patient with tuberculoid leprosy (9).

Photoallergic Dermatitis

Photoallergy is increased reactivity of skin to ultraviolet and visible light and is brought about by a chemical agent on an immunologic basis (10). The eruption of photoallergic dermatitis may be due to topical application of, or oral ingestion of, a photosensitizing agent, resulting in a photocontact dermatitis or photodrug eruption, respectively. Agents that may elicit photocontact dermatitis include soaps and cleansers (containing halogenated salicylanilide), perfumes (such as musk ambrette), topical sulfonamides, sunscreens, benzocaine, and diphenhydramine. Common causes of photodrug eruption include thiazide diuretics, oral hypoglycemics, and phenothiazines. The eruption is pruritic and composed of erythematous papules and confluent plaques on sun-exposed skin, usually the face, dorsal aspect of the arms, and the "V" of the neck.

Histopathology. The features are similar to that of an acute allergic contact dermatitis, showing variable spongiosis, in some cases with vesiculation, and a superficial perivascular lymphohistiocytic infiltrate with exocytosis. A deeper perivascular infiltrate and eosinophils are more common in photoallergic dermatitis induced by systemic ingestion of medications. With chronic exposure to the antigen, there is progression to chronic dermatitis, with diminished spongiosis, less intense inflammation, and more acanthosis. Phototoxic reactions are "sunburn" reactions with epidermal apoptosis and necrosis with intraepidermal to subepidermal blisters—the changes paralleling the degree of damage. Neutrophils may be prominent.

Nummular Dermatitis

In nummular dermatitis, the eruption is characterized by pruritic, coin-shaped (nummular), erythematous, scaly, crusted plaques. The lesions tend to develop on the extensor surfaces of the extremities.

Histopathology. Nummular dermatitis is the prototype of subacute spongiotic dermatitis (Fig. 9-2). There is mild to moderate spongiosis, usually without vesiculation. Irregular acanthosis with some exocytosis of inflammatory cells is usually present. The parakeratotic stratum corneum contains aggregates of coagulated plasma, forming a crust. Mild papillary dermal edema and vascular dilatation may be present.

There is superficial perivascular infiltrate of lymphocytes, some eosinophils, occasional neutrophils, and plasma cells.

Pathogenesis. The etiology of this entity is unknown. The routine and ultrastructural changes in nummular dermatitis resemble those of contact dermatitis. Intercellular edema is the most conspicuous finding. There is shearing and loss of desmosomes as spongiosis becomes marked.

Atopic Dermatitis

The eruption in atopic dermatitis is characterized by areas of severe pruritus, erythema, scaling, and excoriation, with chronicity, lichenification, and lichen simplex chronicus. Many of the cutaneous changes are due to chronic rubbing and scratching. Most patients are diagnosed in childhood, with approximately one third of cases diagnosed before 1 year of age (11). There is a female predominance, and many patients have other atopic disorders such as allergic rhinitis or asthma. Increased incidence of contact dermatitis is also noted among patients with atopic dermatitis. In infants, the lesions predominate on the face and extensor surfaces of the extremities, but they later affect the flexural surfaces. The classically involved sites in older children and adults are the popliteal and antecubital fossae and the sides of the neck. Secondary bacterial infection is common.

Histopathology. In early phases, there is mild spongiosis, exocytosis of lymphocytes, and parakeratosis. Lymphocytes and scattered histiocytes are present around the superficial vascular plexus. In long-standing lesions, the rete ridges are regularly elongated, with less prominent spongiosis and cellular infiltrate. Hyperkeratosis and wedge-shaped hypergranulosis with areas of parakeratosis develop. There appear to be an increased number of small vessels with thickened walls. Eosinophils are less conspicuous than in allergic contact or nummular dermatitis. With time, the changes may be those of lichen simplex chronicus.

Pathogenesis. The current understanding of the disease remains incomplete. Atopic dermatitis develops as a result of complex interactions of genetic, environmental, and immunologic factors. Allergic reactions appear to play a role in some patients, but in other patients, factors such as disturbance of skin function, infection, and stress may be more important. Atopic dermatitis can be exacerbated by fungal, bacterial, and viral skin infections. In particular, *Staphylococcus aureus* may exacerbate or maintain skin inflammation in atopic dermatitis by secreting a group of toxins known to act as superantigens (12).

Factors identified as being involved in the pathogenesis of atopic dermatitis include the differentiation of helper T cells, increased life span of eosinophils, multiple roles of IgE, the pattern of local cytokine expression, infectious agents, and superantigens (13).

The initiation of atopic dermatitis appears to be driven by allergen-induced activation of type 2 T-helper cells (Th-2 cells), leading to increased levels of IL-4, -10, and -13. Elevated IgE ensues. IgE contributes to the inflammatory cell infiltrate by several mechanisms, including immediate/late-phase reaction, allergen presentation by IgE-bearing Langerhans cells, and allergen-induced activation of IgE-bearing macrophages.

The mononuclear cell infiltrate in the lesions probably reflects a combination of both IgE-dependent mast cell/basophil degranulation and Th-2 cell-mediated responses elicited during acute exposure to allergens, including ingestants, inhalants, or contact aeroallergens such as human dander, grass pollens, and house dust mites (14).

The pattern of local cytokine expression plays an important role in modulating tissue inflammation and depends on the activity and/or duration of the lesion. Acute skin inflammation is associated with a predominance of IL-4 and IL-13 expression, and little interferon-gamma (INF-γ) But in chronic lesions, there are increased INF-γ producing cells (15,16).

No specific single gene is a unique marker for atopic dermatitis. Genome screens of families with atopic dermatitis have implicated chromosomal regions that overlap with other skin diseases, including inflammatory and autoimmune skin disease (17). The dysfunctional skin barrier genes, which include loss of functional filaggrin (18), increase of protease activity, and lack of protease inhibitor, predispose the patients to the harmful effects of environmental agents (19). Chromosome 5q31 contains the IL-4 gene cluster family. Because IL-4 is central to the induction of IgE synthesis by B cells, it has been suggested that polymorphisms in the chromosome 5q31 region may be linked to the gene controlling total serum IgE in atopic individuals. Another possible candidate gene found on chromosome 11q13 is the high-affinity IgE receptor (20,21).

Lichen Simplex Chronicus

The vast majority of patients with pruritus who chronically rub the skin may develop lichen simplex chronicus. It often develops in the setting of atopic dermatitis or allergic contact dermatitis. Thick plaques often with excoriation, the normal skin markings accentuate producing the finding known as *lichenification*. Uncommonly, some patients develop macular or lichen amyloidosis. Some patients, due to the character of their underlying disease such as dermatitis herpetiformis, only rarely develop lichen simplex chronicus. Lastly, skin with severe chronic dermatoheliosis does not develop typical lichen simplex chronicus.

Histopathology. Lichen simplex chronicus is the prototype for chronic dermatitis (Fig. 9-3). There is hyperkeratosis interspersed with areas of parakeratosis, acanthosis with irregular elongation of the rete ridges, wedge-shaped hypergranulosis, and broadening of the dermal papillae. Slight spongiosis may be observed, but vesiculation is absent. Minimal papillomatosis is sometimes present. Excoriations, which are punctate ulcerations lined by necrotic superficial papillary dermis, fibrin, and neutrophils, are often present; however, they are often present in many pruritic dermatoses. There may be a sparse superficial perivascular infiltrate without

exocytosis. In the papillary dermis, there are an increased number of fibroblasts and vertically oriented collagen bundles. As rubbing increases in intensity and chronicity, epidermal hyperplasia becomes more florid and the fibrosis more marked. Searching for features of dermatitis associated with chronic rubbing and scratching may give a hint as to the initial underlying dermatitis.

Seborrheic Dermatitis

Clinically, patients develop erythema and greasy scale on the scalp, ears, eyebrows, nasolabial areas, and central chest. Rarely, patients with seborrheic dermatitis develop generalized lesions. In infants, the scalp ("cradle cap"), face, and diaper areas are often involved. It is said to be a rare cause of erythroderma. Seborrheic dermatitis is seen with increased frequency in patients with Parkinson's disease, epilepsy, congestive heart failure, chronic alcoholism, zinc deficiency, and HIV infection. Patients with HIV infection often have severe refractory disease and atypical distribution (22).

Histopathology. The histopathologic features are a combination of those observed in psoriasis and spongiotic dermatitis. Mild cases may exhibit only slight subacute spongiotic dermatitis. The stratum corneum contains focal parakeratosis, with a predilection for the follicular ostia, a finding known as *shoulder parakeratosis* (Fig. 9-6). Occasional pyknotic neutrophils are present within parakeratotic foci (neutrophilic parakeratosis), sometimes with fluid (neutrophilic crust). There is moderate acanthosis with regular elongation of the rete ridges, mild spongiosis, and focal exocytosis of lymphocytes. The dermis contains a sparse mononuclear cell infiltrate. In HIV-infected patients, the epidermis contains apoptotic keratinocytes, and the dermal infiltrate usually contains plasma cells.

Pathogenesis. The pathogenesis is unknown; the role of *Malassezia* sp. (*Pityrosporum*) in the etiology is controversial even though many patients have a good response to oral or topical ketoconazole (23,24).

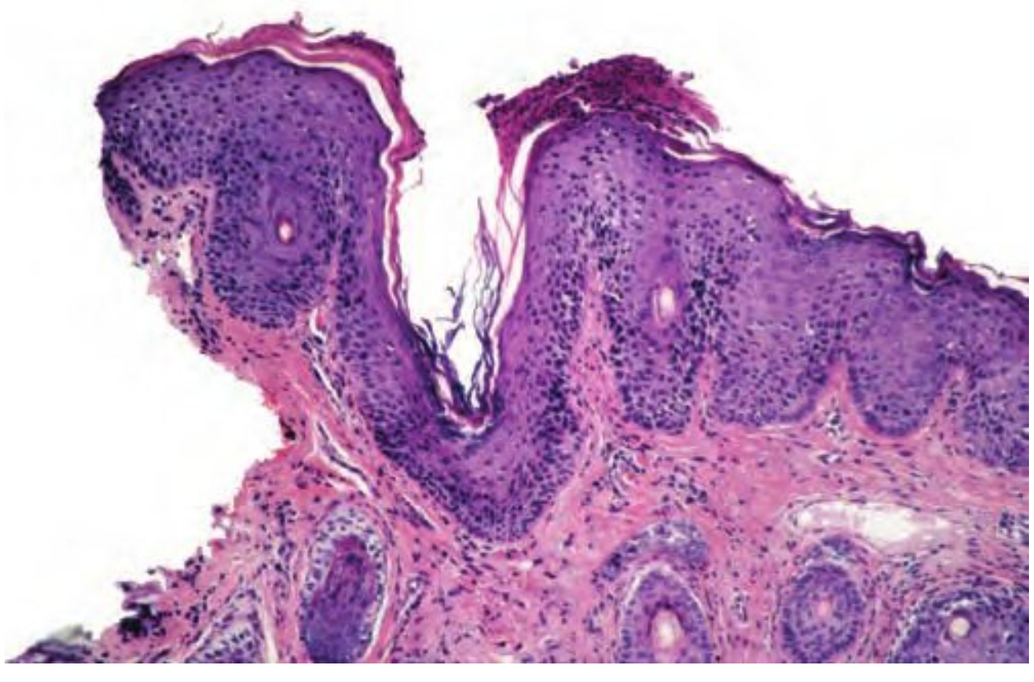


FIGURE 9-6. Seborrheic dermatitis. There is neutrophilic parakeratosis on the follicular ostial shoulder. The epidermis is hyperplastic. Spongiosis is minimal in this biopsy.

Stasis Dermatitis

Patients with long-standing venous insufficiency and lower extremity edema may develop pruritic, erythematous, scaly papules and plaques on the lower legs, often in association with brown pigmentation and hair loss. Ulceration is a frequent complication of long-standing stasis dermatitis.

Histopathology. The variable epidermis may be hyperkeratotic with focal parakeratosis, acanthotic to atrophic, and with focal spongiosis. There is proliferation of small blood vessels in the papillary dermis, forming lobular aggregates (glomeruloid proliferation). The proliferation may be florid, mimicking Kaposi's sarcoma (acroangiodermatitis) (25). There is a superficial perivascular lymphocytic infiltrate that surrounds thickened capillaries and venules. The reticular dermis is often fibrotic. Extravasated erythrocytes and hemosiderin are usually present superficially, but they may be identified about the deep vascular plexus as well. Fibrin thrombi may be observed in the small vessels, likely reflecting flow disruption and anoxia. They do not indicate a concurrent coagulopathy. Endothelial necrosis and neutrophils may be present as well, reflecting similar changes, and do not indicate a leukocytoclastic vasculitis.

Differential Diagnosis of Spongiotic Dermatitis

Acute spongiotic dermatitis may be seen histologically in pityriasis rosea, guttate parapsoriasis, spongiotic drug eruptions, arthropod bite reactions, and dermatophyte infections. Lesions of pityriasis rosea contain discontiguous suprapapillary areas of spongiosis, exocytosis of lymphocytes, and overlying mounds of (lenticular) parakeratosis. The spongiosis varies from micro- to macrovesicular. In addition, extravasated erythrocytes may be present in the involved papillae and overlying epidermis. Guttate parapsoriasis is similar to pityriasis rosea, but it lacks the intraepidermal erythrocytes and has less lymphohistiocytic infiltrate. Spongiotic drug eruptions tend to have a deeper infiltrate with eosinophils than other forms of acute spongiotic dermatitis. They usually do not vesiculate. In arthropod bite reactions, the epidermal changes are focal, corresponding to the site of attack, and the infiltrate is wedge shaped. Bite or sting parts are often not found. A PAS stain is necessary to exclude dermatophyte infection.

Pityriasis lichenoides, dermatophyte infection, spongiotic drug eruption, or an arthropod bite reaction may show histopathologic features similar to *subacute spongiotic dermatitis.* In pityriasis lichenoides et varioliformis acuta, the lesions are sharply circumscribed. Apoptotic keratinocytes, dry neutrophil-rich scale, bandlike interface dermatitis, areas of epidermal necrosis, and a deeper perivascular infiltrate are present. Dermatophyte infections characteristically have neutrophils within the stratum corneum, along with fungal hyphae; however, PAS stain is often necessary to identify the fungal hyphae.

Conditions that reveal a *chronic dermatitis* include pellagra and other nutritional deficiencies, mycosis fungoides, and psoriasis, particularly if altered by therapy. In the nutritional deficiencies, upper epidermal pallor, necrosis, and neutrophilic infiltrate are characteristic. In mycosis fungoides, psoriasiform epidermal hyperplasia may be present, but the lymphocytes have nuclear atypia and cerebriform morphology with epidermotropism in the absence of spongiosis. Lesions of psoriasis may resemble lichen simplex chronicus, but thinning of the suprapapillary plates, confluent parakeratosis, neutrophils within the stratum corneum and upper epidermis, and dilated tortuous capillaries are distinctive.

Other Disorders with Spongiotic Dermatitis

Erythroderma and Generalized Exfoliative Dermatitis

Erythroderma is characterized by generalized erythema and scale, often in association with fever. The eruption is nonspecific and may be caused by a variety of underlying conditions. In one study, 74.4% were associated with a preexisting dermatosis, 14.6% were idiopathic, and 5.5% were related to drugs and malignancy (26). Psoriasis is the most common preexisting dermatosis; others include spongiotic dermatitis, pityriasis rubra pilaris, photosensitivity syndromes, and, rarely, stasis dermatitis, dermatophytosis, pemphigus foliaceus, and even bullous pemphigoid. Many drugs have been incriminated, such as phenytoin, thiazides, nonsteroidal anti-inflammatory drugs (NSAIDS), and recombinant cytokines. A small percentage of erythroderma is associated with lymphoma, most frequently cutaneous T cell lymphoma, in the form of Sézary syndrome or erythrodermic mycosis fungoides. The "red man syndrome" is erythroderma without knowing underlying causes. Some cases may progress to mycosis fungoides after many years.

Histopathology. A careful search for histologic features of any of the above listed etiologies must be undertaken; however, the nature of the underlying dermatosis is not always discernible in the erythrodermic phase, and the changes are often those of nonspecific subacute or chronic spongiotic dermatitis. Erythrodermic lesions associated with underlying psoriasis (27) resemble early lesions of psoriasis with only mild epidermal hyperplasia, mild spongiosis, mounds of parakeratosis with a few neutrophils, and red cell extravasation in the papillary dermis. Blood vessels in the upper dermis are usually dilated. In cases of erythroderma related to mycosis fungoides, atypical cells with cerebriform nuclei are present in the infiltrate. Eosinophils may be present. Drug-related cases might simulate mycosis fungoides with exocytosis, lymphocytic atypia, and the presence of eosinophils. The presence of rare apoptotic keratinocytes may be a clue to the drug etiology.

The histopathologic findings are helpful in establishing the etiologic diagnosis in only about 40% of cases (28). Repeat biopsies and hematologic studies at regular intervals are recommended in patients without definitive diagnosis.

Miliaria

Miliaria develops when sweating is associated with obstruction of the intraepidermal sweat duct. There are three types: miliaria crystallina, miliaria rubra, and miliaria profunda.

Miliaria crystallina develops when the sweat duct is obstructed within the stratum corneum. Asymptomatic, small, superficial, noninflammatory vesicles resembling dewdrops develop, mainly on the trunk, after severe sunburn or with profuse sweating during a febrile illness. The vesicles rapidly subside when sweating ceases or the horny layer overlying the vesicles exfoliates. In some cases, the eruption may be present at birth (29).

Miliaria rubra (prickly heat) ensues when the sweat duct is obstructed within the deeper layers of the epidermis. It generally develops during and after excessive sweating in skin covered by clothing. It may also occur after prolonged covering of the skin by occlusive polyethylene wraps. Anhidrosis and heat intolerance result, particularly when the trunk is occluded. The lesions consist of pruritic small papulovesicles surrounded by erythema. Pustules may develop.

Miliaria profunda usually develops after recurrent episodes of miliaria rubra, particularly in tropical climates. The sweat duct is occluded at the dermal–epidermal junction. Lesions are nonpruritic, flesh-colored papules and can result in widespread anhidrosis.

Histopathology. In *miliaria crystallina*, intracorneal or subcorneal vesicles that are in continuity with the underlying sweat duct are observed. A sparse to moderate infiltrate of neutrophils is seen at the periphery of the vesicle. The surrounding epidermis is spongiotic, and there is papillary dermal edema and sparse superficial perivascular inflammation.

In *miliaria rubra*, spongiotic vesicles are found in the stratum malpighii. Serial sectioning shows these vesicles to be in continuity with a sweat duct. Periductal lymphocyte infiltration and spongiosis are seen, as is an infiltrate in the underlying dermis (Fig. 9-7). In many instances, the distal, intraepidermal sweat duct is filled with amorphous "casts" that are PAS positive and diastase resistant.

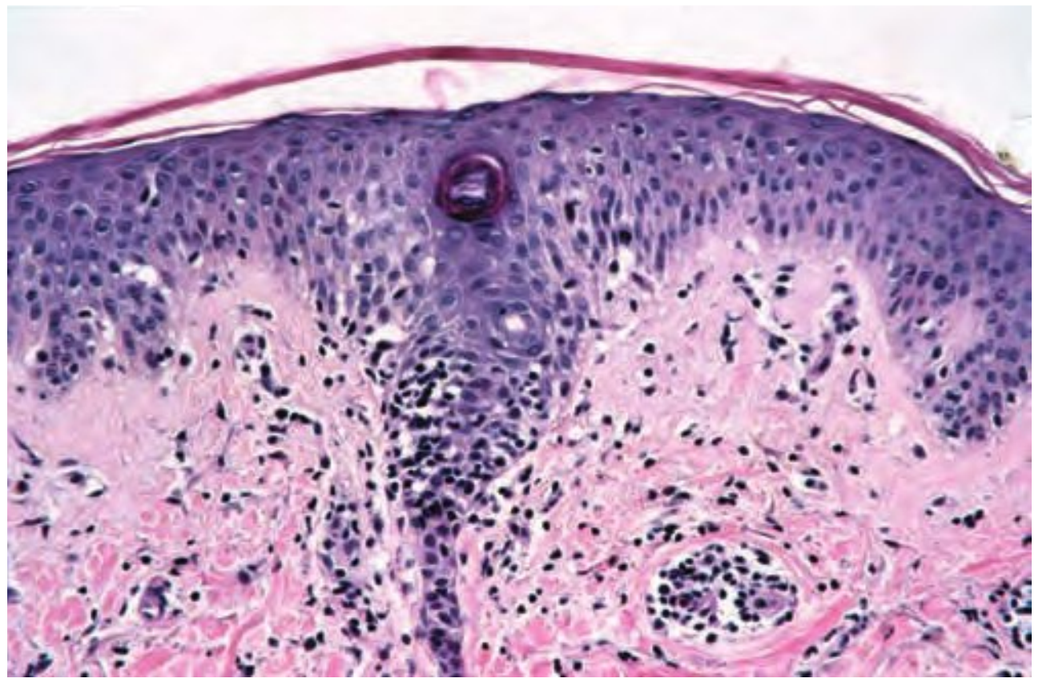


FIGURE 9-7. Miliaria rubra. There is spongiosis about and within the epidermal eccrine duct. Lymphocytes are present in the areas of spongiosis.

In *miliaria profunda*, the features are similar to those of miliaria rubra, but the inflammatory changes involve the lower epidermis and superficial dermis.

Pathogenesis. In *miliaria crystallina*, the obstruction of the sweat duct within the stratum corneum is caused either by mild damage to the epidermis from a preceding sunburn or by excessive hydration of the stratum corneum. In neonates, excess hydration of the stratum corneum *in utero* in combination with immature eccrine ducts may cause swelling of the ductal epithelial cells and occlusion of the duct (29).

In *miliaria rubra*, increased environmental temperature plays an important role (30). Aerobic bacteria are thought to contribute to the obstruction of the acrosyringium. In favor of this view are the frequent presence of *S. aureus* within the sweat ducts and the fact that the development of miliaria rubra under an occlusive polyethylene film can be prevented by application of antibacterial solutions.

The PAS-positive, diastase-resistant, amorphous plug within the acrosyringium may occur as a result of injury to the luminal cells, inflammation, and ductal and periductal spongiosis. These changes occur after 48 hours of occlusion and resolve after 14 days, when old, damaged stratum corneum is desquamated. Tape stripping can restore sweating, which supports a reversible, high-level blockage.

Immunologic Deficiency Diseases Associated with Spongiotic Dermatitis

Familial Leiner's Disease

In familial Leiner's disease, infants develop generalized seborrheic dermatitis, severe diarrhea, recurrent local and systemic infections, and marked wasting. Death is usually due to septicemia. A dysfunction of the fifth component of complement (C5) exists in addition to other cellular and humoral immune defects.

Hyperimmunoglobulin E Syndrome (Job's syndrome)

In hyperimmunoglobulin E syndrome, patients have recurrent pyogenic infections, atopic dermatitis, extreme elevation of serum IgE, and defective neutrophil chemotaxis due to decreased production of INF-γ (31). The infectious complications include recurrent cold staphylococcal abscesses, furunculosis, otitis, sinusitis, and staphylococcal pneumonia.

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome is an X-linked recessive disorder that affects males and is characterized by recurrent, systemic bacterial and viral infections; purpura due to thrombocytopenia; and an atopic dermatitis–like eruption because of progressive depletion of nodal and circulating T cells, death due to infection, or lymphoma ensuing in the first decade of life.

Chronic Granulomatous Disease

Chronic granulomatous disease is an X-linked recessive disorder affecting males, beginning in infancy with perioral dermatitis. The dermatitis often progresses to granulomatous lesions accompanied by cervical adenitis. Suppurative and granulomatous infections develop in the skin, lungs, bone, and liver, most commonly due to *S. aureus*. Death occurs in most cases in childhood or adolescence. The defect lies in decreased capacity of neutrophils to generate hydrogen peroxide and kill catalase-positive bacteria and fungi. *In vitro*, neutrophils are unable to reduce nitroblue tetrazolium dye after phagocytosis, which is a useful screening test for the disease.

PEMPHIGUS GROUP

As first demonstrated in 1943, acantholysis is the characteristic feature of the bullae of pemphigus. The acantholysis results from *in vivo*–bound antibodies first discovered in 1964 (32). Pemphigus is now characterized as an autoimmune blistering disease presenting clinically with flaccid intraepithelial blisters, erosions, and ulcerations of the skin and mucous membranes; histologically with acantholysis; and immunologically with *in vivo*–bound and circulating autoantibodies against the cell membrane components of keratinocytes important in cell-cell adhesion. Circulating autoantibodies are present in about 80% of patients with active disease, and their titer usually correlates with disease activity. These antibodies are demonstrable by direct immunofluorescence (DIF) testing of skin and indirect immunofluorescence (IIF) testing of serum. The use of these techniques is now the accepted practice in the diagnosis of all antibody-mediated primary vesiculobullous disorders (see Table 9-4). Pemphigus can be divided into five types: (a) pemphigus vulgaris, with its reactive state, pemphigus vegetans; (b) pemphigus foliaceus, with its lupus-like variant, pemphigus erythematosus, and its endemic variant, Fogo selvagem; (c) drug-induced pemphigus; (d) IgA pemphigus; and (e) paraneoplastic pemphigus (PNP). Rarely, IgM mediated pemphigus may occur secondary to IgM production by B cell lymphoproliferative disease.

Pathophysiology of Pemphigus

The target antigens of pemphigus (Table 9-5) are located in the desmosomes, which are the most prominent adhesion junctions in stratified squamous epithelium. The desmosome complex contains desmogleins and desmocollins as transmembrane constituents and plakoglobin, plakophilin, and desmoplakin as cytoplasmic constituents (Fig. 9-8). Desmogleins and desmocollins are members of the cadherin supergene family (33,34), a group of calcium-dependent proteins that play an important role in the formation and maintenance of tissue integrity. The cadherin molecules form dimers as their functional unit, with the extracellular domain from one cell binding to an opposing cell. The cytoplasmic domain of the cadherin associates with plakoglobin, which links intermediate filaments (i.e., keratins) to the desmosome through desmoplakin. The extracellular epitopes of the desmogleins and desmocollins are targets of the pathogenic antibodies. Of these, desmoglein 1 and desmoglein 3 are the best characterized. Desmoglein 1 is a 160-kD molecule that is expressed primarily in the upper layers of the

TABLE 9-4 Direct Immunofluorescence in Vesiculobullous Dermatoses*

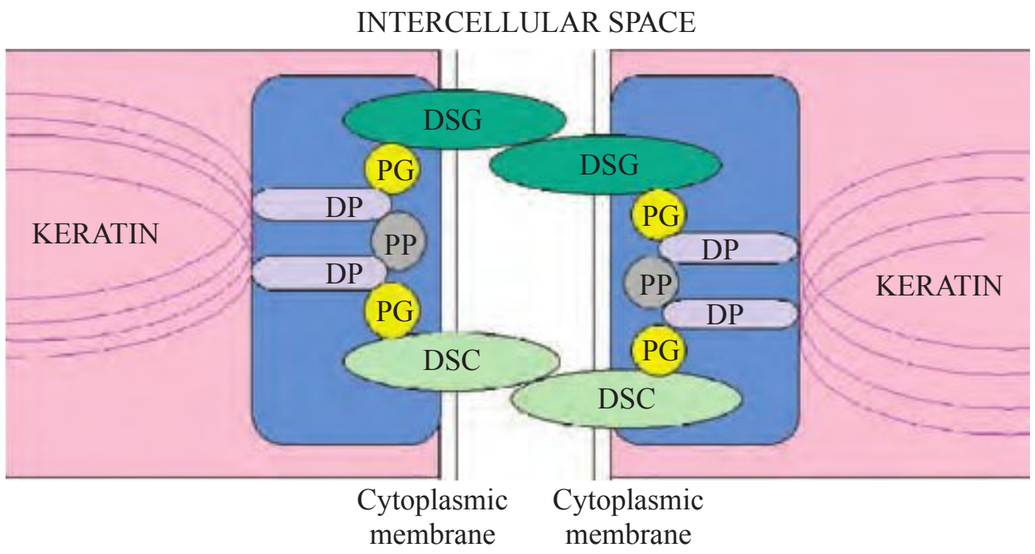
Dermatosis	Principal immunoreactant	Site	Pattern
Pemphigus, all variants except:	IgG	ICS	Lacelike, dotlike
IgA pemphigus	IgA	ICS	Lacelike, dotlike
Paraneoplastic pemphigus	IgG	ICS	Lacelike, dotlike
	C3, IgG	BMZ	Linear
	C3, IgG	BMZ	Granular
Bullous pemphigoid	C3, IgG	BMZ	Linear
Cicatricial pemphigoid	C3, IgG	BMZ	Linear
Anti-p200 pemphigoid	C3, IgG	BMZ	Linear
Herpes gestationis	C3	BMZ	Linear
EBA	C3, IgG	BMZ	Linear
Bullous SLE	C3, IgG	BMZ	Linear
	C3, IgG	BMZ	Granular
Dermatitis herpetiformis	IgA	BMZ	Granular
LAD	IgA	BMZ	Linear
EM	C3, IgM	BMZ	Granular
	C3, IgM	Vessels	Granular
Porphyria/Pseudoporphyria/Bullous dermatosis of hemodialysis	IgG	BMZ	Glassy broad
		Vessels	Glassy broad

ICS, squamous intercellular substance; BMZ, epidermal basement membrane zone; EBA, epidermolysis bullosa acquisita; SLE, systemic lupus erythematosus; LAD, linear IgA dermatosis; EM, erythema multiforme.
*Other immunoglobulins may be present, but they are less intense when present and less frequently observed.

TABLE 9-5 Target Antigens in Pemphigus

Diseases	Autoantibodies	Antigens	Location of antigens
Pemphigus vulgaris			
Mucosal mainly	IgG	Desmoglein 3 (130 kD)	Desmosomes
Mucocutaneous	IgG	Desmoglein 3 (130 kD) Desmoglein 1 (160 kD)	
Pemphigus foliaceus	IgG	Desmoglein 1 (160 kD)	Desmosomes
Paraneoplastic pemphigus	IgG	Desmoglein 1 (160 kD) Desmoglein 3 (130 kD) Desmoplakin I (250 kD) Envoplakin (210 kD) Periplakin (190 kD) Plectin (500 kD) BPAg1 (230 kD) γ-Catenin (plakoglobin- 82 kD)	Desmosomes or hemidesmosomes
Drug-induced pemphigus (autoimmune variant)	IgG	Desmoglein 3 (130 kD) Desmoglein 1 (160 kD)	Desmosomes
Drug-induced pemphigus (toxic variant)	—	—	—
IgA pemphigus			
SPD type	IgA	Desmocollin 1 (110/100 kD)	Desmosomes
IEN type	IgA	Desmoglein 1 (160 kD) Desmoglein 3 (130 kD)	

BPAg1, bullous pemphigoid antigen; SPD, subcorneal pustular dermatosis; IEN, intraepidermal neutrophilic.



DSG - Desmoglein DSC - Desmocollin PG - Plakoglobin DP - Desmoplakin PP - Plakophilin

FIGURE 9-8. The desmosome. The desmosome complex includes desmogleins and desmocollins as transmembrane components and plakoglobin, plakophilin, and desmoplakin as cytoplasmic components. The cytoplasmic domains of desmoglein and desmocollin associate with plakoglobin, which links intermediate filaments (keratin) to the desmosome through desmoplakin.

epidermis. It is the target antigen in pemphigus foliaceus. Desmoglein 3 is a 130-kD molecule that localizes primarily in the deeper layer of epidermis and mucous membrane. It is the target antigen in pemphigus vulgaris (35). Since mucosal epithelium expresses mainly desmoglein 3 but skin expresses both desmoglein 1 and 3, damage by antibodies to desmoglein 3 alone results in oral lesions with or without skin lesions. If both desmoglein 3 and desmoglein 1 antibodies are present, cutaneous lesions as well as mucosal lesions appear, and the disease tends to be more severe (36). Less is known about the desmocollins. Some cases of IgA pemphigus have had autoantibodies to the desmocollins.

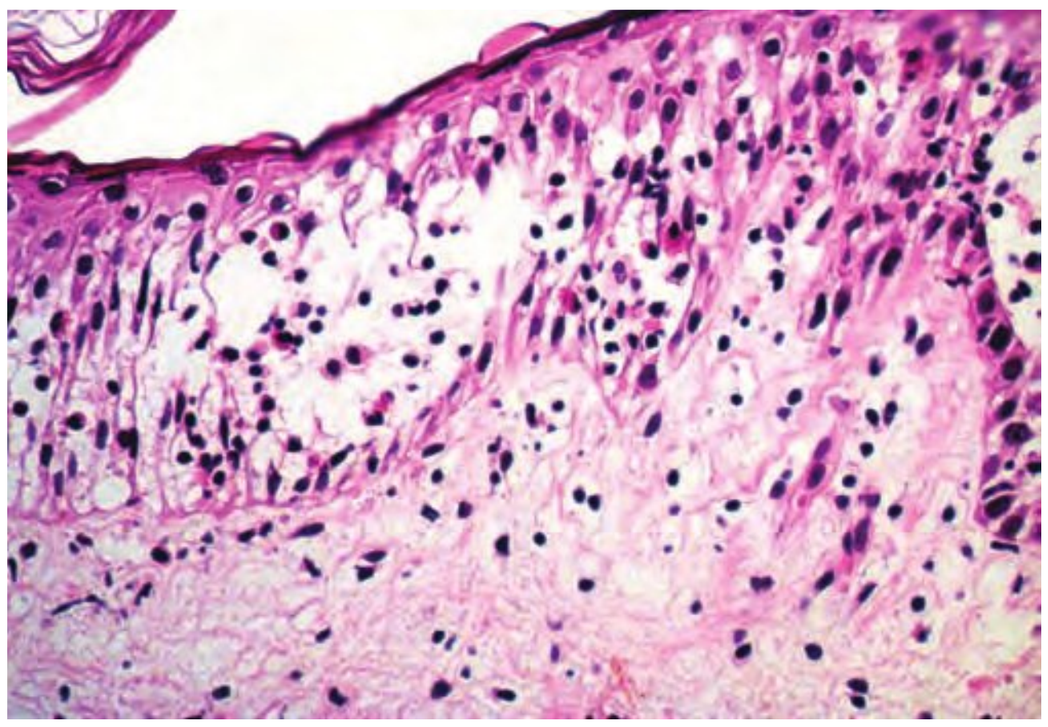
Pemphigus Vulgaris

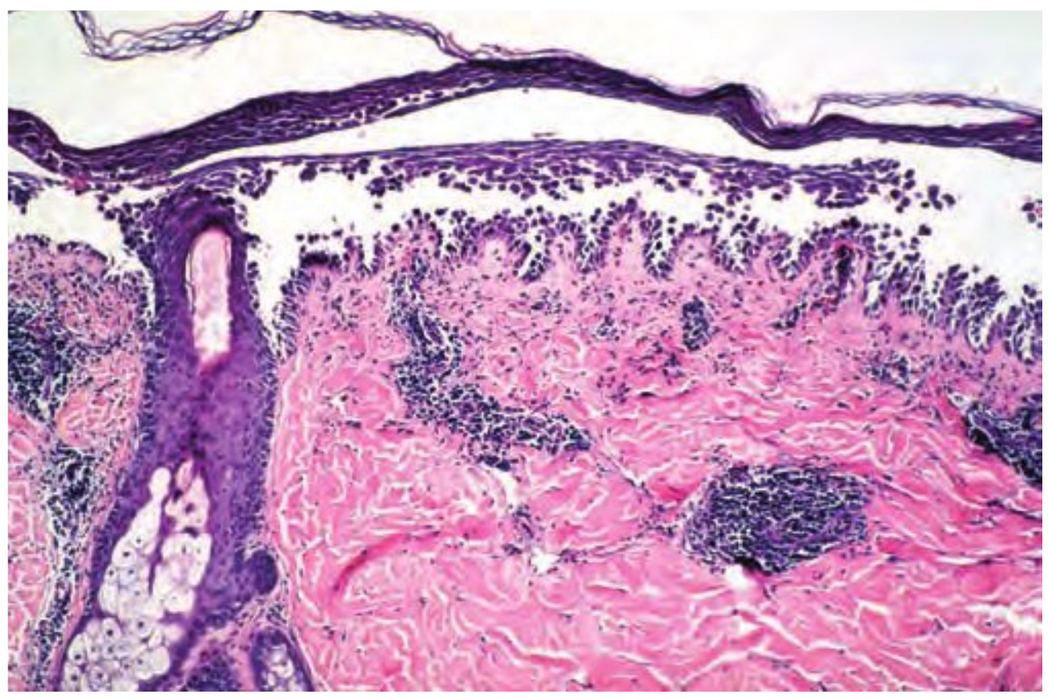
Pemphigus vulgaris develops primarily in older individuals, presenting with large and flaccid bullae. They break easily and leave denuded areas that tend to increase in size by progressive peripheral detachment of the epidermis, leading in some cases to widespread cutaneous involvement. The lesions characteristically involve the oral mucosa, scalp, midface, sternum, groin, and pressure points. Oral lesions (Fig. 9-9A) are almost invariably present and may be the first manifestation of the disease (10% of cases) (37). Before corticosteroids became available, the mortality of this disease was high because of fluid loss and superinfection.

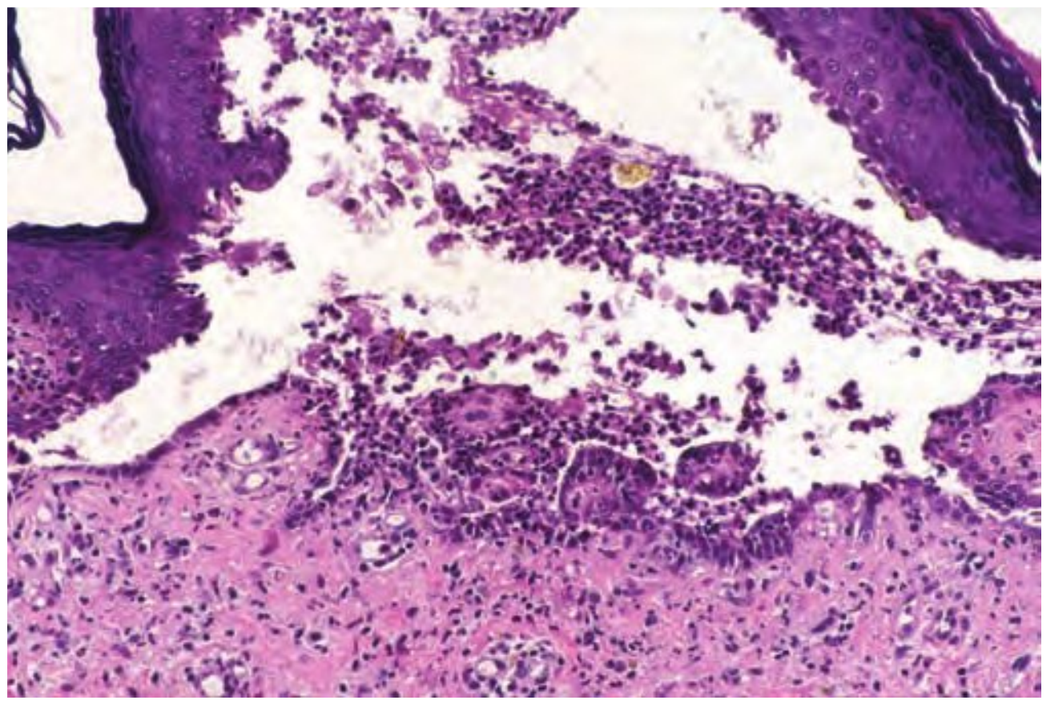
Histopathology. It is important that early blisters, preferably small ones, are selected for biopsy. Care should be given to keeping the epidermis attached to the dermis because the torque applied in punch biopsies may separate the blister roof from the blister base. Therefore, a refrigerant spray may be used before excising the blister with a punch biopsy, or it may be excised with a scalpel. If no recent blister is available, an old one may be moved into the neighboring skin by gentle vertical pressure with a finger (positive Asboe–Hansen sign). The newly created cleavage will reveal early and specific histologic changes.

The earliest recognized change may be either eosinophilic spongiosis rarely or, more commonly, "spongiosis" in the lower epidermis (Fig. 9-9B). This spongiosis may actually represent the earliest manifestation of acantholysis rather than true spongiosis as defined earlier. Acantholysis leads first to the formation of clefts and then to blisters in a predominantly suprabasal location (Fig. 9-9C, D). The intraepithelial acantholysis may extend into adnexal structures or occasionally be higher in the stratum spinosum. The basal keratinocytes, although separated from one another through the loss of attachment, remain firmly attached to the dermis like a "row of tombstones." Within the blister cavity, the acantholytic keratinocytes, singularly or in clusters, have rounded condensed cytoplasm about an enlarged nucleus with peripherally palisaded chromatin and enlarged nucleoli. In some patients, there are varying quantities of antidesmoglein 1 and antidesmoglein 3 antibodies, leading to variable planes of acantholysis. There is little inflammation in the early phase of blister formation. If present, it is usually a sparse, lymphocytic perivascular infiltrate accompanied by dermal edema. However, if eosinophilic spongiosis is apparent, numerous eosinophils may infiltrate the dermis. The phenomenon of eosinophilic spongiosis occurs occasionally in other blistering diseases, particularly in their early phases, including acute contact dermatitis, pemphigus foliaceus, bullous pemphigoid, herpes gestationis, drug eruptions, spongiotic arthropod bite reactions, and transient acantholytic dermatosis. Several important changes ensue as the lesions age. First, a mixed inflammatory cell reaction consisting of neutrophils, lymphocytes, macrophages, and eosinophils may develop. Because of the instability of the blister roof, erosion and ulceration may occur. Older blisters may also have several layers of keratinocytes at the blister base because of keratinocyte migration and proliferation. Last, there may be considerable downward growth of epidermal strands, giving rise to so-called villi (Fig. 9-9D). The evaluation of patients with only oral lesions is difficult, because intact blisters are rarely encountered due to the trauma of mastication, and biopsies may show only erosion and ulceration. Indeed, it is best to sample the edge of a denuded area with intact mucosa in an attempt to demonstrate the typical pathologic changes. Clinicians frequently cannot distinguish between an ulcer and the intact mucosa, as both are often white and shaggy. In patients with only oral lesions, biopsies of intact oral mucosa for DIF testing are more sensitive than biopsies of lesions for routine light microscopic evaluation. Therefore, biopsy from the normal maxillary and upper buccal mucosa is necessary when there is extensive ulceration. Cytologic examination using a Tzanck preparation is useful for the rapid demonstration of acantholytic epidermal keratinocytes in the blisters of pemphigus vulgaris. For this purpose, a smear is taken from the underside of the roof and from the base of an early, freshly opened bulla. Giemsa stain is applied with subsequent rinsing and air-


A


B


C


D

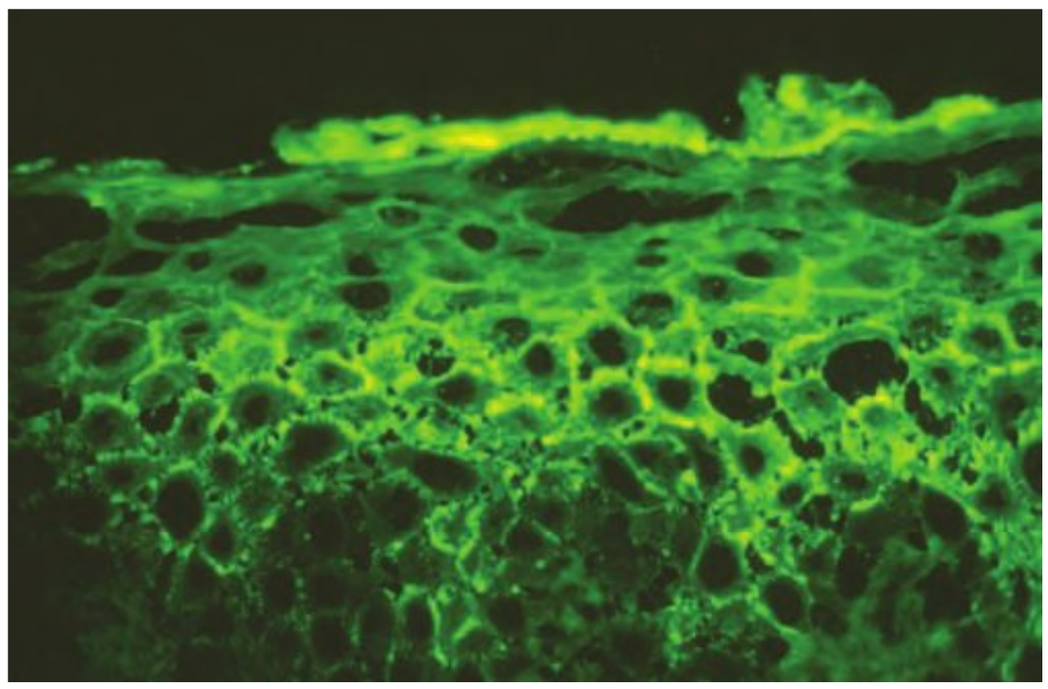

E

FIGURE 9-9. Pemphigus vulgaris. A: Multiple gingival erosions. (Courtesy of Kenneth Tsai, M.D., Ph.D.) B: The earliest changes consist of intercellular edema with eosinophilic spongiosis leading to loss of intercellular bridges in the lower epidermis. C: An intraepidermal acantholytic blister has a suprabasal cleavage plane. Acantholysis may extend into adnexal structures and stratum spinosum. D: The suprabasal blister contains acantholytic cells, neutrophils, and eosinophils. Note the dermal papillae lined by a single layer of basal keratinocytes, so-called villi. E: There is lacelike squamous intercellular space deposition of IgG in the lower epidermis (DIF).

drying. Because acantholytic keratinocytes are occasionally seen in various nonacantholytic vesiculobullous or pustular diseases as a result of secondary acantholysis, cytologic examination represents merely a preliminary test and should not supplant histologic examination.

Immunofluorescence (IF) Testing. The edge of a blister with intact surrounding normal skin, uninvolved skin adjacent to a blister, or adjacent erythematous skin should be supplied for study. The tissue may be snap-frozen or transported in Michel's medium. DIF testing is a very reliable and sensitive diagnostic test for pemphigus vulgaris, in that it demonstrates lacelike IgG in the squamous intercellular/cell surface areas in up to 95% of cases, including early cases and those with very few lesions, and in up to 100% of cases with active disease (Fig. 9-9E). It remains positive, often for many years after clinical disease has subsided. In late lesions, when acantholysis is well developed, the lacelike intercellular/cell surface pattern of IgG may become dotlike, paralleling electron microscopic findings and correlating with aggregation of desmosomes on the cell surface. Negative DIF findings when the patient is in

remission may be a good prognostic indicator (38). At this time, DIF testing is incorrectly thought by most to be free of false positives; however, false positives may occur. On occasion, it may be difficult to distinguish intercellular staining of pemphigus from nonspecific staining; for example, spongiotic dermatitis, psoriasis, bullous impetigo, and epidermis adjacent to ulcers secondary to a number of disorders may have squamous intercellular substance IgG due to the presence of serum in the intercellular substance. Often, IgM, IgA, fibrinogen, and albumin are present as well, indicating nonspecific trapping in the false-positive tests. Immunoperoxidase methods have achieved roughly the same sensitivity as the IF method, but they have not replaced IF testing as the prime diagnostic tool. For IIF testing, unfixed frozen sections of guinea pig esophagus, monkey esophagus, or normal human skin are used as substrate. In general, monkey esophagus is the best substrate for IIF tests. Circulating IgG autoantibody is demonstrated in the squamous intercellular substance in 80% to 90% of cases (39), and the titer correlates with disease activity. False-positive IIF tests occur. In a series of 1,500 patients with circulating pemphigus antibodies, approximately 1% had no evidence of clinical disease. Antibodies that mimic or may give *in vitro* deposition in stratified squamous epithelium in the absence of pemphigus have been reported in burns, penicillin allergy, toxic epidermal necrolysis (TEN), systemic lupus erythematosus (SLE), myasthenia gravis, bullous pemphigoid, cicatricial pemphigoid, and lichen planus and in patients with antibodies directed against blood groups A and B. Such antibodies are present in low titer and are thought to be nonpathogenic. Antidesmoglein autoantibodies are sometimes found in patients with no bullous disease. For example, they have been found in patients with silicosis (40) and in relatives of patients with pemphigus vulgaris (41).

Pathogenesis. Compelling evidence has accumulated that IgG autoantibodies against desmoglein 3 and desmoglein 1 are pathogenic and play a primary role in inducing the blister formation in pemphigus. Affinity-purified IgG from pemphigus vulgaris sera recognizes the extracellular domain of desmoglein 3 and causes suprabasal acantholysis when injected into neonatal mice (42). Furthermore, when anti-desmoglein 3 IgG from pemphigus vulgaris is immunoabsorbed with the extracellular domains of desmoglein 3, those sera no longer have the ability to cause blisters in neonatal mice (43). Although the pathogenic role of anti-desmoglein 3 autoantibodies in blister formation is assured, the exact sequence of events that occur after antibody binding is not totally understood. Conformational epitope mapping of desmoglein 3 in pemphigus vulgaris suggests that the amino terminal residue 1-161 is the target of autoantibodies (44). This segment is in the extracellular domain that is essential for cell-cell adhesion. One possibility is that these antibodies interfere directly with the adhesive interaction of desmogleins between cells by steric hindrance. Another possibility is that the disruption of cell-cell adhesion is mediated by signal transduction. Proteinases, likely induced by pemphigus antigen-antibody union, are thought to play an important role in acantholysis. Although complement fixation by pemphigus antibodies may promote acantholysis, acantholysis occurs in experimental systems in the absence of complement. The stimulus for the formation of autoantibodies is unknown, although drugs, viral infection, trauma, ionizing radiation, and PUVA therapy have been implicated because they have preceded the onset of pemphigus. Pemphigus vulgaris is rarely associated with internal cancer, Castleman's disease, thymoma, myasthenia gravis, localized scleroderma, Grave's disease, and SLE.

Ultrastructural Study. The intercellular cement substance, or glycocalyx, is partially or entirely lysed in lesions with early acantholysis. There is widening of the intercellular spaces with intact desmosomes. As the intercellular space is widened, there is separation of the two opposing attachment plaques of the desmosomes; thus, single attachment plaques, with adherent tonofilaments, are seen at the periphery of keratinocytes. As acantholysis progresses, the desmosomes gradually disappear and the keratinocytes develop numerous cytoplasmic processes that often interdigitate with one another. All of the early ultrastructural changes in pemphigus vulgaris are extracellular. Only subsequent to the dissolution of the desmosomes does retraction of the tonofilaments to the perinuclear area develop with ultimate degeneration of the acantholytic cells. The cohesion of the basal keratinocytes with the basement membrane zone is not affected in pemphigus vulgaris because of the preservation of structures connecting the basal keratinocytes with the dermis. Immunoelectron microscopy shows that the immunoglobulins are deposited on the surface of the keratinocytes in a discontinuous globular pattern in the extracellular domains of desmosomes (45).

Differential Diagnosis. In early blisters that are free of secondary changes, such as the degeneration or regeneration of epidermal cells, the histopathology of pemphigus vulgaris is characteristic. Important differential diagnoses include Hailey-Hailey disease and transient acantholytic dermatosis. Hailey-Hailey disease has full-thickness ("dilapidated brick wall") acantholysis, epidermal hyperplasia, and an impetiginized scale crust. The acantholysis does not extend down follicles as it does in pemphigus. Transient acantholytic dermatosis may exhibit small foci of intraepidermal acantholysis, but these are only a few rete wide in contrast to the uniform widespread acantholysis observed in biopsies of pemphigus vulgaris. Disorders such as Darier's disease that are characterized by acantholytic dyskeratosis are readily separated from pemphigus vulgaris by the presence of abnormal granular keratinocytes and parakeratotic cells, so-called corps ronds and corps grains. Although light microscopic examination of pemphigus lesions is important, positive DIF is the gold standard in diagnosis at this time and must be pursued in all cases in which pemphigus vulgaris is considered.

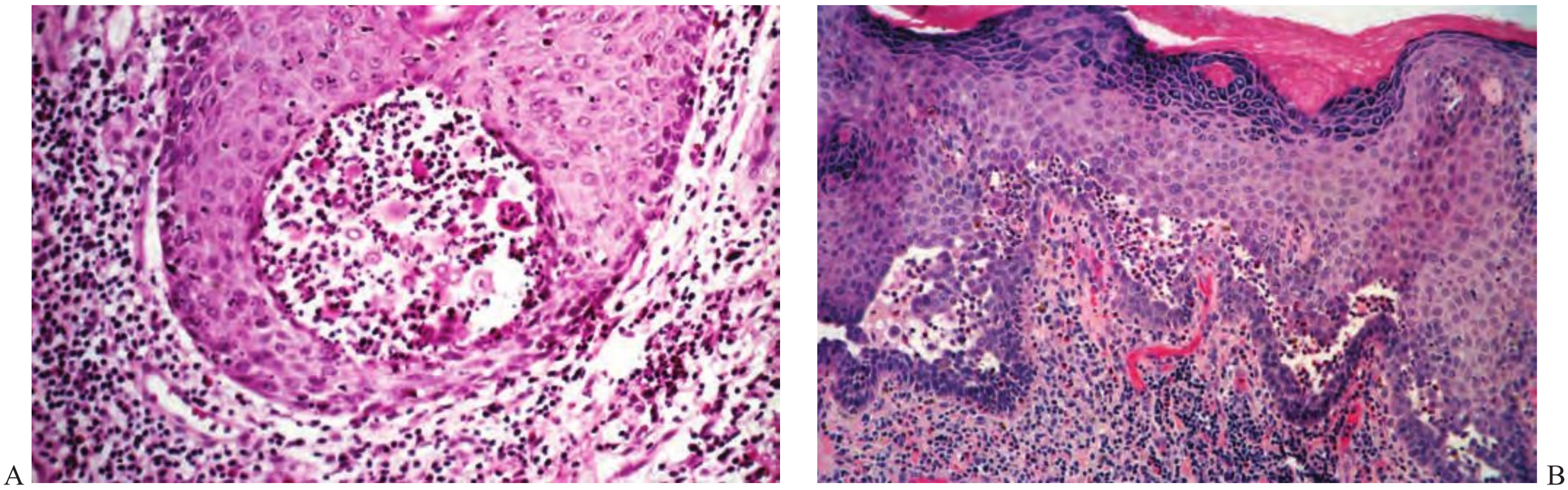


FIGURE 9-10. Pemphigus vegetans. A: Intraepidermal abscesses are composed of eosinophils and a few acantholytic keratinocytes. B: There is marked acanthosis and suprabasal clefts containing eosinophils.

Pemphigus Vegetans

Pemphigus vegetans is an uncommon variant of pemphigus vulgaris, comprising only 1% to 2% of cases (39). Historically, pemphigus vegetans has been divided into the Neumann type and Hallopeau type. In the more severe Neumann type, the disease begins and ends as pemphigus vulgaris, but many of the denuded areas heal with verrucous vegetations that may contain small pustules in early stages. The Hallopeau type is relatively benign, having pustules as the primary lesions instead of bullae. Their development is followed by the formation of gradually enlarging verrucous vegetations, especially in intertriginous areas.

Histopathology. In the Neumann type, the early lesions consist of bullae and denuded areas that have the same histologic picture as that of pemphigus vulgaris. As the lesions age, however, there is formation of villi and verrucous epidermal hyperplasia. Numerous eosinophils are present within the epidermis and dermis, producing both eosinophilic spongiosis and eosinophilic pustules (Fig. 9-10A). Acantholysis may not be present in older lesions. In the Hallopeau type, the early lesions consist of pustules arising on normal skin with acantholysis and formation of small clefts, with many in a suprabasal location. The clefts are filled with numerous eosinophils and degenerated acantholytic epidermal cells (Fig. 9-10B). Early lesions may reveal more eosinophilic abscesses than in the Neumann type. The subsequent verrucous lesions are histologically identical to the Neumann type.

IF Testing. DIF examination reveals squamous intercellular IgG in all reported cases.

Pathogenesis. Pemphigus vegetans is a variant of pemphigus vulgaris in which verrucous vegetations develop. It is unclear why such vegetations develop in some cases of pemphigus vulgaris and not in others. However, they tend to develop in areas of relative occlusion and maceration with subsequent bacterial infection, suggesting a response to superinfection.

Differential Diagnosis. The principal differential diagnosis is pyoderma vegetans, a condition often associated with inflammatory bowel disease, particularly ulcerative colitis. It can mimic pemphigus vegetans clinically and histologically (46). In pyoderma vegetans, neutrophils are more commonly found, and intraepidermal eosinophilic abscesses and acantholysis are rare. DIF is negative in pyoderma vegetans (46). Halogenoderma and blastomycosis-like pyoderma must be excluded as well (see Chapters 11 and 23).

Pemphigus Foliaceus

Usually developing in middle-aged individuals, pemphigus foliaceus may have a chronic generalized course or may rarely present as an exfoliative dermatitis. Patients may present with flaccid bullae that usually arise on an erythematous base or as scaly, crusted erosions without evident blisters (Fig. 9-11A). Because of their superficial location, the blisters break easily, leaving shallow erosions rather than the denuded areas seen in pemphigus vulgaris. Oral lesions do not occur. The Nikolsky sign is positive, and Tzanck preparation reveals acantholytic granular keratinocytes. Fogo selvagem (endemic pemphigus foliaceus) is clinically, histologically, and immunologically indistinguishable from pemphigus foliaceus (47). It develops in those who live or visit areas close to rivers and streams in Brazil, with the peak incidence being at the end of the rainy season. The cause of fogo selvagem is unknown, but substantial epidemiologic evidence suggests that it is precipitated by an environmental factor. A case control study found that farmers exposed to black fly (*Simulium pruinosum*) bites were much more likely to develop fogo selvagem than farmers who were not bitten (48). Sunlight may exacerbate the condition (49).

Histopathology. The earliest change consists of acantholysis in the upper epidermis, within or adjacent to the granular layer, leading to a subcorneal bulla in some instances (Fig. 9-11B, C). More commonly, enlargement of the cleft leads to detachment

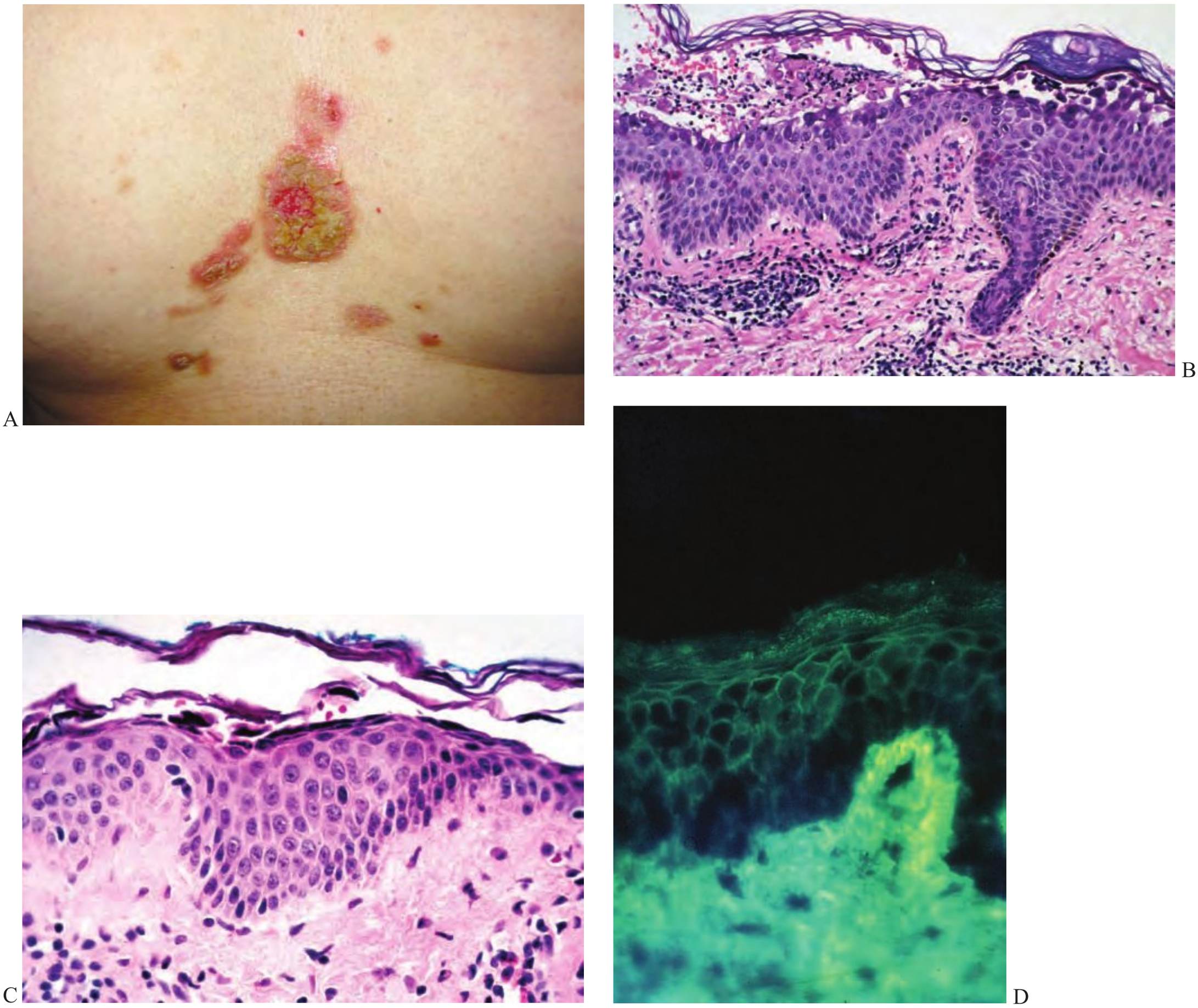


FIGURE 9-11. Pemphigus foliaceus. A: Erosions with thick crusts on the central chest. (Courtesy of Peter Lio, M.D.) B: A subcorneal blister with acantholytic cells and neutrophils in the cavity. C: In the setting of a subcorneal blister, these dyskeratotic acantholytic granular cells are diagnostic of pemphigus foliaceus. D: The intercellular IgG is deposited in the intercellular spaces throughout the epidermis. Rarely, as in this case, the IgG is present in greater quantity in the superficial layers.

of the stratum corneum without bulla being seen. The number of acantholytic keratinocytes is usually small, often requiring a careful search to identify them. Secondary clefts may develop, leading to detachment of the epidermis in its mid level. These clefts may extend to above the basal layer, rarely giving rise to limited areas of suprabasal separation. In the setting of a subcorneal blister, dyskeratotic granular keratinocytes are diagnostic for this disorder. Eosinophilic spongiosis may be prominent with intraepidermal eosinophilic pustules. Thus, the histologic features of pemphigus foliaceus may have three patterns: (a) eosinophilic spongiosis; (b) a subcorneal blister, often with few acantholytic keratinocytes; and (c) a subcorneal blister with dyskeratotic granular keratinocytes (Fig. 9-11C), diagnostic of this disorder. The character of the inflammatory infiltrate is variable and depends on the age of the lesion, whether a blister is present, whether the superficial portion of the epidermis has been detached, and whether there is impetiginization or necrosis of the blister roof.

IF Testing. DIF testing of perilesional skin is positive in the vast majority of cases. Two patterns of pemphigus antibody deposition have been described. In most cases, there is full-thickness squamous intercellular substance deposition of IgG. Rarely, IgG may be localized only to the superficial portion of the epidermis (Fig. 9-11D). IIF testing of serum reveals

squamous intercellular substance deposition of IgG in 80% to 90% of cases.

Pathogenesis. As in pemphigus vulgaris, the autoantibodies of pemphigus foliaceus are pathogenic. During the course of the disease, the antibody levels fluctuate and have some correlation with disease activity. The pemphigus foliaceus antigen, desmoglein 1, is expressed more intensely in the upper layers of the epidermis (35,36), which explains the superficial cleavage plane of pemphigus foliaceus. Interestingly, in staphylococcal scalded skin syndrome (SSSS), and its localized form bullous impetigo, the exfoliative exotoxin produced by *S. aureus* specifically binds and cleaves desmoglein 1, resulting in blister formation at identical levels of the epidermis as pemphigus foliaceus (50,51). In addition, desmoglein 1 is concentrated in the upper torso and is less prominent in the buccal mucosa, scalp, and lower torso, correlating with lesion distribution (52).

Ultrastructural Study. There is early loss of intercellular cement substance within the lower epidermis associated with a decrease in the number of desmosomes and formation of tortuous microvilli from the keratinocyte surface. However, acantholysis is most pronounced in the upper layers of the epidermis. In the mid epidermis, many keratinocytes have perinuclear arrangement of the tonofilaments and homogenization of the perinuclear tonofilament bundles as evidence of dyskeratosis. Marked dyskeratosis distinguishes pemphigus foliaceus from pemphigus vulgaris.

Differential Diagnosis. The differential diagnosis includes SSSS, impetigo, and subcorneal pustular dermatosis (SPD; Sneddon-Wilkinson disease). IF testing may be required to separate SSSS from pemphigus foliaceus, since a small number of acantholytic cells may be observed in SSSS. The lesions of pemphigus foliaceus may become impetiginized and secondarily altered, producing pustules as in impetigo and SPD. Pemphigus foliaceus contains more acantholytic keratinocytes than do the other two disorders, and pustules are the primary lesions in SPD. Because the lesions of pemphigus foliaceus may become superinfected, the finding of bacteria does not confirm a diagnosis of bullous impetigo; therefore, IF testing is critical. SPD usually produces large dome-shaped subcorneal pustules rather than the flaccid flat pustules of pemphigus foliaceus.

Pemphigus Erythematosus

Also known as *Senear-Usher syndrome*, pemphigus erythematosus is a variant of pemphigus foliaceus that gets its name from its lupus erythematosus–like clinical appearance, in which the erythematous plaques and patches are in a butterfly distribution. They may remain localized to this area or may become generalized. No oral lesions are observed.

Histopathology. The light microscopic features are identical to those of pemphigus foliaceus (Fig. 9-12). Interface dermatitis may also be apparent in rare cases, making distinction from lupus erythematosus difficult.

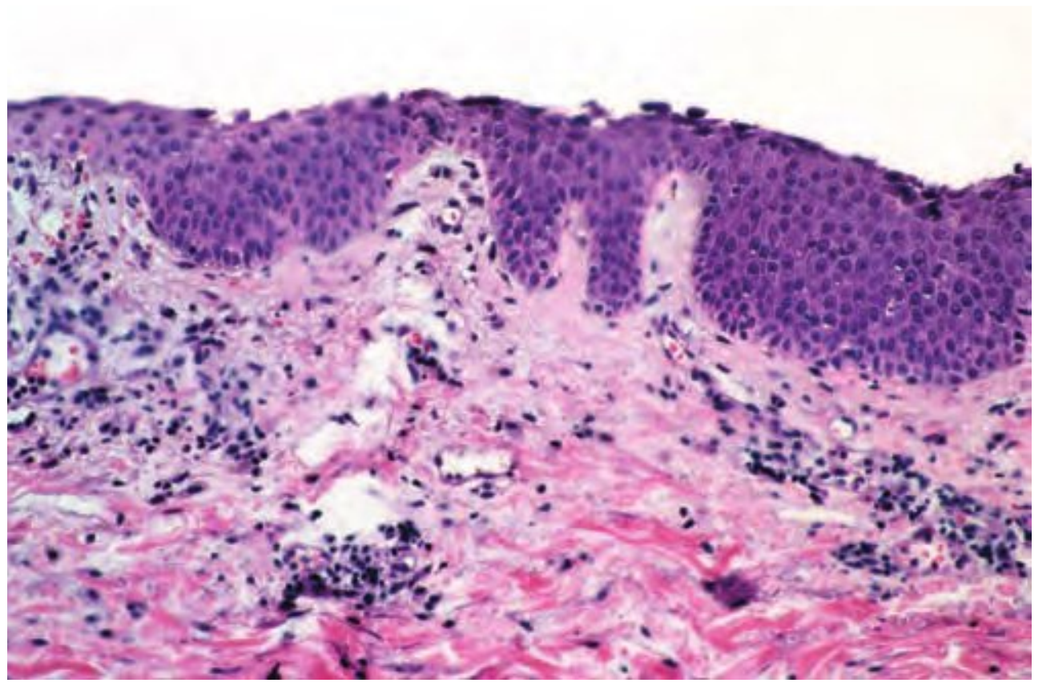


FIGURE 9-12. Pemphigus erythematosus. The histologic appearances are identical to those of pemphigus foliaceus. In this biopsy, the roof of the blister is eroded, which is a frequent event, leaving a diminished but acantholytic granular layer.

IF Testing. DIF testing of perilesional skin reveals squamous intercellular substance deposition of IgG in >75% of cases and granular deposition of IgM and IgG (i.e., a positive lupus band test) at the dermal–epidermal junction. IIF study using monkey esophagus as substrate reveals squamous intercellular substance deposition of IgG in 80% of cases. Antinuclear antibodies are observed in 30% to 80% of cases.

Ultrastructural Study. Pemphigus erythematosus is identical to pemphigus foliaceus in its ultrastructural alterations.

Differential Diagnosis. The differential diagnosis is the same as in pemphigus foliaceus. The presence of interface dermatitis in some cases leads to confusion with lupus erythematosus and PNP. Subcorneal acantholysis is not a feature of lupus erythematosus.

Pemphigus Herpetiformis

Pemphigus herpetiformis combines the clinical features of dermatitis herpetiformis with the immunologic and histologic features of pemphigus, usually the foliaceus type (53). This variant deserves recognition only because of its clinical presentation. Patients present with pruritic, erythematous, vesicular, or papular lesions, often in herpetiform pattern. Mucous membranes are uncommonly involved.

Histopathology. There is eosinophilic spongiosis with or without acantholysis. Variable numbers of neutrophils may be present, leading to neutrophilic spongiosis or subcorneal pustules with both eosinophils and neutrophils.

IF Testing. Because the clinical presentation and histologic findings are often atypical, the most reliable basis for diagnosis of pemphigus herpetiformis is immunopathology. DIF on perilesional skin shows the deposition of IgG on the surface of keratinocytes primarily in the upper epidermis (53). IIF has demonstrated circulating IgG antiepithelial cell surface

autoantibodies in most patients with pemphigus herpetiformis. Most cases have circulating antibodies to desmoglein I, the pemphigus foliaceus antigen. A few cases with antibodies to the pemphigus vulgaris antigen, desmoglein 3, have been reported (54).

Drug-induced Pemphigus

Although immunologic features identical to those of idiopathic pemphigus are reported in most cases of drug-induced pemphigus (55), evidence indicates that some drugs may induce acantholysis without production of antibodies (56). The offending drugs, most frequently penicillamine, captopril, and penicillin derivatives, often contain sulfhydryl groups (57). The earliest clinical manifestation is that of a nonspecific morbilliform or urticarial eruption. In penicillamine-induced pemphigus, the eruption is characteristic and has been labeled "toxic prepemphigus rash" (56). Subsequently, the characteristic lesions of pemphigus develop. On cessation of drug therapy, the rash regresses in those patients who do NOT have pemphigus antibodies in contrast to those patients with pemphigus antibodies, in whom the rash frequently persists. This latter subset has the clinical waxing and waning course of pemphigus.

Histopathology. The findings in the early eruption are nonspecific, consisting of spongiosis, parakeratosis, and a variable dermal infiltrate. Well-developed lesions are essentially identical to those of pemphigus foliaceus or pemphigus vulgaris. Eosinophilic spongiosis may be prominent.

IF Testing. DIF testing is positive in approximately 90% of patients with drug-induced pemphigus (56). IIF study of serum reveals circulating squamous intercellular substance IgG antibodies in 70% of cases. The antibody titers are usually low and do not appear to correlate with the severity of disease.

Pathogenesis. In those cases in which there is antibody production with subsequent acantholysis, the pathogenesis appears to be identical to that of idiopathic pemphigus. Because the pemphigus antigens have disulfide bonds, sulfhydryl-containing drugs may bind to them. These drugs have been shown to localize in high concentration in the epidermis. Therefore, the drug appears to directly affect the keratinocyte adhesion molecules, interferes with their function, and causes subsequent acantholysis, explaining those cases of drug-induced pemphigus that do not have pemphigus antibodies.

IgA Pemphigus

IgA pemphigus is a pruritic pustular eruption characterized by squamous intercellular IgA deposits and intraepidermal neutrophils. It occurs in primarily middle-aged and elderly individuals, but several cases have been described in children (58,61). The clinical findings are similar to those in pemphigus foliaceus or SPD. There are flaccid pustules that arise on an erythematous base. They often appear in an annular arrangement. The most common sites of involvement are the axilla and groin, but trunk, proximal extremities, and lower abdomen can also be involved. Mucous membrane involvement is rare. Mild leukocytosis, eosinophilia, and IgA paraproteinemia may be present (59).

IgA pemphigus is a clinically heterogeneous group reflecting differences in the autoantigens involved (60). In general, patients may develop one of two types: an SPD type or an intraepidermal neutrophilic (IEN) dermatosis type (58,61,62). The presence of cases with overlap features supports the notion that this is one disease with variable expression.

Histopathology. Two patterns are observed that parallel the two clinical presentations (Fig. 9-13). In the SPD type, there are subcorneal vesicopustules or pustules with minimal acantholysis. In the IEN type, there are intraepidermal vesicopustules or pustules containing small to moderate numbers of neutrophils. One case of IgA pemphigus, which

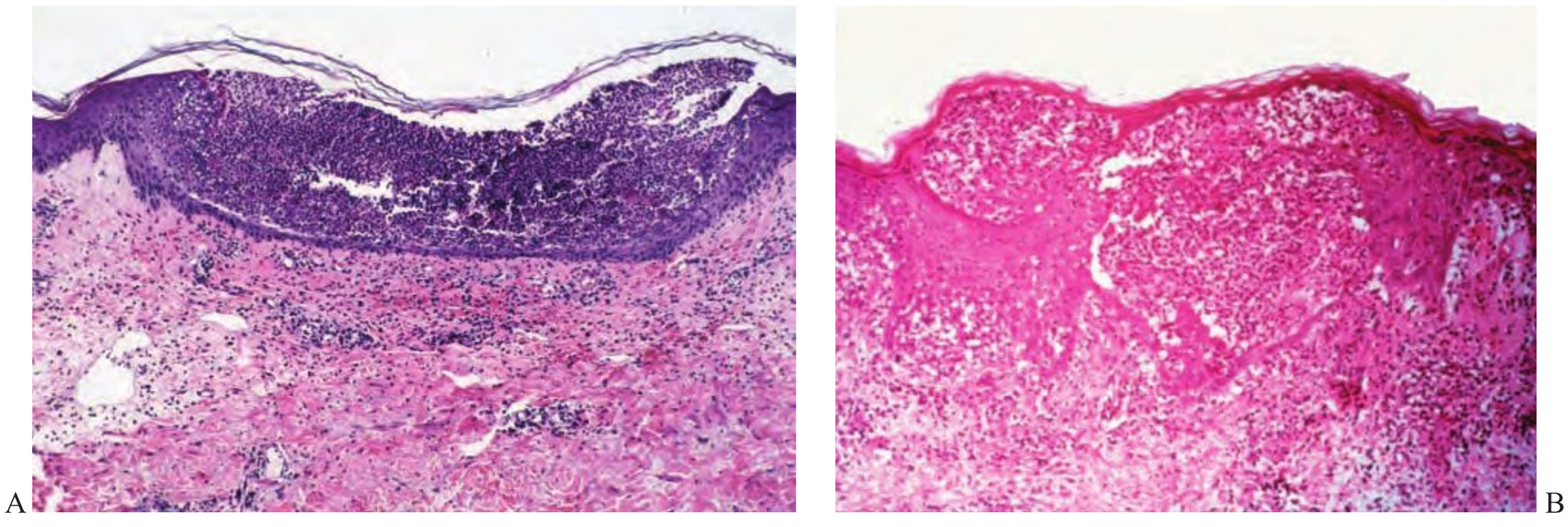


FIGURE 9-13. IgA pemphigus. A: In the SPD type, intraepidermal pustule with numerous neutrophils is seen subcorneally. B: In the IEN type, the neutrophils are in the suprabasal and stratum spinosum.

resembled pemphigus foliaceus without neutrophil infiltration, has been described (63).

IF Testing. DIF testing reveals IgA deposition in the squamous intercellular substance throughout the epidermis with increased intensity in the upper layers in some cases of the subcorneal pustular type. Complement and other immunoglobulins are usually not present (58). However, some cases may have both IgG and IgA present and thus may make a specific diagnosis difficult (i.e., pemphigus vulgaris vs. IgA pemphigus) unless evaluation for antigen specificity is available (64). IIF results are positive in <50% of reported cases. In the SPD type, IgA autoantibodies have been shown to recognize desmocollin 1 (65). In the IEN type, the autoantigens remain to be identified; the antibodies have been variously characterized as reacting to desmoglein 1 or desmoglein 3 in a subset of patients (59,60,66).

Differential Diagnosis. The SPD variant is identical to Sneddon-Wilkinson disease. Indeed, many cases reported as Sneddon-Wilkinson disease, in which IF testing was not performed, likely represent the SPD variant of IgA pemphigus. Pustular psoriasis, bullous impetigo, and pemphigus vulgaris are the principal differential diagnoses. Pustular psoriasis may not be distinguishable on routine light microscopic study; therefore, IF testing may be required.

Paraneoplastic Autoimmune Multiorgan Syndrome: Paraneoplastic Pemphigus

Paraneoplastic autoimmune multiorgan syndrome (PAMS), first described as paraneoplastic pemphigus (PNP), is an autoimmune vesiculobullous and erosive mucocutaneous disease associated with an underlying malignancy. The most commonly associated neoplasms include non-Hodgkin's lymphoma (42%), chronic lymphocytic leukemia (29%), Castleman's disease (10%), thymoma (6%), spindle cell sarcoma (6%), and Waldenström's macroglobulinemia (6%) (67). The age of onset is variable, although the majority of patients are between 45 and 70 years of age.

Cutaneous lesions are quite polymorphic. The most consistent clinical feature of PNP is the presence of intractable stomatitis, which presents as erosions and ulcerations that affect all surfaces of the oropharynx and characteristically extend onto the lips mimicking Stevens-Johnson syndrome (SJS). Multiple organ systems may be involved, and the high rate of mortality often stems from constrictive bronchiolitis obliterans. Autoantibodies are deposited in the kidneys, bladder, muscle, heart, lung, mucous membrane, and skin. The extent and diversity of the clinical presentations and immunopathologic mechanisms have led to the suggestion that PNP, a disease of epithelial adhesion, represents one manifestation of PAMS, which is a heterogeneous autoimmune syndrome (68). At least six different clinical variants are recognized: bullous pemphigoid–like, cicatricial pemphigoid–like, pemphigus-like, erythema multiforme (EM)-like, graft-versus-host disease (GVHD)-like, and lichen planus–like (68–73).

Histopathology. The histologic features are variable, depending on the various clinical presentations. The lesions show a unique combination of EM-like, lichen planus–like, pemphigus vulgaris–like, and pemphigoid-like features. The principal findings are suprabasal acantholysis with basal apoptosis in association with vacuolar interface dermatitis (EM-like) with or without lichenoid inflammation (lichen planus–like) (Fig. 9-14A, B) (74). PNP may present exclusively with lichenoid interface dermatitis in the absence of acantholysis (75). In pemphigoid-like lesions, a subepidermal blister is present.

IF Testing. DIF testing of perilesional skin and mucosa reveals IgG in the squamous intercellular substance in concert with immune reactant deposition at the dermal–epidermal junction (Fig. 9-14C). At the dermal–epidermal junction, granular deposition of complement is noted most frequently (70). Linear deposition of complement, IgG and IgM, as well as granular deposition of complement and IgG have been identified in one case each (69). When present, basement membrane zone staining helps to distinguish PNP from other forms of pemphigus in which basement membrane zone immunoglobulin and complement deposition are generally not present (76). Whereas circulating PNP antibodies bind to squamous keratinocytes in routine substrates in the majority of cases, the antibodies bind to rat bladder epithelium in all cases.

Pathogenesis. Patients with PNP develop IgG autoantibodies against multiple antigens (Table 9-5). It appears that all the members of the plakin family, as well as desmogleins, have been reported to be targeted by IgG autoantibodies in PNP. While antidesmoglein antibodies play a role in inducing the loss of cellular adhesion of keratinocytes and blister formation, the pathophysiologic relevance of the antiplakin autoantibodies is unclear. In addition to the humoral autoimmunity, mounting evidence suggests that cytotoxic T cells play a prominent role. Cases with clinical features of PNP in the absence of detectable autoantibodies have been reported (77). In those patients, the affected areas have high levels of $CD8^+$ cytotoxic T cells, which mediate damage, including interface dermatitis with dyskeratosis (78). IL-6, which activates $CD8^+$ T cells and $CD56^+$ natural killer (NK) cells, has been reported to be significantly increased in the blood of PNP patients (79). The association of PNP with bronchiolitis obliterans provides additional evidence that cytotoxic T cells may play a critical role in PNP.

SUBEPIDERMAL BULLOUS DISEASE

Subepidermal bullous diseases are disorders in which a blister forms along the dermal–epidermal junction. This group of diseases includes conditions with different clinical presentations, histologic findings, and pathogenesis. Both inherited and acquired alterations in key adhesion proteins at or in the dermal–epidermal junction result in blister formation. In the subgroup of autoimmune subepidermal bullous diseases, major target antigens bound by autoantibodies from patients have

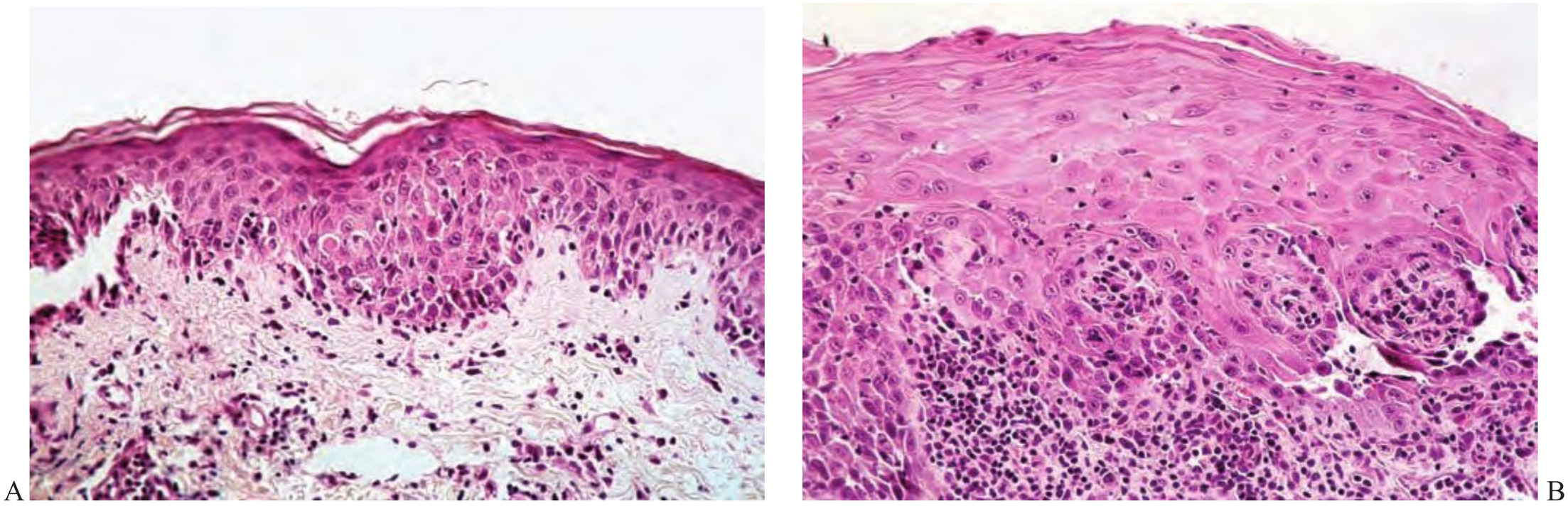


FIGURE 9-14. Paraneoplastic pemphigus. A: EM-like pattern. There is a cell-poor interface dermatitis with apoptosis of keratinocytes. There are also pemphigus vulgaris–like changes with a suprabasal blister. B: Lichen planus–like pattern. There is a cell-rich lichenoid dermatitis associated with a suprabasal blister. C: There are both intercellular and basement membrane staining with IgG by DIF.

been characterized (Table 9-6). Importantly, some of the genes encoding these autoantigens harbor mutations responsible for various mechanobullous diseases (i.e., epidermolysis bullosa [EB]). To understand subepidermal bullous disease, it is essential to have some knowledge of the epidermal basement membrane zone and the various target proteins associated with it (Fig. 9-15).

Proceeding from the epidermis to the dermis, there are four distinct structural components of the epidermal basement membrane:

TABLE 9-6 Targets Common to Autoimmune and Inherited Blistering Diseases*

Protein target	Structural target	Autoimmune disease	Genetic disease
BPAg1 (BP230)	HD	BP	None identified
BPAg2 (BP180, type XVII collagen)	HD-anchoring filament complexes	BP, PG, CP, LABD	GABEB
α6β4 integrin, Subunit β4	HD-anchoring filament complexes	Ocular CP	Junctional EB with pyloric atresia
Laminin 5 (epiligrin)	Lamina lucida–lamina densa interface	Antiepiligrin CP	Junctional EB–Herlitz
P200	Lower lamina lucida	Anti-p200 pemphigoid	None identified
Type VII collagen	Anchoring fibrils	EBA	Dystrophic EB
		Bullous SLE	

BPAg, bullous pemphigoid antigen; HD, hemidesmosome; BP, bullous pemphigoid; PG, pemphigoid gestationis; CP, cicatricial pemphigoid; LABD, linear IgA bullous dermatosis; GABEB, generalized atrophic benign epidermolysis bullosa; EB, epidermolysis bullosa; SLE, systemic lupus erythematosus.
*The targets are bound by antibody in autoimmune disease; however, in genetic disease, the target compounds are absent or aberrantly synthesized.

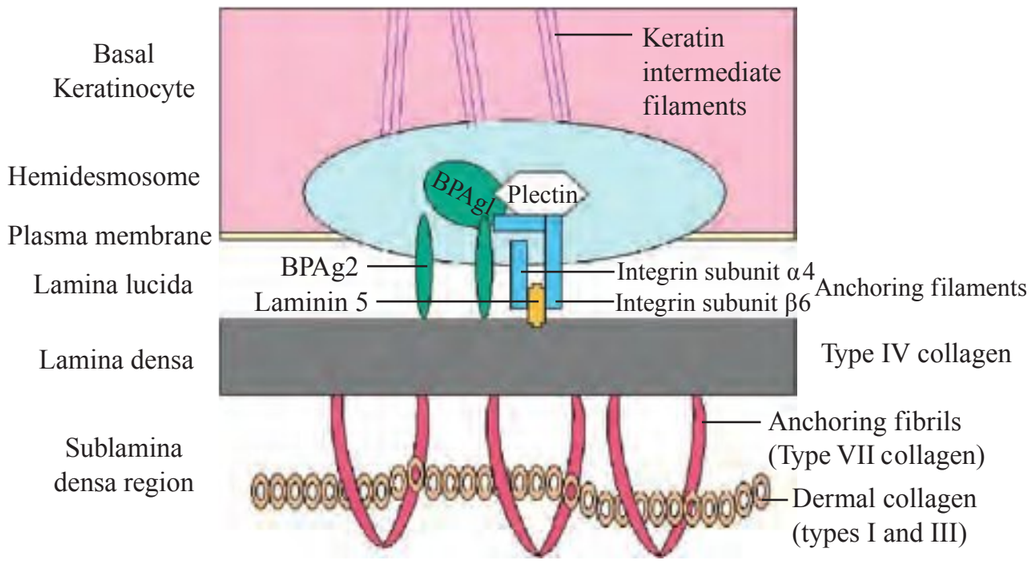


FIGURE 9-15. Schematic model of the dermal–epidermal junction. Along the basal surface of the keratinocytes, keratin intermediate filaments attach to hemidesmosomes on the basal plasma membrane. Major intracellular components of hemidesmosomes include the bullous pemphigoid antigen (BPAg1) and plectin. The transmembrane components of the hemidesmosomes include $\alpha 6\beta 4$ integrin and the bullous pemphigoid antigen (BPAg2). Both extend to the lamina lucida at the site where anchoring filaments are located. The anchoring filaments straddle the lamina lucida between hemidesmosomes and the lamina densa. Multiple antigens are associated with the lamina lucida, including laminin 5 (epiligrin). The lamina densa is an electron-dense layer that lies parallel to and contiguous to the lamina lucida. The main component is type IV collagen. In the sublamina densa region, the lamina densa and the overlying epidermis are tethered to the papillary dermis by anchoring fibrils. Type VII collagen is the major component of anchoring fibrils.

- The intermediate filaments, hemidesmosomal plaques, and plasma membranes of the basal keratinocytes.
- The lamina lucida, which contains delicate anchoring filaments connecting hemidesmosomes in basal keratinocytes to the underlying lamina densa.
- The lamina densa, which provides the basement membrane with much of its strength. The main component is type IV collagen.
- The sublaminar densa region, which contains anchoring fibrils (type VII collagen), anchoring plaques, and filamentous proteins of the papillary dermis.

Along the basal surface of the keratinocytes at the dermal–epidermal junction, keratin intermediate filaments (keratin 5 and 14) attach to hemidesmosomes. Major intracellular components of hemidesmosomes include the 230-kD bullous pemphigoid antigen (BPAg1) and plectin. The transmembrane components of the hemidesmosomes include $\alpha_6\beta_4$ integrin and the 180-kD bullous pemphigoid antigen (BPAg2) or collagen XVII (80). Both extend to the lamina lucida at the site where anchoring filaments are located. The anchoring filaments straddle the lamina lucida between hemidesmosomes and the lamina densa. Antibodies to the BPAg1 are of the most common autoimmune subepidermal bullous disease, bullous pemphigoid. BPAg2 is targeted by autoantibodies from patients with bullous pemphigoid, pemphigoid gestationis, cicatricial pemphigoid, and a subgroup of linear IgA bullous dermatosis (81–83). Some patients with generalized atrophic benign EB have a congenital deficiency of BPAg2. Mutation of the β_4 subunit of $\alpha_6\beta_4$ integrin leads to junctional EB associated with pyloric atresia (84). Patients with one form of ocular cicatricial pemphigoid have autoantibodies directed against the β_4 subunit (85).

The lamina lucida is the weakest link in the dermal–epidermal junction, and it is the cleavage plane in the salt-split skin test. Multiple antigens are associated with the lamina lucida, particularly the anchoring filaments. The antigens include laminin 5, laminin 6, uncein, nidogen, and P200 (86,87). Autoantibodies to epiligrin, the α_3 subunit of laminin 5, result in antiepiligrin of cicatricial pemphigoid. Nonsense mutation of the laminin 5 gene is associated with the Herlitz subtype of junctional EB (88).

The lamina densa is an electron-dense layer that lies parallel to and contiguous to the lamina lucida. The main component is type IV collagen, which is thought to provide the basement membrane with much of its strength. Other antigenic components are laminin 1, nidogen, and heparan sulfate proteoglycans.

In the sublamina densa region, the lamina densa and the overlying epidermis are tethered to the papillary dermis by anchoring fibrils, which is a series of looping elements along the underside of the lamina densa that serve as attachment sites for collagens in the papillary dermis. Type VII collagen is the major component of anchoring fibrils. Autoantibodies against type VII collagen have been identified in EBA, bullous SLE, and some variants of linear IgA disease (IgA-mediated EBA) (89). Nonsense mutation of the type VII collagen gene (COL7A1) is associated with dystrophic EB.

Bullous Pemphigoid

First described in 1953 by Lever, bullous pemphigoid affects primarily elderly patients with large tense bullae arising on urticarial erythematous bases or on nonerythematous skin (Fig. 9-16A) (90). In contrast to pemphigus, the Nikolsky sign is negative. The lesions involve the trunk, the extremities, and the intertriginous areas, with the oral mucosa involved in about one third of cases. Bullous pemphigoid may start as a nonspecific eruption suggestive of urticaria or dermatitis, which can persist for weeks or months. Rarely, bullous pemphigoid may present as erythroderma.

Histopathology. In early lesions, papillary dermal edema in combination with a cell-poor or cell-rich perivascular lymphocytic and eosinophilic infiltrate is present (Fig. 9-16B). The blister arises at the dermal–epidermal junction (90). In the cell-rich pattern, which correlates clinically with blisters arising on erythematous skin (Fig. 9-16C), eosinophilic papillary abscesses may develop with numerous perivascular and interstitial eosinophils intermingled with lymphocytes and neutrophils in the superficial and deep dermis. Early lesions may have the histologic features of eosinophilic cellulitis (Well's syndrome). Eosinophilic spongiosis may occur. The cell-poor pattern is observed

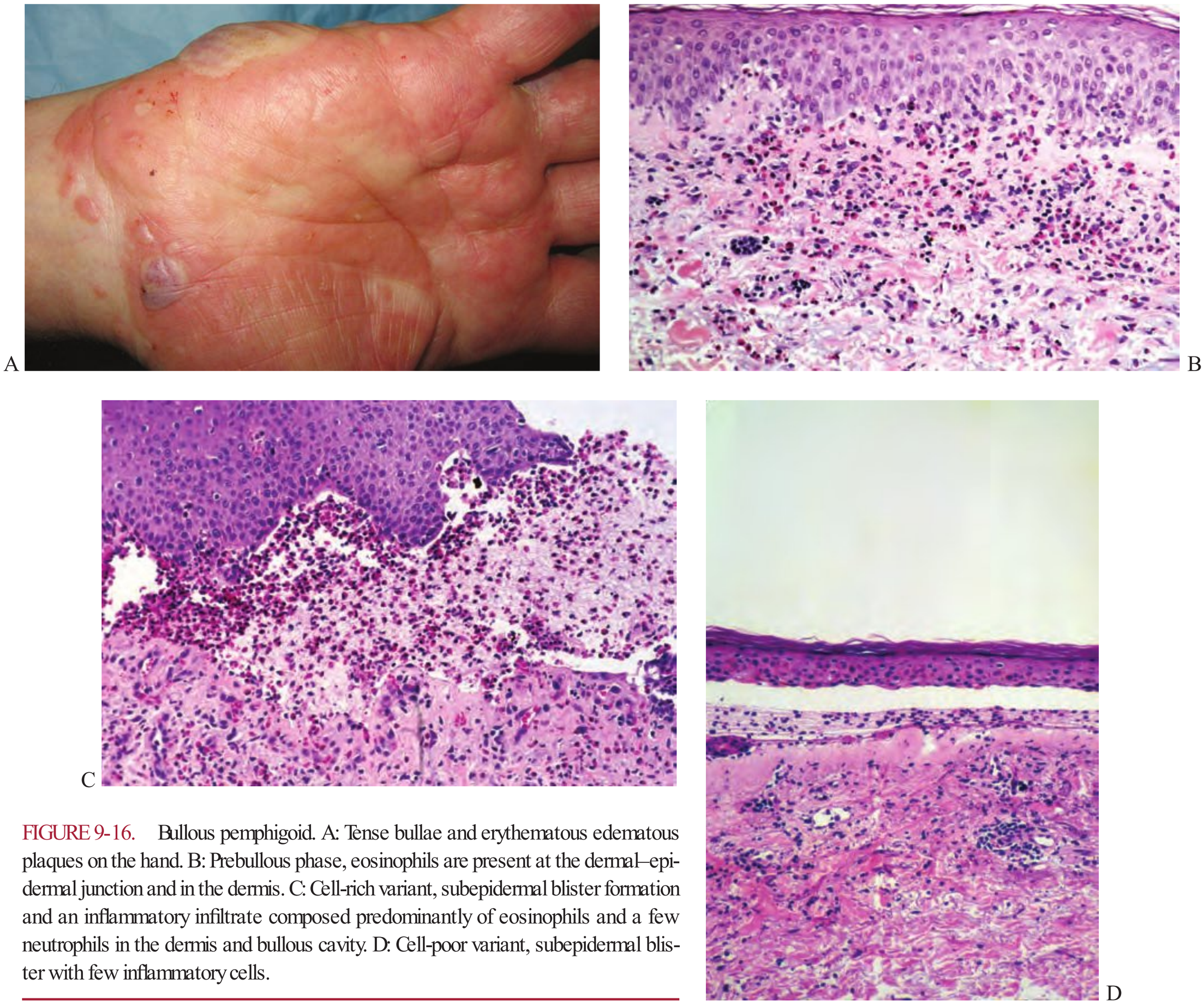


FIGURE 9-16. Bullous pemphigoid. A: Tense bullae and erythematous edematous plaques on the hand. B: Prebullous phase, eosinophils are present at the dermal–epidermal junction and in the dermis. C: Cell-rich variant, subepidermal blister formation and an inflammatory infiltrate composed predominantly of eosinophils and a few neutrophils in the dermis and bullous cavity. D: Cell-poor variant, subepidermal blister with few inflammatory cells.

when blisters develop on relatively normal skin (Fig. 9-16D), in which there is usually a scant perivascular lymphocytic infiltrate with few eosinophils, some scattered throughout the dermis and others near the epidermis. The blister contains few inflammatory cells. Epithelial migration and regeneration may result in an intraepidermal split in older blisters. Similar to pemphigus vegetans, a hyperplasia of the epidermis, subepidermal bullae, and accumulations of eosinophils and lymphocytes may be seen.

IF Testing. DIF testing of perilesional skin has shown linear C3 deposition (Fig. 9-17A and Table 9-4) at the dermal–epidermal junction in virtually 100% of cases and IgG in 65% to 95%. IIF studies reveal circulating anti–basement membrane zone IgG antibodies in 70% to 80%. Similarly deposited IgA and IgM are observed in about 25% of cases. No correlation exists between the antibody titer and the clinical severity of the disease. The IgG is located within the lamina lucida, where it appears to be bound specifically to the hemidesmosomes.

Salt-split skin IF studies are an important diagnostic tool. The technique was first developed in 1984, in which normal human skin was used as a substrate and patient serum as a test (indirect salt-split skin technique) (91). Incubation of normal or patient skin in 1 mol/L NaCl results in a split of the epidermis in the lamina lucida. Pemphigoid antibodies bind solely to the lower aspect of the basal keratinocytes (the blister roof) in 80% of cases; in about 20% of cases, the antibodies bind to both the lower basal keratinocytes (the roof) and the superior aspect of the dermis (the blister floor) (Table 9-7). It must be made clear that the antigenic specificity of the IgG binding to the base or roof is unknown. The IgG cannot be said to be directly against BPAg 1, 2, or other antigen. As time goes on, it is likely that it will be found that a number of cases have different antigenic specificity and should be labeled as different diseases.

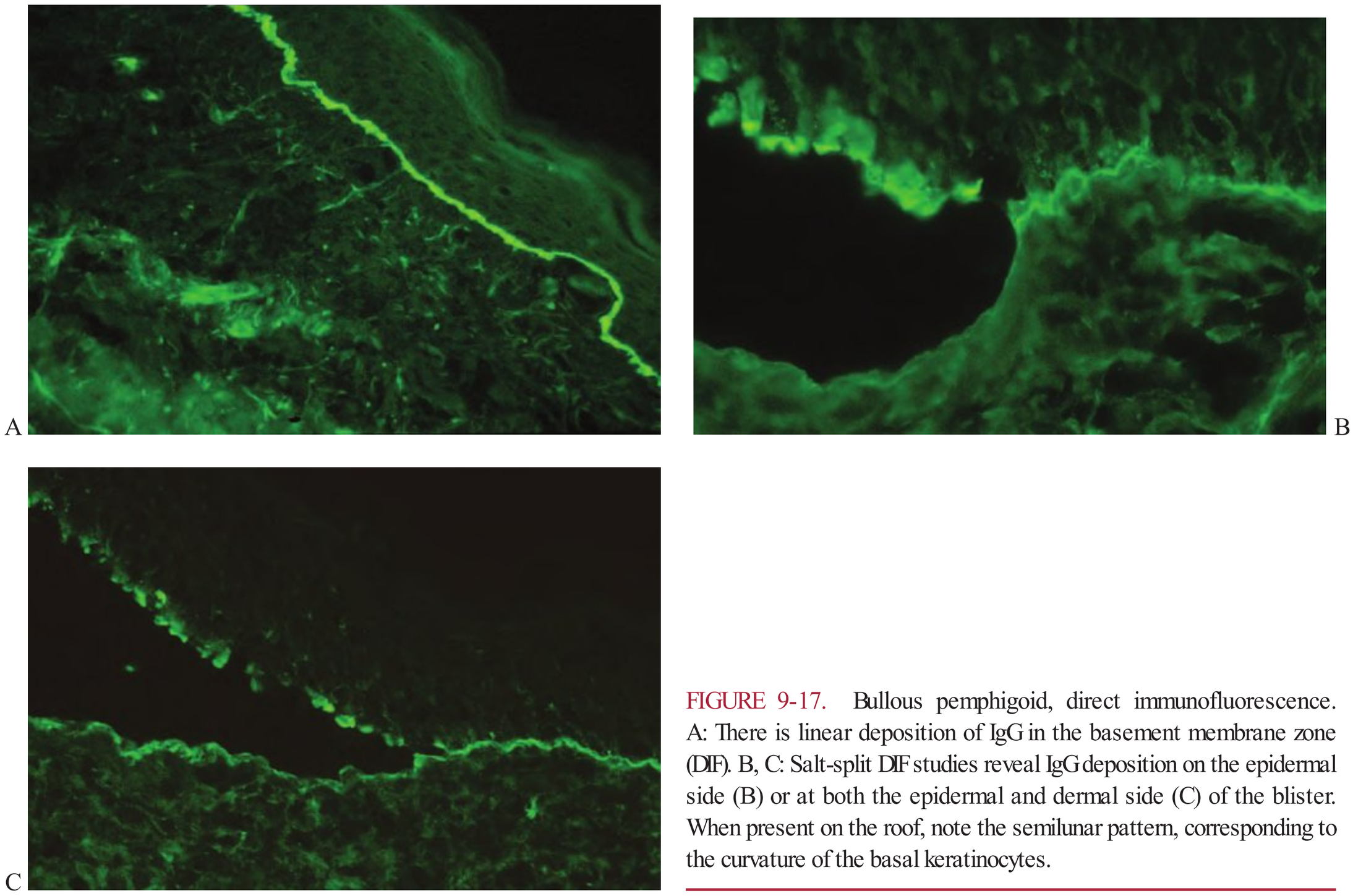


FIGURE 9-17. Bullous pemphigoid, direct immunofluorescence. A: There is linear deposition of IgG in the basement membrane zone (DIF). B, C: Salt-split DIF studies reveal IgG deposition on the epidermal side (B) or at both the epidermal and dermal side (C) of the blister. When present on the roof, note the semilunar pattern, corresponding to the curvature of the basal keratinocytes.

Perilesional skin submitted for DIF examination may also be salt split (direct salt-split skin technique) (92,93). When this technique is used in pemphigoid, IgG is present on the roof or on the roof and the floor (Fig. 9-17B, C). Localization to only the dermal base is characteristic for EBA (see also Fig. 9-20C, page 262) and anti-P200 pemphigoid.

Pathogenesis. Pemphigoid antibodies bind to two antigens, a 230-kD protein (BPAg1) and a second 180-kD protein (BPAg2) (94,95). The principal antigen, BPAg1, is associated with the cytoplasmic attachment site of hemidesmosomes and is largely within the basal keratinocyte. BPAg2 is transmembrane collagen that extends through the lamina lucida. The distribution of these antigens within the skin correlates with lesion location. A blistering disorder clinically similar to pemphigoid has antibodies that recognize a 105-kD protein synthesized by both keratinocytes and fibroblasts (96,97).

Given the known data, a sequence of pathogenetic events may be proposed. Pemphigoid antibodies bind with BPAg1 and BPAg2, activating the complement cascade. The anaphylatoxins, C3a and C4a, are elaborated, activating mast cells. Mast cell activation may be augmented by pemphigoid IgG4, which has homocytotropic properties for mast cells. The mast

TABLE 9-7 Salt-Split Skin Immunofluorescence Results (Indirect Method)

Roof only	Roof and base	Base only
Bullous pemphigoid (80%) herpes gestationis	Bullous pemphigoid (~15%) herpes gestationis	Anti-p200 pemphigoid
Cicatricial pemphigoid	Cicatricial pemphigoid	Antiepiligrin cicatricial pemphigoid EBA Bullous SLE Porphyria cutanea tarda
LAD	LAD	IgA EBA

EBA, epidermolysis bullosa acquisita; SLE, systemic lupus erythematosus; LAD, linear IgA dermatosis.

cells degranulate, releasing a variety of inflammatory mediators, including eosinophil chemotactic factor, neutrophil chemotactic factor, leukotriene B4, proteolytic enzymes, and eosinophil stimulating factor. Eosinophil infiltration ensues with subsequent degranulation and release of major basic protein and other proteolytic enzymes. The vessels are hyperpermeable, probably because of the release of vascular permeability factor by keratinocytes (98). Lamina lucida separation develops from injury of basal keratinocytes, disruption of hemidesmosomes, and proteolysis (99). The role of infiltrating lymphocytes that are predominantly $CD4^+$ is unclear. IL-1 and IL-2, as well as INF-γ, have been identified in blister fluids (100).

Ultrastructural Study. Pemphigoid antibodies bind within the lamina lucida, in particular, to the hemidesmosomes. The blister arises within the lamina lucida in both the cell-poor and cell-rich lesions. In cell-poor lesions, there is disruption of the anchoring filaments without lamina densa fragmentation. In contrast, inflammatory lesions of bullous pemphigoid with numerous eosinophils and mononuclear cells in the dermis result in greater local destruction or blister formation in the lamina lucida with fragmentation of the lamina densa.

Clinical Variants

Drug-associated Bullous Pemphigoid

Furosemide, phenacetin, and various penicillins have been associated with bullous pemphigoid (101). It is possible that drug hypersensitivity may not be a cause of pemphigoid, but that the patients had subclinical pemphigoid with a superimposed drug eruption, which produces damage to the dermal–epidermal junction. The combination hits the threshold of basal damage necessary to produce subepidermal blister formation.

Pemphigoid Localized to the Lower Extremities

Some patients, usually women, present with tense bullae localized to the lower extremities. Histologically, these reveal a cell-poor pattern and have positive IF findings less frequently (50%) than routine bullous pemphigoid. At least in one instance, it has been shown that the IgG is directed against BPAg1 (102). The exact nosology of the DIF-negative cases is unclear. In our estimation, they likely represent subepidermal blisters in ischemic lower extremities secondary to chronic stasis dermatitis or other causes of chronic ischemic dermatitis such as diabetic microangiopathy, due to the high metabolic activity of basal keratinocytes and inhibition of hemidesmosome formation and maintenance. The hemidesmosome turnover rate is quite rapid, 4 to 6 hours.

Vesicular Pemphigoid

Vesicular pemphigoid is worthy of designation only because of its clinical similarity to dermatitis herpetiformis with small grouped blisters, which may lead to misdiagnosis.

Differential Diagnosis. Histologic differentiation of bullous pemphigoid from pemphigus vulgaris is not difficult because of the difference in cleavage planes and the mechanism of blister formation. Bullous pemphigoid is frequently indistinguishable from herpes gestationis; however, herpes gestationis may have greater quantities of infiltrating neutrophils and more basal keratinocyte damage. EBA (inflammatory variant) may have greater numbers of infiltrating neutrophils, but differentiation may be impossible on routine hematoxylin and eosin stain. Dermatitis herpetiformis is characterized by a subepidermal infiltrate of neutrophils with papillary microabscesses. Similarly, linear IgA dermatosis (LAD) is characterized, in the vast majority of cases, by a neutrophil-rich infiltrate. EM is an interface dermatitis characterized by basal vasculopathy, basal apoptosis, and a tagging lymphohistiocytic infiltrate along the dermal–epidermal junction. Diabetic blisters are noninflammatory, subepidermal in location, and often associated with fibrosis. Some patients with pemphigoid may present only with a superficial perivascular lymphoeosinophilic infiltrate without migration of eosinophils to the dermal–epidermal junction. This histologic reaction pattern is most commonly associated with morbilliform drug eruptions. Rarely, the changes of eosinophilic cellulitis (Well's syndrome) may also herald the presence of pemphigoid. Bullous drug eruptions may present with subepidermal vesicles and eosinophils, and later lesions of dermatitis herpetiformis may contain eosinophils. IF study is necessary to make a specific diagnosis.

Cicatricial Pemphigoid

Cicatricial pemphigoid is a bullous disorder characterized by a chronic course, scarring, and predilection for mucosal surfaces. Most patients are elderly, and there is a male predilection. Oral blisters are present in virtually all cases, and ocular involvement is observed in 75%, with cutaneous involvement in 33%. The oral lesions are usually small blisters that subsequently erode and ulcerate. Other mucosal surfaces, including the larynx, esophagus, nose, vulva, and anus, may also be involved. Scarring is less evident in these locations than in the conjunctiva, where erythema, without blisters and ulceration, and subsequent scarring are the rule. Unilateral blindness occurs in up to 20% of cases. The cutaneous lesions are of two types: (a) an extensive eruption of bullae that heals without scarring, and (b) areas of erythema mainly on the face and scalp in which bullae erupt intermittently followed by atrophy and scarring. Both types of lesions may be present in the same patient. In the Brunsting-Perry variant, there are no mucosal lesions, but rather one to several circumscribed erythematous patches on which recurrent crops of blisters appear with atrophic scarring. The patches are usually confined to the head and neck area. Other clinical variants include a widespread nonscarring bullous eruption in which scarring lesions develop only on the head and widespread bullae that heal with atrophic scars.

Histopathology. In cutaneous lesions, a subepidermal blister develops that may extend down adnexa (Fig. 9-18). Neutrophils, histiocytes, and lymphocytes predominate in the inflammatory infiltrate. Eosinophils may or may not be

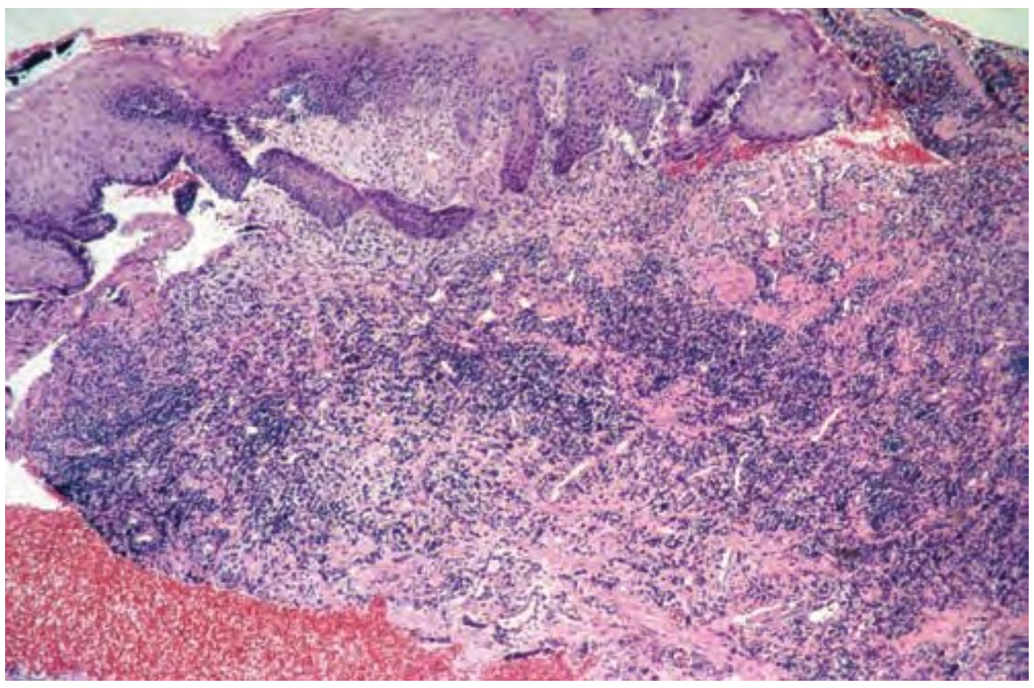


FIGURE 9-18. Cicatricial pemphigoid. There is fibrosis beneath the subepidermal blister containing fibrin. There is often a cell-rich lichenoid infiltrate.

numerous. Lamellar fibrosis beneath the epidermis is a hallmark but may not be present in the initial lesions. Mucosal lesions generally have a lichenoid lymphocytic infiltrate in which neutrophils or eosinophils or both may be present. The changes are often nonspecific in both mucosal and cutaneous lesions, but the above features should lead to consideration of cicatricial pemphigoid.

IF Testing. DIF studies reveal linear IgG and C3 in lesional and perilesional skin in approximately 80% of cases. In most cases, IgG and C3 are present, occasionally in association with IgA or IgM. Rarely, only C3 is present. In that past, cases labeled as cicatricial pemphigoid were found to have only linear IgA deposits, these cases are now best considered linear IgA bullous dermatosis.

IIF testing of serum yields variable results depending on the substrate used (monkey esophagus, guinea pig esophagus, normal human skin, salt-split skin). It appears that circulating antibodies in this disorder may be more readily demonstrated when salt-split human skin is used as substrate, in which IgG may be localized only to the roof or, as in the antiepiligrin subgroup, to the base of the induced separation (see Table 9-7).

The difference in clinical presentation, as well as the localization of the immunoreactants, may be explained by differing antigenic specificity of the antibodies. The known autoantigens include the following: (a) epiligrin (103), also known as *laminin 5*, which is associated with the disease previously termed *antiepiligrin cicatricial pemphigoid*; (b) β4 subunit of the α6β4 integrin, which is predominantly associated with ocular cicatricial pemphigoid (104); and (c) BPAg2 (105) and BPAg1 (95). It is noteworthy that autoantibodies from patients with cicatricial pemphigoid tend to target the C-terminus of BPAg2, whereas those from patients with BP, pemphigoid gestationis, and lamina lucida type linear IgA bullous dermatosis typically target the NC16A domain of BPAg2. All of these antigens occur within the lamina lucida, with epiligrin present in the lower lamina lucida. This may explain the localization of the antibody to the artifactually created blister base in salt-split skin preparations (see Table 9-7). Currently, cicatricial pemphigoid is best considered not one disease but several diseases with a similar clinical phenotype of scarring, predilection for mucosal and conjunctival surfaces, and subepidermal bullae. Many cases in the literature labeled cicatricial pemphigoid without adequate immunologic study may be better classified as linear IgA disease or EBA involving principally mucosal surfaces.

Ultrastructural Study. Electron microscopic examination revealed in two studies that the oral and cutaneous lesions possess an intact basement membrane zone at the base of the blister. In another study of both the oral and cutaneous lesions, the basement membrane zone was destroyed.

Herpes Gestationis

Herpes gestationis is a blistering disorder that usually develops during the second to third trimester in pregnant women. It is estimated to occur in 1 in 50,000 pregnancies. Intensely pruritic, urticarial lesions usually develop on the abdomen, with subsequent involvement of the extremities, hands, and feet. They usually progress to tense vesicles and bullae, some herpetiform. The disorder may recur with subsequent pregnancies, menstrual periods, or the use of birth control pills. The course for the mother is benign. There was a debate concerning the possibility of an increased incidence and risk of fetal morbidity and mortality. However, data obtained in the 1990s indicates that no such risk can be confirmed (106). There is an association with prematurity and small-for-gestational-age weights (107). The infant may be born with a mild, transient, vesiculobullous eruption secondary to transplacental transfer of the mediating antibody.

Histopathology. In zones of erythema and edema, there is a perivascular infiltrate composed of lymphocytes and eosinophils. There is marked papillary dermal edema. As well, there may be spongiosis, which may be eosinophilic in type. Focal necrosis of the basal keratinocytes, which has been emphasized by some authors, leads to a subepidermal blister (Fig. 9-19).

IF Testing. DIF testing reveals linear deposition of C3 in perilesional skin in virtually all patients. IgG is similarly deposited in 30% to 40%. Immunoelectron microscopic study has revealed that IgG and C3 reside within the lamina lucida. Using routine IIF studies of serum, it is uncommon to demonstrate circulating anti–squamous basement membrane zone antibody. Using *in vitro* complement fixation, a circulating anti–basement membrane zone IgG is demonstrable in most cases. At this point in time, the use of the label *HG factor* for these IgG antibodies is of historical interest only. The BPAg2 is the principal antigen, but the BPAg1 is recognized in some patients as well (108).



FIGURE 9-19. Herpes gestationis. A subepidermal blister with eosinophils and neutrophils. The epidermis shows focal spongiosis.

Ultrastructural Study. The epidermis at the periphery of bullae shows significant damage, most pronounced in basal keratinocytes, with resultant complete or partial necrosis of epidermal cells. Despite the fact that basal keratinocytes show severe damage, the basal cell plasma membrane and the lamina densa are well preserved and are present at the floor of the blister. The hemidesmosomes may be intact in some areas.

VESICULOBULLOUS DERMATOSES WITH AUTOIMMUNITY TO TYPE VII COLLAGEN

Epidermolysis Bullosa Acquisita

Classically, EBA is a noninherited disorder of acquired skin fragility. This presentation of EBA was the only one recognized until later. Blisters develop on noninflammatory bases with a predilection for acral areas. Scarring and milia formation ensue. A characteristic nail dystrophy and alopecia are noted. This presentation is associated with malignant lymphoma, amyloidosis, and colitis or enteritis. Some patients with EBA may have significant involvement of oral and conjunctival mucosa and therefore may be *cicatricial pemphigoid–like*. However, acral lesions are prominent and nail dystrophy may be noted In this type, biopsy from mucosal lesions reveals inflammatory, subepidermal bullae with scarring and milia similar to cicatricial pemphigoid.

In 1984, five EBA patients with clinical and histologic features of bullous pemphigoid were described (109). They had generalized pruritic, erythematous macules and papules on which bullae arose. There was less tendency for the lesions to develop acrally and greater involvement of flexural surfaces than in the previously described forms of EBA. At presentation, neither scarring nor milia were discerned; however, delicate scars developed later at the sites of blister formation.

Histopathology. The *bullous pemphigoid–like* presentation described above is the most common form of EBA. The subepidermal blisters are inflammatory. The predominant infiltrating cells are lymphocytes and neutrophils in perivascular and focal interstitial array. Eosinophils are present in variable numbers (Fig. 9-20A). In the classic form, the subepidermal blisters are noninflammatory (Fig. 9-20B); fibrosis and milia formation are often present.

IF Testing. Examination of perilesional skin using DIF reveals linear deposition of complement at the basement membrane zone in the vast majority of cases. IgG is by far the most common immunoglobulin found, but IgM and IgA may be present as well. Increasing numbers of immunoglobulin subclasses noted at the dermal–epidermal junction favor a diagnosis of EBA over bullous pemphigoid. The presence of linear C3 at the dermal–epidermal junction alone favors bullous pemphigoid over EBA. However, use of routine DIF cannot reliably distinguish between bullous pemphigoid and EBA. IIF reveals circulating anti–basement membrane zone antibodies in up to 50%.

The use of the salt-split skin technique leads to the appropriate diagnosis in most cases (110). The antibodies in EBA have specificity for the globular carboxyl terminus of type VII collagen and are deposited beneath the lamina densa. Therefore, on salt-split skin studies, IgG is on the floor and not on the roof of the split (Fig. 9-20C).

Bullous Systemic Lupus Erythematosus

Vesicles and bullae may develop in patients with SLE. In contrast to dermatitis herpetiformis, the lesions are not symmetrical and do not have a predilection for extensor surfaces of arms, elbows, or scalp; they may be photodistributed or widespread and are not pruritic. These patients rarely have classic lesions of discoid, systemic, or subacute cutaneous lupus erythematosus when they develop blisters. In cases from the literature, the vast majority of patients have had a previous history of lupus erythematosus, and most authors have required definitive American Rheumatologic Association criteria before making the diagnosis in those patients with bullous lesions. Uncommonly, patients (who later developed other stigmata of lupus) have presented with a blistering eruption but without previous signs or symptoms of connective tissue disease. Bullous lupus erythematosus is most common in women, particularly black women. Most of these cases were exquisitely sensitive to dapsone therapy, with rapid involution of the lesions. No correlation with clinical activity of lupus erythematosus was apparent. Some patients with EBA will progress to SLE. (See also Chapter 10.)

Histopathology. Three histologic patterns have been identified in such lesions. The first is striking basal layer vacuolization with subsequent blister formation. The second is vasculitis with subepidermal blister and pustule formation (Fig. 9-21A, B). The third and most common is a dermatitis herpetiformis–like histologic pattern. Approximately 25% of

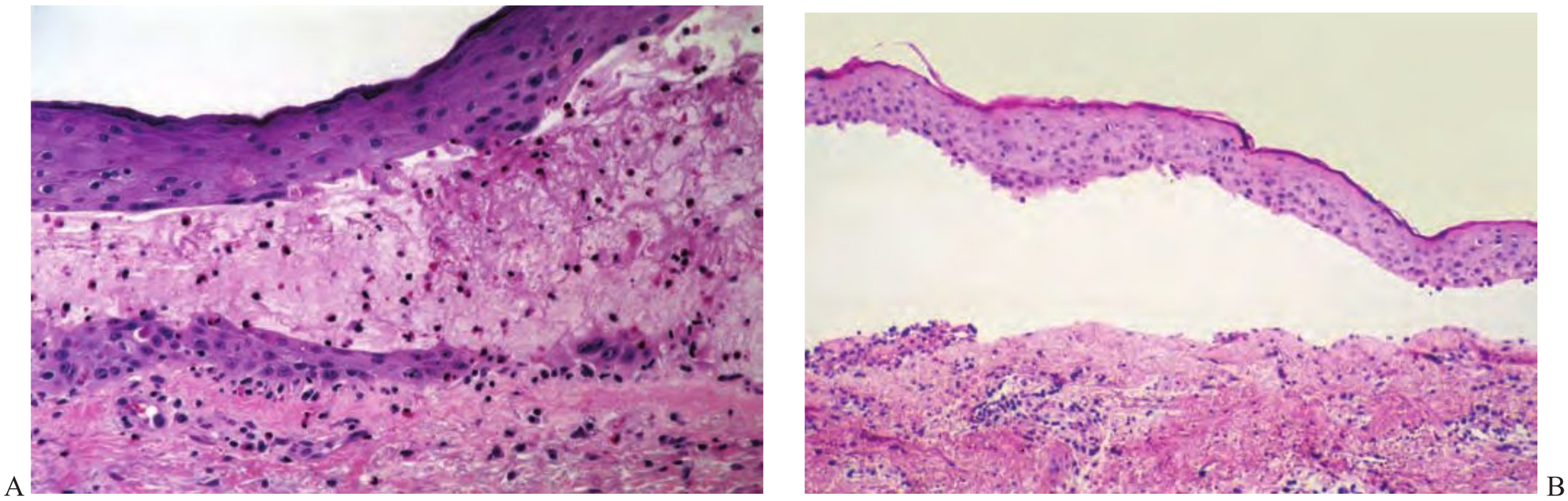


FIGURE 9-20. Epidermolysis bullosa acquisita. A: In the inflammatory type, some neutrophils and eosinophils are in the blister cavity and the superficial dermis. The blister is partially re-epithelialized. B: Non-inflammatory type with a subepidermal blister. C: Salt-split DIF reveals linear deposition of IgG in the blister base.

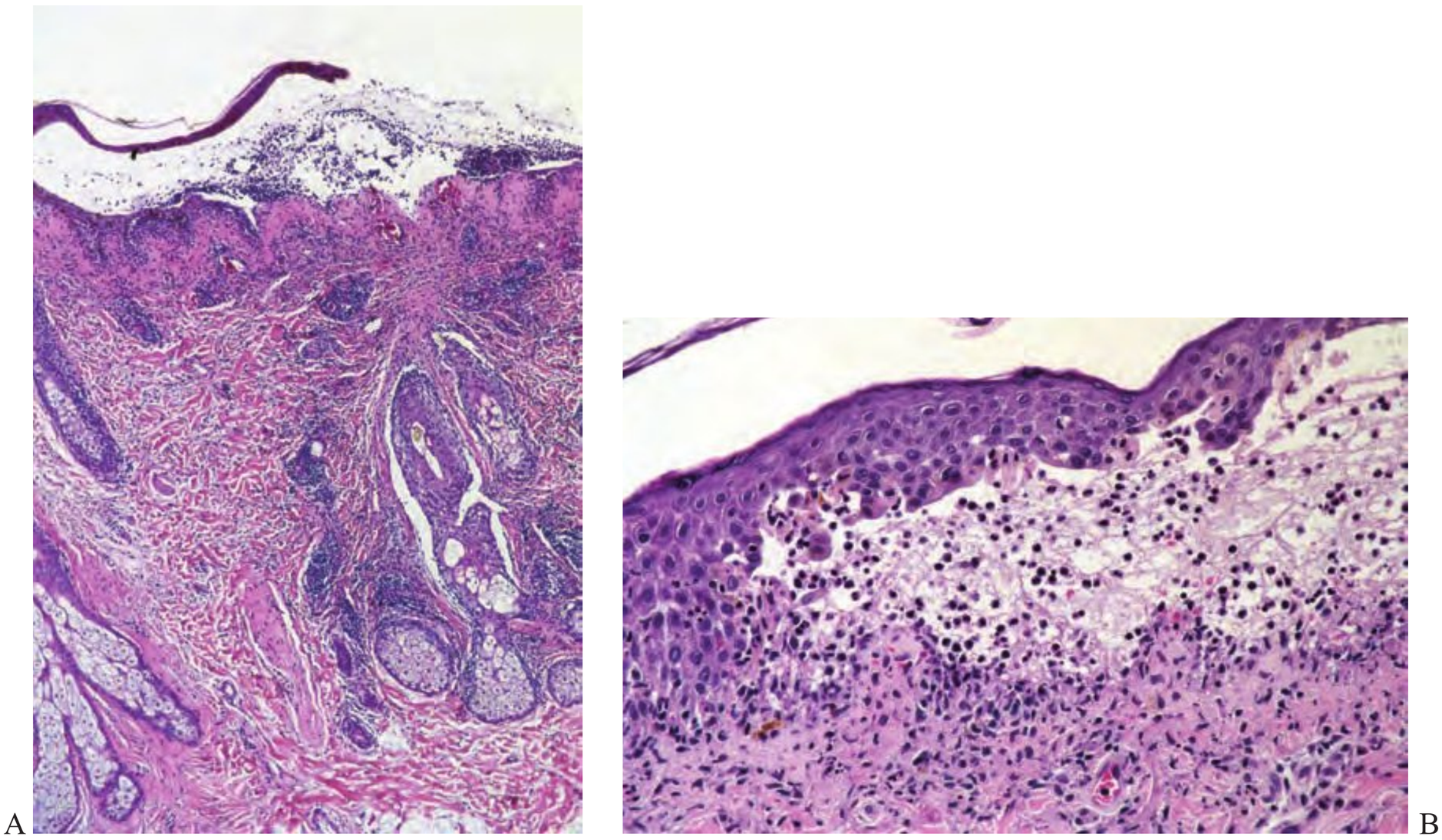


FIGURE 9-21. Bullous systemic lupus erythematosus. A: There is a subepidermal blister and perifollicular inflammatory cell infiltrate. B: The neutrophils are predominant in the blister and superficial dermis.

cases are said to have a small-vessel, neutrophil-rich leukocytoclastic vasculitis beneath the blister. Histologic features more routinely identified with lupus erythematosus are not present. Another histologic finding that is not emphasized in most case reports is the presence of dermal mucin and hyaluronic acid as defined by Alcian blue stain at pH 2.5 (111). The frequency of mucin deposition is unknown.

IF Testing. In all reported cases, IgG and C3 are deposited at the epidermal basement membrane zone. The pattern was linear in more than 50% and was referred to as "granular bandlike" in approximately 25%. IgM and IgA were present in approximately 50% and 60% of cases, respectively. The conflicting pattern of immune reactant deposition is difficult to explain. In these reports, the pattern varies from a "thick band" to a "fine ribbon-like" or "tubular" pattern. The ribbon-like or linear pattern represents antibodies that are bound to rigid, anatomically compartmentalized antigens such as in bullous pemphigoid or EBA. In general, granular patterns represent deposition of circulating immune complexes *in situ* or *in situ* binding of antigen and antibody in non-compartmentalized zones. Therefore, perhaps some of the cases represent tubular or linear deposition obscured by confluent granular bands (positive lupus band test). IIF study of serum rarely reveals circulating anti–squamous basement membrane zone antibodies that are detected against type VII collagen. It should be noted, however, that salt-split skin preparations might be a more sensitive substrate than whole-skin mounts.

A salt-split skin preparation using patient serum reveals localization to the split floor, as in EBA (Table 9-7). As well, Western immunoblot reveals binding to 290-kD or 145-kD dermal proteins, which are components of type VII collagen. However, antibodies to type VII collagen are not present in all cases.

Ultrastructural Study. Immunoelectron microscopic examination reveals electron-dense deposits of IgG at the lower edge of the basal lamina and immediately subjacent dermis in an identical location to the antibody in EBA.

Anti-p200 Pemphigoid

Patients with anti-p200 pemphigoid usually present with a generalized eruption composed of urticarial papules and plaques in combination with tense blisters, closely mimicking BP. In Asian patients, an association with coexisting psoriasis has been reported (86). Mucosal involvement has been observed (87). Since the original description in 1996, about 30 cases of anti-p200 pemphigoid have been reported (112). The real incidence of this disease is probably much higher. It is important to recognize the entity because it shares similar histologic features and immunofluorescence pattern with EBA. In contrast to EB, anti-p200 pemphigoid runs a self-limiting course and rapidly resolves without scarring under immunosuppressive treatment. Unless further immunoblot studies are performed, anti-p200 pemphigoid is indistinguishable from EBA.

P200 is a glycoprotein localized to the lower lamina of the basement membrane zone. Although the exact identity of the adhesion molecule remains unknown, it has been shown to be distinct from all known autoantigens of the dermal–epidermal junction.

Histopathology. The lesions are characterized by subepidermal blistering and a superficial inflammatory infiltrate, usually of neutrophils but occasionally containing significant numbers of eosinophils. Microabscess formation in the papillary dermis adjacent to the blister cavity, as well as eosinophilic or neutrophilic spongiosis, may be observed. A moderate to dense inflammatory infiltrate in the upper dermis is usually present (113).

IF Testing. DIF shows linear IgG and C3 deposition at the basement membrane zone, whereas IIF study of patient sera demonstrates IgG labeling exclusively on the dermal side (floor) of salt-split human skin. By indirect immunogold electron microscopy, immunoreactants are localized to the lower lamina lucida.

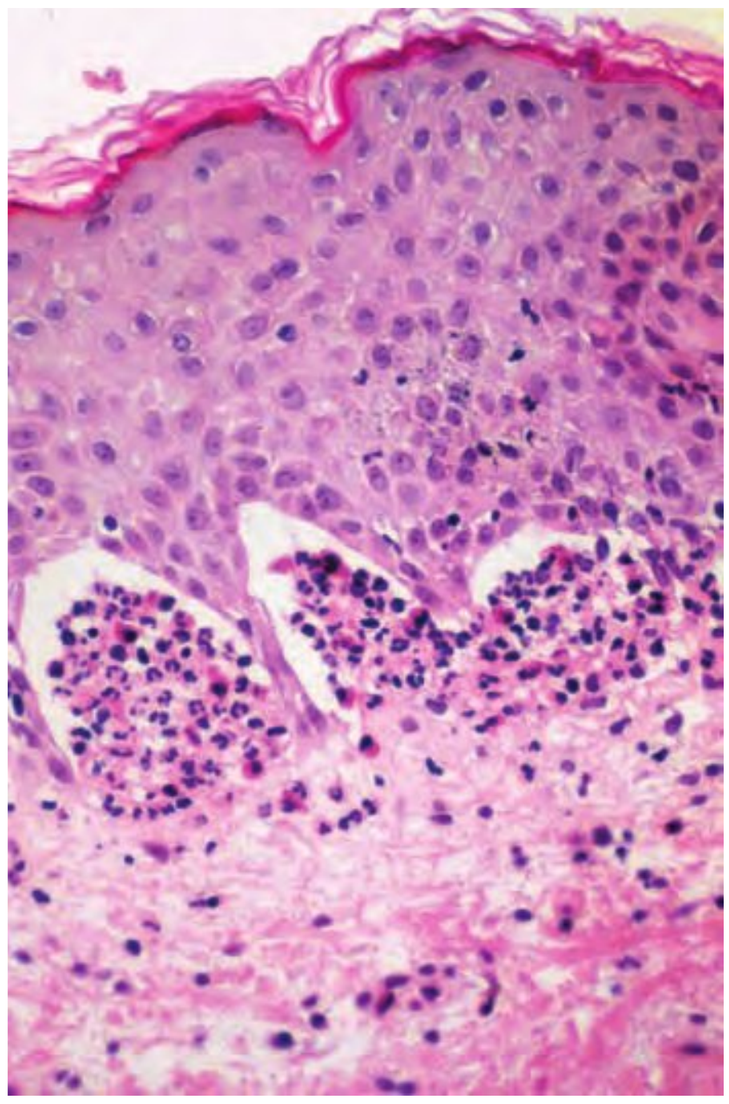
SUBEPIDERMAL IgA-MEDIATED VESICULOBULLOUS DERMATOSES

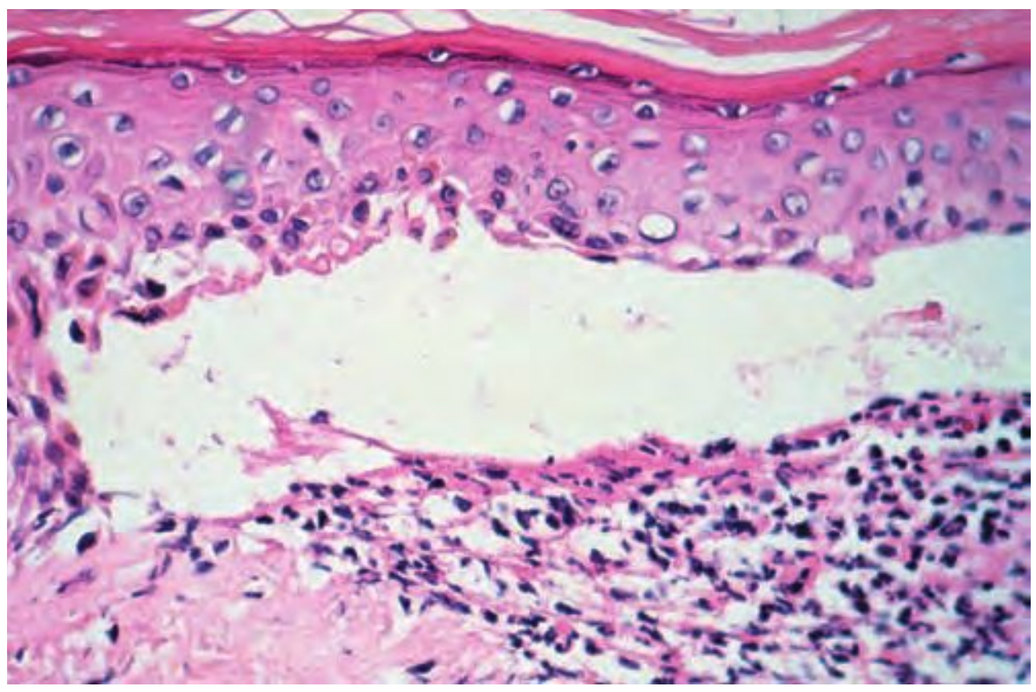
Dermatitis Herpetiformis

Dermatitis herpetiformis is an intensely pruritic, chronic recurrent dermatitis that has a slight male predilection. The lesions usually develop in young to middle-aged adults as symmetrical grouped erythematous papulovesicles, vesicles, or crusts (Fig. 9-22A). Oral lesions are absent. The elbows, knees, buttocks, scapula, and scalp are commonly involved. There is a high incidence (about 90%) of gluten-sensitive enteropathy and an increased but rare risk of lymphoma (114). Dermatitis herpetiformis in association with SLE has also been reported.

Histopathology. The typical histologic features are best observed in erythematous skin adjacent to early blisters. In these zones, neutrophils accumulate at the tips of dermal papillae. With an increase in size to microabscesses, a significant admixture of eosinophils may be noted. As microabscesses form, a separation develops between the tips of the dermal papillae and the overlying epidermis; thus, the early blisters are multiloculated (Fig. 9-22B). The presence of fibrin in the papillae may give them a bluish appearance. Within 1 to 2 days, the rete ridges lose their attachment to the dermis, and the blisters then become unilocular (Fig. 9-22C) and clinically apparent. At this time, the characteristic papillary microabscesses may be observed at the blister periphery. For this reason, the inclusion of perivesicular skin in the biopsy specimen is of


A


B


C

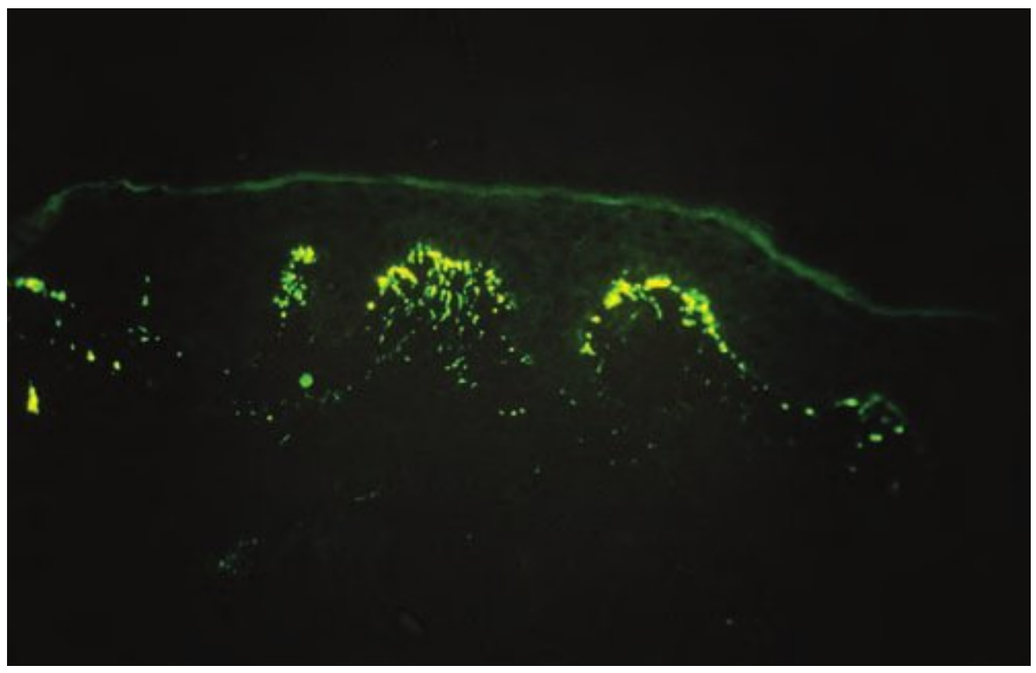

D

FIGURE 9-22. Dermatitis herpetiformis. A: Erythematous excoriated papulovesicles on the extensor forearms. (Courtesy of Kenneth Tsai, M.D., Ph.D.) B: Dermal papillary neutrophilic microabscesses are characteristic. C: A fully developed subepidermal blister is no longer multilocular; most of the infiltrating cells are neutrophils. D: There is granular and thready IgA predominantly at the tips of dermal papillae (DIF).

utmost value. The papillary dermis beneath the papillae may have a relatively intense inflammatory infiltrate of neutrophils and some eosinophils. Many neutrophils may exhibit leukocytoclasis. Subjacent to this, a perivascular infiltrate composed of lymphocytes, neutrophils, and eosinophils may be apparent. The diagnostic finding of papillary microabscesses may not be present in all patients. Apoptotic keratinocytes may be noted above the papillary microabscesses.

IF Testing. In 1967, Cormane described the presence of granular deposits of IgA within the dermal papillae in both lesional and nonlesional skin. IgA is found alone or in combination with other immune reactants in over 95% of cases when uninvolved skin of the forearm or buttock is tested (Fig. 9-22D). Fibrillary IgA deposits may also be present. Early in the course of the disease, IgA deposits may be absent and repeat DIF is necessary. Some recommend that biopsies be taken from clinically normal skin immediately adjacent to

erythema, because false-negative results may occur when blistered or inflamed skin is evaluated. The presence of IgA within the skin is not altered by dapsone therapy. After as long as 2 years, a gluten-free diet results in the disappearance of IgA from the skin. Negative results of DIF testing of two appropriately selected biopsy sites are a strong indication that the patient does not have dermatitis herpetiformis.

Circulating IgA antibodies that react against reticulin, smooth muscle endomysium, the dietary antigen gluten, bovine serum albumin, and β-lactoglobin may be present. Only the presence of IgA endomysial antibodies is of diagnostic importance, but their presence is not specific or very sensitive. Using monkey or pig gut as substrate, IIF has been used to detect antiendomysial antibodies, which are present in 52% to 100% of patients.

Pathogenesis. Three important findings must be considered in the pathogenesis of dermatitis herpetiformis. First, the disease is associated with a gluten-sensitive enteropathy; second, granular IgA is deposited in the skin; and third, patients have a high frequency of certain HLA antigens. HLA-B8, DR3, and Dqw2 have been identified in high frequency in patients with dermatitis herpetiformis and celiac disease. The majority of patients show focal celiac spruelike changes on jejunal biopsy. Patients with celiac disease develop IgA autoantibodies to tissue transglutaminase, which degrades gliadin. Antitissue transglutaminase antibodies and antiendomysial antibodies are detected in patients with dermatitis herpetiformis (115). Papillary dermal-bound IgA immune precipitates in dermatitis herpetiformis have been shown to contain epidermal transglutaminase (116).

The IgA deposition results in activation of the complement system followed by chemotaxis of neutrophils into the papillary dermis (117). Enzymes released from these neutrophils degrade laminin and type IV collagen, contributing to blister formation.

Ultrastructural Study. The changes in dermatitis herpetiformis resemble those observed in the inflammatory bullae of bullous pemphigoid. Neutrophils are the major inflammatory cell in the former, whereas eosinophils predominate in the latter. Fibrin appears earlier and in greater amount in dermatitis herpetiformis, particularly in dermal papillae. While it has been shown immunohistochemically that the early blister forms above the apparently intact lamina lucida (118), in more advanced lesions the lamina densa has been destroyed, as is noted in the "inflammatory bullae" of bullous pemphigoid.

Linear IgA Dermatosis

A group of bullous disorders mediated by IgA antibodies with differing specificities for epidermal basement membrane zone antigens has been labeled as LAD. The first and second relatively definitive clinical phenotypes are based on patient age and clinical features—adult LAD and childhood LAD (chronic benign bullous dermatosis of childhood). They differ slightly in their clinical presentations but have identical immunopathologic features. Third, a clinical phenotype similar to cicatricial pemphigoid has been described. Fourth, a subset of patients has been described with drug-induced LAD. On the basis of immunoelectron microscopic localization of the IgA deposition, there are at least two distinct types of LAD: a lamina lucida type and a sublamina densa type. Some of the sublamina densa types of LAD are best classified as IgA EBA.

Adult Type

Vesicles and bullae usually develop in patients >40 years of age, with a slight female predilection. The lesions are less symmetrical and less pruritic than those in dermatitis herpetiformis but may be distributed in similar locations. Ocular and oral lesions may be present in up to 50% of cases. Plantar and palmar bullae may develop in contrast to dermatitis herpetiformis. Cutaneous lesions in LAD are heterogeneous and may mimic other bullous diseases. LAD has been associated with an increased risk of lymphoma (119). Ulcerative colitis has been correlated with LAD in various studies, one of which found ulcerative colitis in 7.1% of LAD patients (120). A rare association with SLE has been reported (121).

Histopathology. The features are similar, if not identical, to dermatitis herpetiformis (Fig. 9-23A, B). According to some, there is less tendency for papillary microabscess formation and greater tendency for uniform neutrophil infiltration along the entire dermal–epidermal junction and rete in inflamed skin. Rarely, a principally lymphocytic infiltrate may be observed, sometimes with numerous neutrophils (121).

IF Testing. As this test defines the disease, DIF reveals linear IgA along the basement membrane zone in perilesional skin in 100% of cases (Fig. 9-23C). In the lamina lucida type of LAD, IgA antibodies bind to the epidermal side of salt-split skin, whereas in the sublamina densa type, such as IgA-mediated EBA, IgA antibodies bind to the dermal side of salt-split skin (Table 9-7).

In the vast majority of cases, IgA1, but rarely IgA2, is present. When IgG and IgA are present, some detailed immunologic study may be needed to allow differential diagnosis with bullous pemphigoid (122). It has been suggested that if the IgA deposits are more intense than the IgG deposits and C3 deposition is strong, then LAD is the best diagnosis. However, it is best considered a distinct disorder labeled as *linear IgA/IgG dermatosis* until more data are available. One patient presented with linearly deposited IgG initially and only subsequently developed linear IgA deposits. Low titers of circulating anti–squamous basement membrane zone IgA have been identified in only 20% to 30% of cases (123). Another study, however, has noted such antibodies in up to 75% of patients.

Pathogenesis. In the lamina lucida type of LAD, the antigens against which the IgA is directed include a 97-kD and a 120-kD protein that may be found in epidermal and dermal extracts (124). Both of them are part of the cleaved ectodomain of the 180-kD bullous pemphigoid antigen (BPAg2) (125,126). In the sublamina densa type, the antigen in many instances is unknown. In some cases, the antigen is

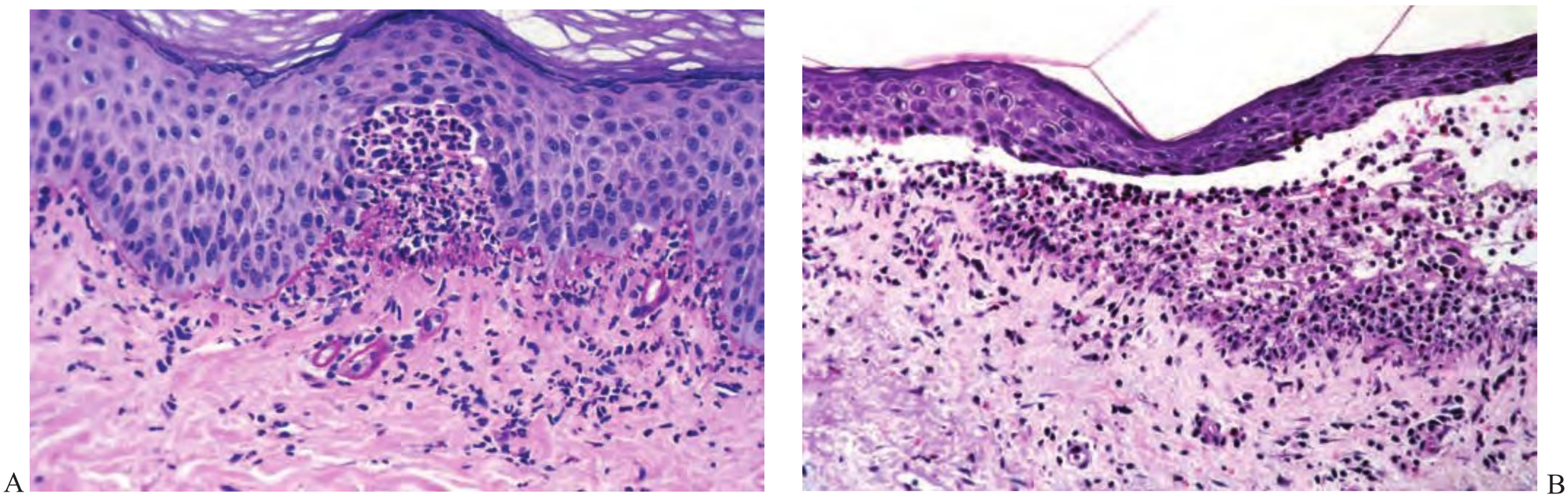


FIGURE 9-23. Linear IgA bullous dermatosis. A: An earlier lesion, where the neutrophils are along the dermal–epidermal junction and are concentrated in the dermal papillae. B: There is a subepidermal blister with inflammatory cells and fibrin in the lumen and in the base. Most of the inflammatory cells are neutrophils. A few eosinophils are also present. C: DIF study reveals deposition of IgA in a linear pattern along the basement membrane zone.

type VII collagen, specifically the NC-1 domain, which is the immunodominant epitope for EBA (127). The events of the inflammatory cascade in IgA-mediated diseases are not well understood.

Ultrastructural Study: The antibodies are deposited principally within the lamina lucida and less commonly beneath the lamina densa (IgA-mediated EBA).

Drug-associated Linear IgA Dermatosis

It is important to note that it is not infrequent for adult-type LAD to be associated with drug therapy. Vancomycin, lithium, diclofenac, captopril, cefamandole, and somatostatin have been associated with such presentations (128). Histologically, the changes are identical to idiopathic LAD in most cases. In some cases, there is an associated lymphoeosinophilic infiltrate in combination with the interface neutrophilic infiltration.

Childhood Type

Originally known as *chronic bullous dermatosis of childhood*, this disorder presents in prepubertal, often preschool, children and rarely in infancy. Vesicles or bullae develop on an erythematous or normal base, occasionally giving rise to a so-called "string of pearls," a characteristic lesion in which peripheral vesicles develop on a polycyclic plaque (Fig. 9-24). They involve the buttocks, lower abdomen, and genitalia and characteristically have a perioral distribution on the face. Oral lesions may occur. The disorder usually remits by 6 to 8 years of age, but 12% in one series experienced persistent disease.

Histopathology: The features are similar to those of the adult-type disease. Some cases, however, resemble bullous pemphigoid because of the presence of eosinophils.



FIGURE 9-24. Childhood linear IgA dermatitis. Crusted erosions on the scrotum. (Courtesy of Kenneth Tsai, M.D., Ph.D.)

IF Testing. DIF testing reveals linearly deposited IgA in virtually 100% of cases. At this time, the targeted antigens are thought to be identical to those noted in the adult-type disease. The sublamina densa type is uncommon in children (129).

NONINFECTIOUS VESICULOPUSTULAR DERMATOSES

Erythema Toxicum Neonatorum

A benign, asymptomatic eruption affecting about 40% of term infants usually within 12 to 48 hours after birth, erythema toxicum neonatorum lasts 2 to 3 days and consists of blotchy macular erythema, papules, and pustules that tend to develop at sites of pressure. The eruption is occasionally associated with blood eosinophilia.

Histopathology. The macular erythema is characterized by sparse eosinophils in the upper dermis, largely in a perivascular location, and mild papillary dermal edema.

The papules show an accumulation of numerous eosinophils and some neutrophils in the area of the follicle and overlying epidermis. Papillary dermal edema is more intense and eosinophils more numerous.

Mature pustules are subcorneal and are filled with eosinophils and occasional neutrophils. The pustules form as a result of the upward migration of eosinophils to the surface epidermis from within and around the hair follicles.

Pathogenesis. The etiology is unknown. However, two hypotheses have been offered. The first is that high-viscosity ground substance in the newborn because of osmotic changes at birth causes tissue dilution and inflammation with minor trauma (130). Second, the eruption has been suggested to be a minor acute graft-versus-host reaction caused by maternal–fetal transfer of lymphocytes during delivery (131).

Differential Diagnosis. Eosinophilic pustular folliculitis is similar to erythema toxicum neonatorum histologically but has completely different clinical features as well as a predilection for the scalp. The subcorneal pustules of impetigo and transient neonatal pustular melanosis are not follicular in origin and contain primarily neutrophils rather than eosinophils. A smear of a pustule is helpful to characterize the predominant inflammatory cell. Although many eosinophils are present in the vesicles of incontinentia pigmenti, the vesicle is intraepidermal rather than subcorneal, and spongiosis is present. In addition, necrotic keratinocytes may be prominent in incontinentia pigmenti but are absent in erythema toxicum neonatorum.

Transient Neonatal Pustular Melanosis

In transient neonatal pustular melanosis, affecting 4.4% of black newborns and 0.6% of white newborns, flaccid vesicopustules with a predilection for the face, trunk, and diaper area develop at birth. These easily rupture, leaving hyperpigmented macules with collarettes of scale. The development of typical lesions of erythema toxicum neonatorum has been observed days later (132). Perhaps the two eruptions represent the same disease in different phases, or their coexistence may be on the basis of the frequent occurrence of erythema toxicum neonatorum.

Histopathology. The vesicopustules consist of intracorneal or subcorneal aggregates of neutrophils with an admixture of eosinophils. Fragmented hair shafts may reside within the blister cavity (132). Within the dermis is an inflammatory infiltrate with some neutrophils and eosinophils. The macules show focal basal hypermelanosis. There is no melanin in the dermis.

Acropustulosis of Infancy

In infantile acropustulosis, intensely pruritic vesicles or pustules that are 1 to 3 mm in diameter occur most commonly on the palms and soles in recurrent crops. The condition more commonly affects darker skin types, and onset is at birth or during the first year of life. The lesions heal with hyperpigmentation and resolve in most cases by 2 to 3 years of age. Rare cases have been reported in older children (133). Scabies infestation must be considered on the differential diagnosis, and acropustulosis may be a postscabetic phenomenon.

Histopathology. The intraepidermal or subcorneal vesicopustules contain neutrophils and sparse eosinophils. There is mild papillary dermal edema and a sparse, mixed, superficial perivascular infiltrate.

Pathogenesis. The etiology of infantile acropustulosis is unknown. The disease may be associated with atopic dermatitis and elevated serum IgE levels. DIF and IIF studies have been negative.

Differential Diagnosis. Impetigo, SPD, candidiasis, and transient neonatal pustular melanosis may be histologically identical to acropustulosis of infancy, so clinical data are necessary for differentiation. Special stains are necessary to rule out an infectious etiology.

Subcorneal Pustular Dermatosis

SPD (Sneddon-Wilkinson disease) is a chronic disorder that was first described in 1956 and is characterized by superficial sterile pustules that have a predilection for flexural surfaces and the axillary and inguinal folds. Many cases have been shown to be a variant of IgA pemphigus (134,135). It usually spares the face and mucous membranes. The pustules develop in an annular or polycyclic arrangement. Pus characteristically accumulates in the lower half of large pustules.

SPD may be associated with a monoclonal gammopathy, which most commonly is an IgA paraproteinemia. Some of these cases eventuate in an IgA myeloma (136) and may have IgA squamous intercellular substance deposits.

Histopathology. The pustules are subcorneal and contain neutrophils, with only an occasional eosinophil (Fig. 9-25).

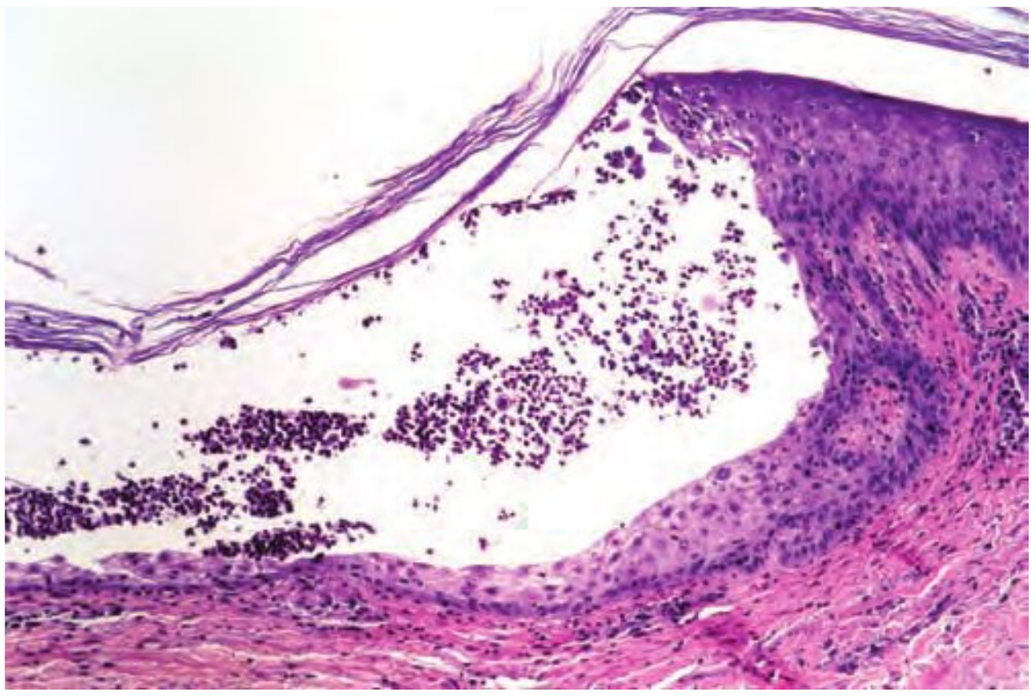


FIGURE 9-25. Subcorneal pustular dermatosis. There is a subcorneal vesicle filled with neutrophils. A few acanthotic keratinocytes are mixed with numerous neutrophils. Only a few spongiform pustules are formed.

The underlying slightly edematous stratum malpighii contains a small number of neutrophils. Only a few spongiform pustules are formed. In some instances, a few acantholytic cells are found in the base of the pustule, most likely because of proteolytic enzymes present in the pustular contents. They may be partially attached to the epidermis or may lie free in the pustule among the neutrophils. The dermal papillae contain dilated capillaries and a perivascular infiltrate composed of neutrophils and a few eosinophils and mononuclear cells.

IF Testing. While most original DIF studies were reported as negative, as more cases accumulate, many cases have squamous intercellular IgA, indicating that they are best considered to be IgA pemphigus (intraepidermal IgA pustulosis) (134).

Pathogenesis. The squamous intercellular substance IgA leads to neutrophilic infiltration. In some patients, elevated levels of tumor necrosis factor-α in the serum and pustules may be responsible for neutrophil activation (137).

Ultrastructural Study. The edge of the pustules shows cytolytic changes in the upper epidermis, especially in the granular layer. Dissolution of the plasma membrane and of the cytoplasm of granular cells causes the formation of a subcorneal split. The transepidermal migration of neutrophils and their subcorneal accumulation are regarded as events secondary to the cellular destruction in the stratum granulosum seen in one study.

Differential Diagnosis. The differential diagnosis includes other entities that show subcorneal pustules. Histologic differentiation from impetigo may be impossible unless bacteria can be demonstrated with a Gram stain. Cultures may be necessary for diagnosis. Histologic differentiation from pemphigus foliaceus or pemphigus erythematosus may also be difficult, as both diseases show subcorneal blisters with acantholysis, although the acantholysis tends to be more pronounced in pemphigus than in SPD. Clinical information, IF testing, and a therapeutic trial of sulfones may be necessary for definitive diagnosis.

Although subcorneal pustules occur in both pustular psoriasis and SPD, spongiform pustules occur only in pustular psoriasis. Some authors regard SPD as a variant of pustular psoriasis, but with the association to IgA gammopathies and squamous intercellular substance deposits of IgA, this view is discredited.

Erythema Multiforme/Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

There has been controversy in the literature regarding the clinical definitions of EM, SJS, and TEN and whether they are distinct entities or represent a spectrum of one disease process. While EM major and SJS were once considered synonymous, many now consider EM and SJS to be separate diseases (138). SJS and TEN are widely but not universally regarded as a continuum.

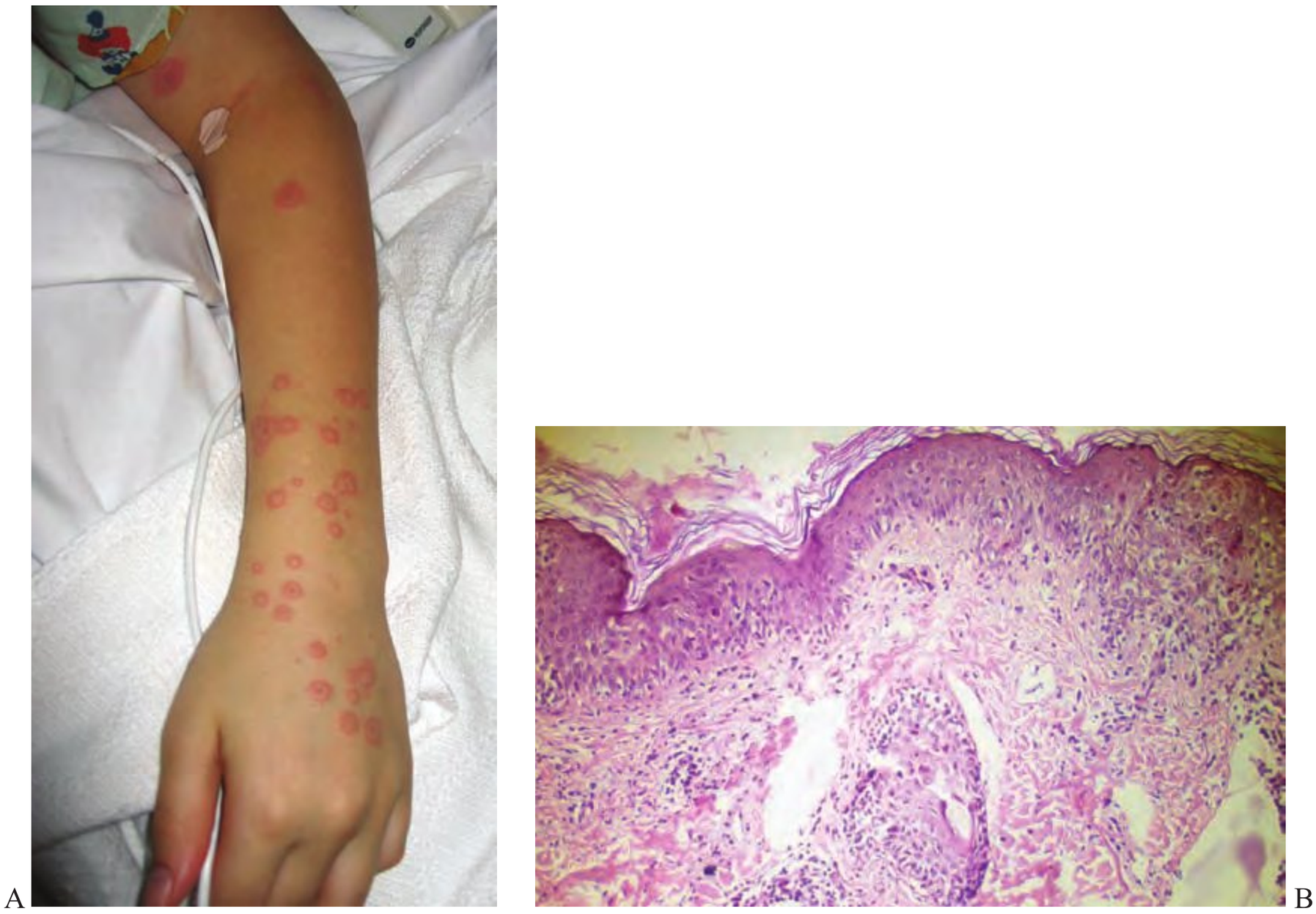
EM, as classically described by von Hebra, is a benign, self-limited condition with symmetric, fixed lesions, some of which evolve into typical targets composed of three concentric rings. The lesions are located primarily on the extremities (Fig. 9-26A). Bullous EM is a more severe form, which was defined by an international consensus group in 1993 as having typical targets or raised atypical targets with <10% of body surface area detachment (139).

Patients with SJS often present with fever and malaise and develop a cutaneous eruption consisting of "flat atypical targets," or erythematous or purpuric macules, many with central epidermal necrosis or blister formation. The lesions usually start on the trunk and spread centrifugally. Again, epidermal detachment is <10% of the body surface area (138).

TEN, also referred to as *Lyell's syndrome*, is characterized by widespread, full-thickness epidermal necrosis involving >30% of the body surface area (Fig. 9-27A). These patients also have systemic symptoms and may initially present with diffuse erythema and skin tenderness, followed by the development of large, flaccid bullae and detachment of the epidermis in sheets (140). SJS/TEN overlap is used to refer to patients with epidermal detachment between 10% and 30% of the body surface area (138). TEN has a high mortality rate because of fluid loss and sepsis.

Mucosal involvement (oral, ocular, and/or genital) is common in all of these severe acute bullous diseases and is a serious cause of morbidity. *Mycoplasma pneumoniae* infection has been associated with severe mucositis without skin lesions, which has been referred to by some as *atypical SJS* (141,142), while others argue that the classification of SJS requires cutaneous involvement (143).

EM, which may be recurrent, is most commonly associated with herpes simplex infection (144,145). Other infections, (Epstein-Barr virus [146], cytomegalovirus [147], and Lyme disease [148]), and rarely drugs, have been implicated in EM. SJS is most commonly drug-induced (138), except in



A B

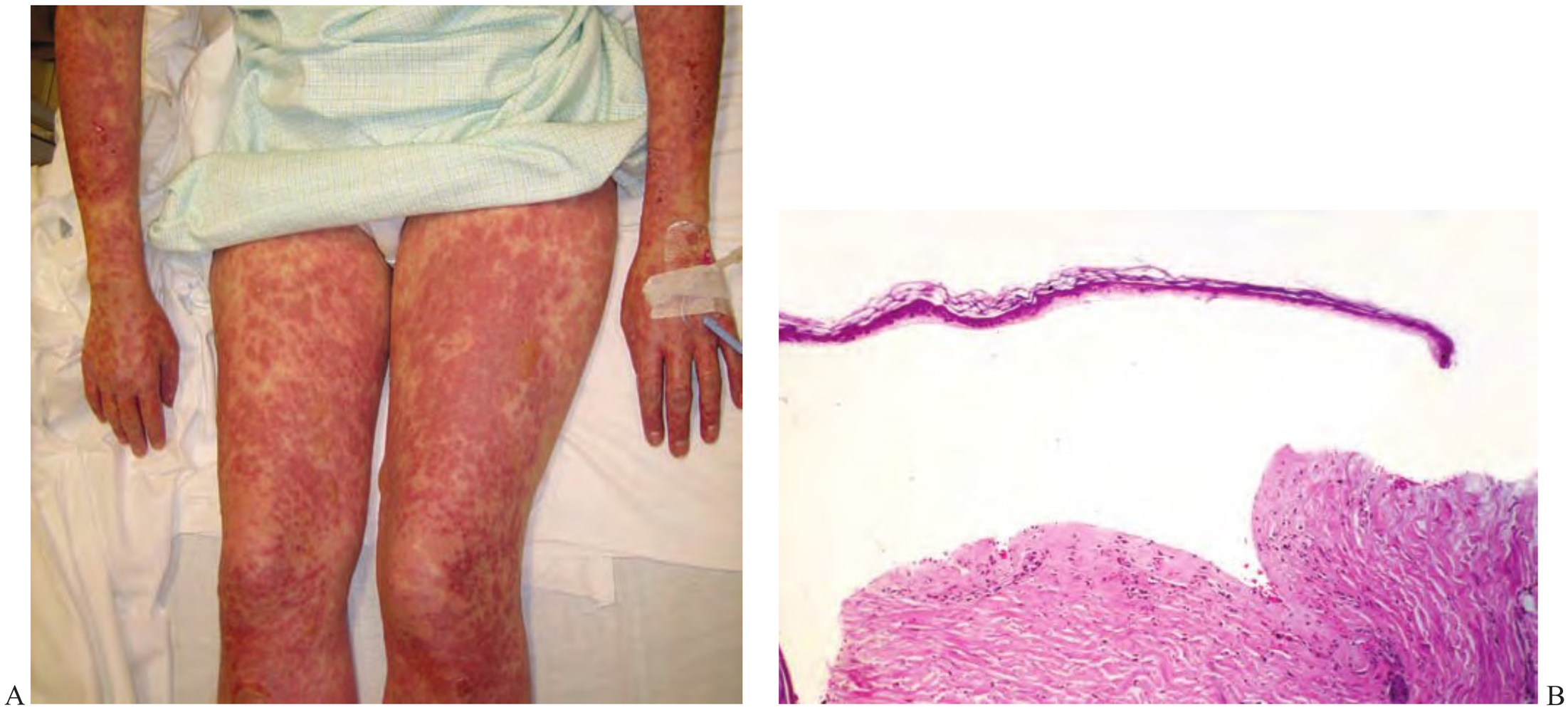
FIGURE 9-26. Erythema multiforme. A: Target lesions on the arm of a young boy. (Courtesy of Peter Lio, MD.) B: There is a superficial perivascular and interface dermatitis with apoptotic keratinocytes. Lymphocytes are "tagging" along the dermal–epidermal junction with apoptotic keratinocytes, which have eosinophilic cytoplasm and pyknotic nucleus. The stratum corneum is normal.

children where the majority of cases have been associated with infection, notably *M. pneumoniae* (149). Immunizations are another etiology to consider. TEN is almost always attributed to drugs, and only rare cases have been thought to have an infectious etiology (150). The most commonly implicated drugs include NSAIDs, sulfonamides and other antibiotics, anticonvulsants, antiretrovirals, and allopurinol (151,152).

Histopathology. EM is considered the prototype of the vacuolar form of interface dermatitis (153). The early changes include vacuolization of the basal cell layer; tagging of lymphocytes along the dermal–epidermal junction; and a sparse, superficial, perivascular lymphoid infiltrate (Fig. 9-26B). Necrosis of individual keratinocytes in the basal unit occurs, which is the hallmark of EM. Because of its acute nature, there is an orthokeratotic stratum corneum. Mild spongiosis, papillary dermal edema, and extravasation of red blood cells are seen. As the lesion becomes more developed, there is a moderate lichenoid infiltrate of lymphohistiocytes at the dermal–epidermal junction with exocytosis. More apoptotic keratinocytes within and above the basal epidermal layer are present. The intensity of epidermal necrosis varies from vacuolated individual keratinocytes surrounded by lymphocytes (satellite cell necrosis) at the basal unit to confluent necrosis in association with intraepidermal and subepidermal vesicles. The dermal infiltrate comprises lymphocytes and histiocytes. Eosinophils may also be present. Although one study has noted a significant number of eosinophils in drug-induced EM, this has not been noted by others. In the authors' estimation, a generous number of eosinophils exclude EM. One study has found that an acrosyringium concentration of apoptotic keratinocytes in EM is a clue to a drug etiology (154).

In early lesions of SJS/TEN, apoptotic keratinocytes are observed scattered in the basal layer of the epidermis. In established lesions, there are numerous necrotic keratinocytes, even full-thickness epidermal necrosis, and a subepidermal bulla. The dermal inflammatory infiltrate is sparser in TEN than in EM (Fig.9-27B). Extravasated erythrocytes are commonly found within the blister cavity. Melanophages within the papillary dermis occur in late lesions. Eccrine epithelium shows a variety of changes from basal cell apoptosis to necrosis of the duct.

In general, EM shows less epidermal necrosis, more dermal inflammation, and exocytosis, whereas SJS and TEN reveal more epidermal necrosis, less dermal inflammation, and exocytosis. However, due to the overlapping histologic features among EM, SJS, and TEN, histologic examination—while important for recognizing the spectrum of disorders—is not reliable for classifying the disease. Correlation with clinical presentation is essential.



A B

FIGURE 9-27. Toxic epidermal necrolysis. A: Diffuse coalescing erythematous macules and patches with dusky centers and multiple bullae in a patient recently started on several new medications. B: There is a cell-poor subepidermal blister and epidermal necrosis. The dermal inflammatory infiltrate is sparse.

IF Testing. In many patients with EM, deposits of IgM and C3 are found in the walls of the superficial dermal vessels. Granular deposits of C3, IgM, and fibrinogen may also be present along the dermal–epidermal junction. Nonspecific deposition of immune reactants in apoptotic or necrotic keratinocytes may be observed in other disorders with apoptosis, lymphocyte satellite necrosis, and epidermal necrosis.

Pathogenesis. EM appears to result from a cell-mediated immune reaction. In the case of herpes simplex, polymerase chain reaction and *in situ* hybridization have detected herpes simplex virus (HSV) DNA within lesions of EM (155). The virus remains in the skin for up to 3 months after the lesions have healed (156). Some authors hypothesize that disease development begins with deposition and expression of HSV genes, leading to recruitment of HSV-specific $CD4^+$ T cells with production of INF-γ. This step initiates an inflammatory cascade that includes increased infiltration of leukocytes, monocytes, NK cells, and T cells (157). The infiltrate consists largely of $CD4^+$ (helper) lymphocytes in the dermis and $CD8^+$ (cytotoxic) cells in the epidermis. The mononuclear cells that are associated with necrotic keratinocytes in the process referred to as *satellite cell necrosis* are largely $CD8^+$ cytotoxic lymphocytes similar to those occurring in GVHD. The pathogenesis of TEN remains unclear but is thought to be mediated by cytotoxic T lymphocytes. As is EM, mainly $CD8^+$ cells are found in the epidermis and blister fluid, while $CD4^+$ cells are in the dermis. Macrophages are also thought to play an important role, along with cytokines such as tumor necrosis factor-α (TNF-α). *In vitro* studies suggests Fas-FasL and other death receptors, as well as perforin/granzyme trigger apoptosis in TEN (158,159).

Ultrastructural Study. The basal lamina is located on the floor or the roof of the blister. The basal cells show marked intracytoplasmic damage with a loss of organelles. Neutrophils and macrophages, which are rich in lysosomes, are present in the lower epidermis phagocytizing the damaged keratinocytes. In the mid-epidermis, large, electron-dense, dyskeratotic bodies correspond to the cells with eosinophilic necrosis seen by light microscopy. The damaged epidermal cells often contain few or no organelles. Large granular lymphocytes have been identified within the epidermis in close contact with keratinocytes, a finding that supports cell-mediated cytotoxic injury to keratinocytes (160).

Differential Diagnosis. Necrotic keratinocytes are also a characteristic feature in drug eruption, especially fixed drug eruptions, pityriasis lichenoides, connective tissue disease, subacute radiation dermatitis, phototoxic dermatitis, acute GVHD, and viral exanthems. Clinicopathologic correlation will help in their distinction. In patients with widespread desquamation or detachment, the clinical differential diagnosis includes TEN and SSSS. Whereas the former involves subepidermal separation, the latter results from separation of the epidermis subcorneally or within the granular layer. Frozen section evaluation of the blister roof is a rapid diagnostic tool to determine the level of the split.

Graft-Versus-Host Disease

GVHD occurs in situations in which donor immunocompetent T cells transferred into allogenic hosts are incapable of rejecting them. The sources of the T cells include primarily peripheral blood stem cell and bone marrow transplants and,

infrequently, unirradiated blood products (161), solid organ transplants (162), and maternal–fetal lymphocyte engraftment. Graft-versus-host–like reaction has been reported in patients with a thymoma or lymphoma (163,164).

The disease can be divided into an acute and a chronic phase. Acute GVHD typically occurs between 7 and 21 days after transplantation but may be seen as late as 3 months; chronic GVHD arises after a mean of 4 months but may occur as soon as 40 days posttransplantation. The two phases were originally defined on the basis of time of presentation (165,166). However, the use of donor lymphocytes and the withdrawal of immunosuppression in relapsed patients have obscured these time-based divisions. In addition, many patients have both phases, either merging with one another or separated by an asymptomatic period. The frequency of acute GVHD depends on the disparity of HLA antigens (167). The risk of chronic GVHD is 11 times greater if the patients had prior acute GVHD.

In the *acute phase*, the classic triad includes skin lesions, hepatic dysfunction, and diarrhea. The clinical severity is judged on the extent of the cutaneous eruption, total bilirubin, and stool volume. The eruption is characterized by extensive macular erythema, a morbilliform eruption, purpuric lesions, violaceous scaly papules and plaques, bullae, or in rare cases a TEN-like epidermal detachment. There is a predilection for the cheeks, ears, neck, upper chest, and palms and soles. Occasionally, follicular papules are seen simulating a folliculitis. Oral lesions may be present. About 30% of patients die from complications of acute GVHD. The overall clinical stage, during the first 40 days after transplantation, is useful in identifying patients with progressive and fatal disease (165). Cutaneous GVHD may be due to a synergistic effect from local irradiation (168).

In the *chronic phase*, an early lichenoid stage and a late sclerodermoid stage can be distinguished. Each stage can occur without the other. Although usually generalized, the involvement is in rare instances localized to a few areas. In the lichenoid stage, both the cutaneous and oral lesions may be clinically similar to those in lichen planus. In addition, the skin may show extensive erythema and irregular hyperpigmentation. A poikiloderma phase may precede the eventual sclerodermoid stage (Fig. 9-28). Other late manifestations include a lupus erythematosus–like eruption, cicatricial alopecia, chronic ulcerations, pyogenic granuloma, and angiomatous lesions (169).



FIGURE 9-28. Chronic graft-versus-host disease. Sclerodermatous skin with dyspigmentation. (Courtesy of Kenneth Tsai, MD, PhD.)

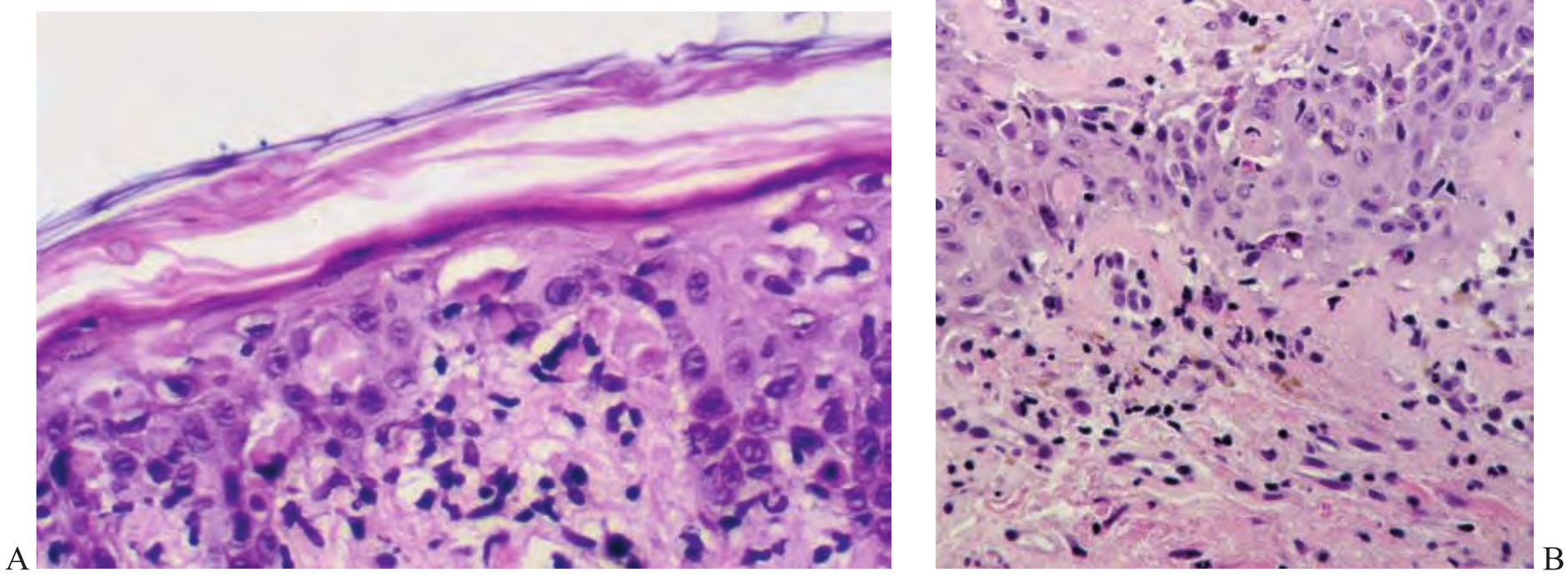
Histopathology. The early changes in the acute phase consist of focal basal vacuolation and sparse superficial perivascular lymphocytic infiltrate with exocytosis of individual cells into the epidermis and follicular epithelium. The number of lymphocytes correlates positively with the probability of developing more severe acute GVHD (170). In association with the perivascular infiltrate, there is marked endothelial cell swelling and narrowing of the vascular lumen. Established lesions show more pronounced vacuolation, focal spongiosis, lymphocytic infiltration, and dyskeratosis at all levels of epidermis. The *acute phase* has been divided into four histopathologic grades (171). In grade 1 disease, there is focal or diffuse vacuolization of the basal cell layer. In grade 2 lesions, spongiosis and dyskeratotic keratinocytes are identified (Fig. 9-29A), with some accompanied by two or more epidermal lymphocytes, a phenomenon known as *satellite cell necrosis*. The necrotic keratinocytes contain a pyknotic nucleus and eosinophilic cytoplasm. Grade 3 lesions are characterized by subepidermal cleft formation. In grade 4, there is complete loss of the epidermis. In cases with follicular papules, the involved follicles show degenerate changes in the cells of the follicular epithelium similar to those in the epidermis. In rare cases, basal vacuolization and dyskeratosis of the follicular epithelium may be the only changes (172).

In the *chronic phase*, the early lichenoid stage may still show evidence of satellite cell necrosis within the epidermis (Fig. 9-29B). The overall histologic picture greatly resembles that of lichen planus with hyperkeratosis, hypergranulosis, acanthosis, apoptotic keratinocytes, and a mononuclear cell infiltrate immediately below the epidermis with pigmentary incontinence. As in lichen planus, apoptotic keratinocytes may "drop" into the upper dermis. There may be areas of separation of the basal cell layer from the dermal papillae resembling the clefts seen in severe lichen planus. A rare manifestation is so-called columnar epidermal necrosis, characterized by small foci of total epidermal necrosis accompanied by a lichenoid tissue reaction (173).

In the late sclerodermoid phase, the epidermis is atrophic, with the keratinocytes being small, flattened, and hyperpigmented. Basal layer vacuolization, inflammation, and colloid body formation are rare or absent. The dermis is thickened, with sclerosis extending into the subcutaneous tissue resulting in septal hyalinization. The adnexal structures are destroyed (174). Subepidermal bullae were present in one reported case.

IF Testing. Epithelial basement membrane zone granular IgM and complement deposition is present in 39% of patients with the acute form and in 86% of patients with the chronic form of GVHD. In addition, IgM and C3 have been found in the walls of dermal vessels.

Pathogenesis. Acute and chronic forms of the disease have a different pathogenesis. In acute GVHD, it is believed that preparative regimen before the infusion of the graft causes extensive tissue damage, which releases inflammatory cytokines and exposes recipient major histocompatibility complex (MHC) antigens. Recognition of the host antigen by donor T cells and activation and proliferation of them is crucial in the initial phase.



A B

FIGURE 9-29. Graft-versus-host disease. A: An acute lesion with interface changes and apoptosis of keratinocytes. B: There is lichenoid dermatitis with basal vasculopathy and apoptosis. There is fibrosis of the papillary dermis.

The greater the disparity between donor and recipient MHC, the greater the T-cell response. In identical pairs, the donor T cells recognize minor antigen difference. Infiltration of both $CD4^+$ and $CD8^+$ T cells or with either one of them predominating has been reported (171,175–177). γδ T cells represent a minority of infiltrates (178,179). B cells are not found.

The inflammatory cytokines (ILs, GM-CSF, TNF-α IFN-γ) produced by activated T cells and by tissue damage during the preparative regimen also activate mononuclear phagocytes and NK cells (180). Both Fas/FasL-dependent apoptosis and perforin/granzyme-dependent killing are important in GVHD-induced damage (181). In skin, young rete ridge keratinocytes, follicular stem cells (182), and Langerhans cells are preferred targets. However, the exact mechanisms by which the skin, liver, and gastrointestinal tract are targeted are not clear.

Less is understood about the pathophysiology of chronic GVHD. The role of donor T cells against the recipient's tissue has been demonstrated. In addition, autoreactivity has also been suggested. Most immunohistochemical studies have shown that $CD8^+$ T cells predominate. Tumor necrosis factor-α and IL-1α are constantly produced by keratinocytes in the lesional skin (183).

Ultrastructural Study. The necrotic keratinocytic cytoplasm is filled with numerous aggregated tonofilaments. Granule-producing cytotoxic lymphocytes, NK-like cells, have been identified in direct cytolytic attack on epithelial cells undergoing apoptosis.

Differential Diagnosis. The acute phase of GVHD is similar to EM, with scattered necrotic keratinocytes and the formation of subepidermal clefts through hydropic degeneration of basal cells. In severe cases, the fulminant lesions resemble TEN. These patients are also at increased risk for drug eruptions, chemotherapy-induced eruptions, and radiation dermatitis, all of which may be indistinguishable from acute GVHD. If there is follicular dyskeratosis, the diagnosis is much more likely to be acute GVHD. The presence of eosinophils is not necessarily in favor of drug reaction, as eosinophils are occasionally observed in GVHD. Epidermal changes identical to acute GVHD may be seen in bone marrow transplant patients without cutaneous lesions.

The *eruption of lymphocyte recovery* occurs predominantly in patients after receiving cytoreductive therapy (without bone marrow transplant) for acute myelogenous leukemia. The eruption is typically morbilliform and develops between 6 and 21 days of chemotherapy, correlating with the earliest recovery of lymphocytes to the circulation. In contrast to patients with GVHD, these patients do not develop diarrhea or liver abnormalities. Resolution occurs over several days. Histopathologically, a superficial perivascular mononuclear cell infiltrate, basal vacuolization, spongiosis, and rare dyskeratotic keratinocytes are present. The changes may be indistinguishable from those of early allogeneic or autologous GVHD, and clinical information is essential (184). The systemic administration of recombinant cytokines prior to marrow recovery leads to a relatively heavy lymphocytic infiltrate with nuclear pleomorphism and hyperchromasia (185).

Distinguishing between the lichenoid lesions of GVHD and lichen planus is often impossible. However, late sclerotic lesions can be differentiated from scleroderma by the marked atrophy of the epidermis. Active synthesis of collagen takes place largely in the upper third of the dermis; in scleroderma, collagen is synthesized mainly in the lower dermis and in the subcutaneous tissue.

Diabetic Bullae

Diabetic bullae (bullosis diabeticorum) is an uncommon condition associated with diabetes mellitus. It usually presents as sudden and spontaneous blisters on the distal extremities. The most frequent locations are the feet, lower legs, hands, forearms, and rarely the trunk. The lesions arise on a noninflamed base, are tense, and vary in diameter from 0.5 cm to several centimeters. A mild burning sensation may be present. The blisters heal in several weeks, usually without scarring.

The cause of diabetic bullae is unknown. The reported histopathologic features have been variable and include subcorneal, intraepidermal, and subepidermal bullae. However, further investigation reveals that the level of cleavage is subepidermal and that the intraepidermal blisters represent older lesions undergoing reepithelialization of the blister base. The bullae contain fibrin and a few inflammatory cells. There may be diabetic microangiopathy with thickening of the walls of small dermal vessels. There is usually only a sparse perivascular lymphotic infiltrate.

DIF is negative for specific reactants at the dermal–epidermal junction. But nonspecific findings such as vascular deposition of fibrin and C3 along with glassy thick wall staining for IgG that correlate with the underlying diabetic microangiopathy may be present.

Coma Blisters

Classically described in patients with barbiturate overdose, coma blisters have been described in comatose patients in the setting of overdose of other medications, infections, metabolic disturbances, and neurologic disease. Tense bullae develop on normal-appearing skin, most commonly at sites of pressure.

Histopathology. Blisters are usually subepidermal, sometimes intraepidermal, with a variable degree of epidermal necrosis and a sparse inflammatory cell infiltrate (186,187). Eccrine gland necrosis is a characteristic finding (188).

Pathogenesis. The exact pathogenesis of these blisters is unknown. Pressure, friction, and local hypoxia have all been implicated as causative factors. In cases involving drug overdose, a direct toxic effect has been postulated to explain the eccrine gland necrosis and blister formation.

Edema Blisters

Tense bullae can occur in the setting of acute edema, most commonly on the lower extremities of an elderly patient with an acute exacerbation of chronic edema. Bullae can range in sizes of up to several centimeters and are usually filled with clear or serous fluid. They resolve with marked treatment of the underlying swelling (189).

Histopathology. There is marked epidermal spongiosis. The dermis is edematous with dilated blood vessels and a mild lymphohistiocytic infiltrate. In some cases, subepidermal blisters can be found. DIF and IIF studies are negative.

Transient Acantholytic Dermatosis (Grover's Disease)

First described in 1970, transient acantholytic dermatosis is characterized by pruritic, discrete papules and papulovesicles on the chest, back, and thighs. In rare instances, vesicles and even bullae are seen. Most patients are middle-aged or elderly men. Although the disorder is transient in the majority of patients, lasting from 2 weeks to 3 months, it can persist for several years. The condition has been reported coexisting with other dermatosis, such as asteatotic eczema, allergic contact dermatitis, atopic eczema, psoriasis, and pemphigus foliaceus. There have been reports of patients with transient acantholytic dermatosis and malignancy, most commonly lymphoproliferative and genitourinary neoplasms (190–192).

Histopathology. Focal acantholysis and dyskeratosis (focal acantholytic dyskeratosis) are present. Because these foci are small, they are sometimes found only when serial sections are obtained. The acantholysis may occur in four histologic patterns, resembling Darier's disease (Fig. 9-30), Hailey-Hailey disease, pemphigus vulgaris, or spongiotic dermatitis. Two or more of these patterns may be found in the same specimen. There is usually a superficial dermal infiltrate of lymphocytes and sometimes eosinophils.

IF Testing. In general, IF results are often said to be negative. However, nonspecific granular basement membrane zone staining of C3 alone or in combination with IgM may be found.

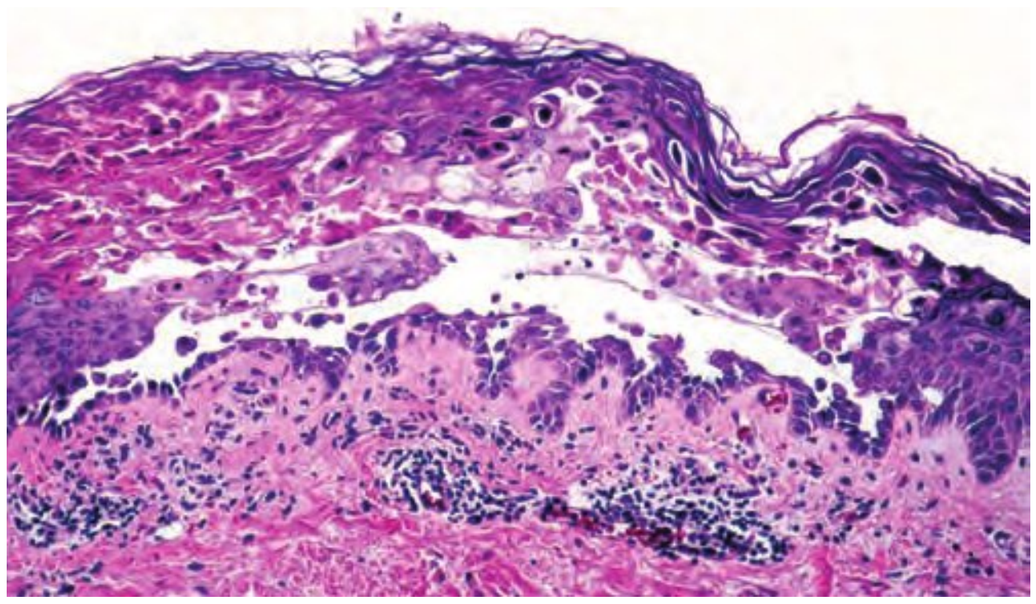


FIGURE 9-30. Transient acantholytic dermatosis. There is hypergranulosis with acantholytic dyskeratotic keratinocytes. The clefts extend to a suprabasal location.

Pathogenesis. Despite the histologic similarity to Darier's disease, Grover's disease does not share an abnormality in the ATP2A2 gene (193), which encodes a keratinocyte Ca^{2+} pump. Mutation of ATP2A2 is responsible for Darier's disease. Although the pathogenesis of Grover's disease remains unknown, there appears to be a relationship to excessive sweating, fever, and bed confinement. Some authors have hypothesized that heat or sweat urea that leaks from the intraepidermal portion of the sweat duct into the surrounding epidermis causes acantholysis. Others dispute this theory and have found the sweat duct to be intact. Finally, IL-4 may be responsible for acantholysis, either by induction of plasminogen activator or by stimulation of antibody production (194). The expression of syndecan-1, a proteoglycan important for keratinocytes intercellular adhesion, is markedly decreased in Grover's disease. The same phenomenon also occurs in other acantholytic conditions such as pemphigus and herpes simplex infection, suggestive of decreased intercellular adhesion and characteristic of these lesions (195).

Ultrastructural Study. In the pemphigus-like zones, there is intradesmosomal separation, fewer desmosomes, and perinuclear aggregation of tonofilament bundles. In the Darier type, features similar to those of Darier's disease are present.

Differential Diagnosis. The features that help to differentiate transient acantholytic dermatosis from the four diseases that it resembles are the focal nature of the histologic changes and the mixture of patterns. The presence of eosinophils in the superficial dermal infiltrate of Grover's disease serves as a distinguishing feature from Darier's disease, in which they are usually absent. It may be important to have clinical information for a definitive diagnosis. IF studies are rarely necessary to exclude pemphigus.

DERMATOPATHIES PRODUCED BY EXTERNAL ENERGY

Friction Blisters

Friction blisters develop mainly on the soles as a result of prolonged walking and on the palms and the palmar surfaces of the fingers as a result of repetitive actions required in certain occupations or sports. They may occur also as self-inflicted artifacts.

Histopathology. In both naturally occurring and experimentally produced friction blisters, intraepidermal cleavage develops as a result of cytolysis and necrosis of keratinocytes in the upper stratum malpighii (Fig. 9-31). The roof of the blister is composed of the stratum corneum, stratum granulosum, and amorphous cellular debris. Most of the degenerated keratinocytes are pale and are located at the floor of the cleft. The deeper part of the epidermis consists of undamaged cells. In severe cases, the cytolysis may extend through the basal layer leading to hemorrhagic blisters.

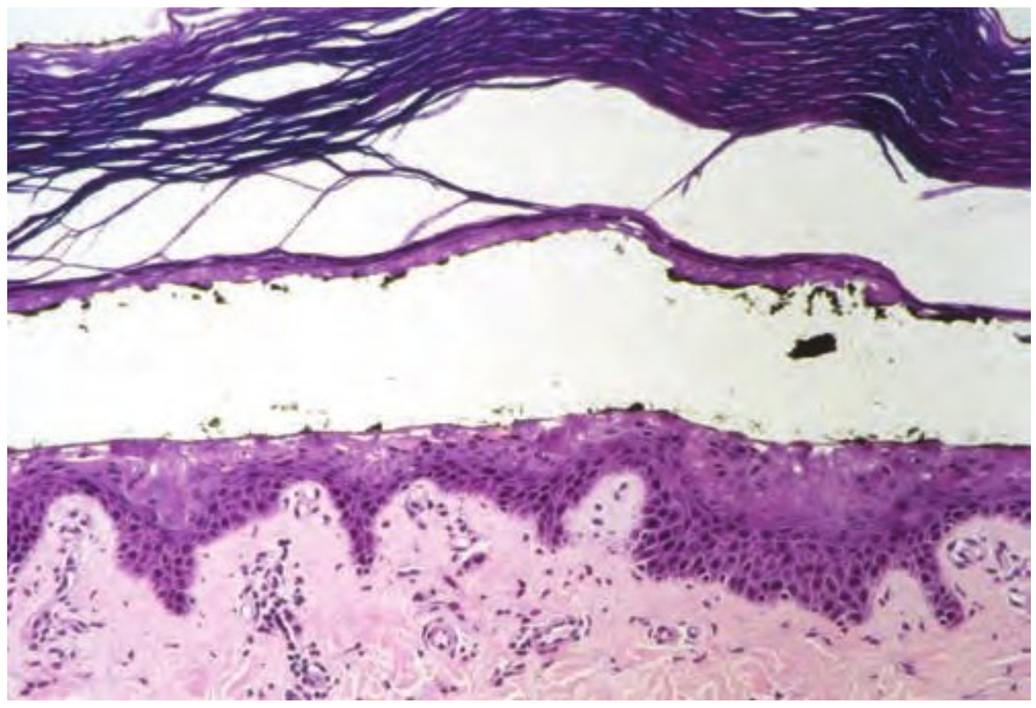


FIGURE 9-31. Friction blister. The intraepidermal blister splits at the level just beneath the stratum granulosum. A thin layer of amorphous cellular debris is present on both sides of the blister.

Pathogenesis. Shearing forces within the epidermis cause friction blisters. They form only where the epidermis is thick and firmly attached to the underlying tissue.

Ultrastructural Study. Electron microscopy reveals clumped tonofilaments, intracellular edema, small vacuoles at the cell periphery, and areas devoid of organelles.

Electric Burns

It is important that dermatopathologists be familiar with the cutaneous effects of electric current as they are used during electrodesiccation and electrocautery.

Histopathology. Electrodesiccation and electrocautery cause a separation of the epidermis from the dermis. A diagnostic histologic feature is the fringe of elongated, degenerated cytoplasmic processes that protrudes from the lower end of the detached basal cells into the subepidermal space (Fig. 9-32). The nuclei of the basal cells appear to be stretched vertically. In addition, the upper dermis is homogenized because of coagulation necrosis.

Thermal Burns

In the evaluation of thermal burns, the depth of penetration is of great importance because first- and second-degree burns heal readily, whereas third-degree burns require grafting.

Histopathology. *First-degree burns* are those in which the lower epidermis, particularly the basal cell layer, remains viable and only the upper epidermis is affected by heat coagulation. In the affected areas, the nuclei may appear pyknotic and contain perinuclear halos. In a more advanced stage, the nuclei stain faintly eosinophilic or not at all, like "architectural ghosts."

Second-degree burns often show subepidermal blisters and are characterized by partial-thickness dermal necrosis. The lower portion of the cutaneous appendages remains intact, allowing re-epithelization to occur. Superficial second-degree

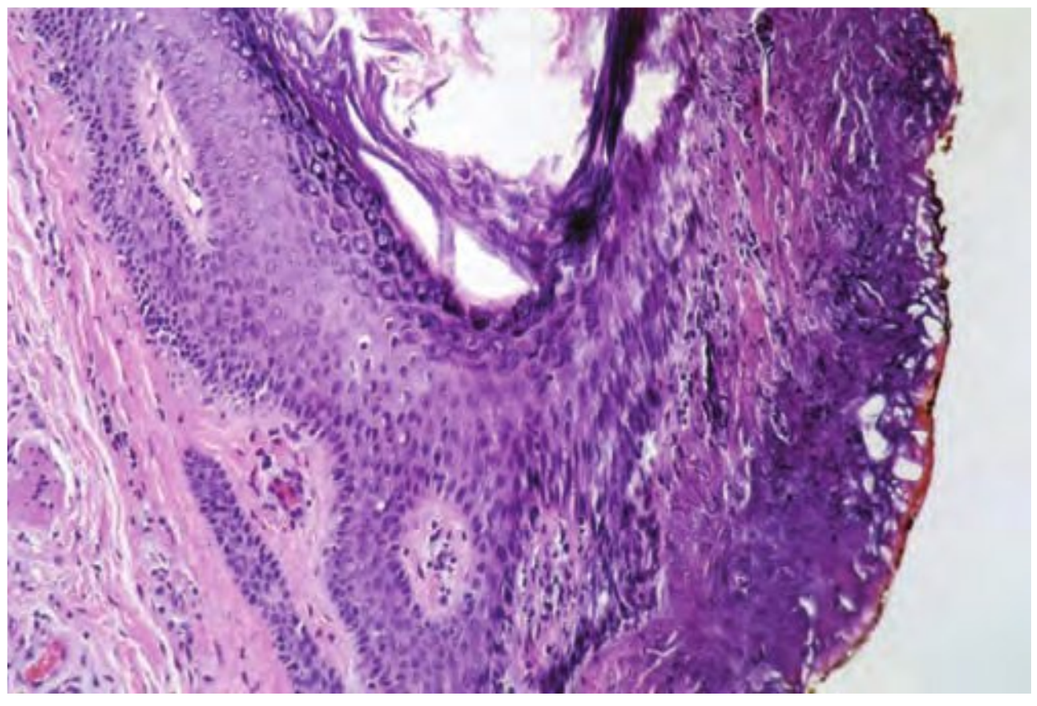


FIGURE 9-32. Electrodesiccation. The keratinocytes are elongated with nuclear pyknosis and cytoplasmic eosinophilia. The collagen is more basophilic compared with that of the unaffected tissue on the left.

burns are associated with necrosis of the surface epidermis and of only a small amount of superficial dermal collagen; in deep second-degree burns, much of the dermal collagen and the cutaneous appendages is injured. In partial-thickness dermal necrosis, the depth of epithelial damage in the cutaneous appendages is a good indicator of the depth of irreversible damage to the collagen. The border between heat-coagulated and normal epithelium is sharp. At a later stage, an inflammatory reaction develops at the junction of the viable and nonviable tissue.

Third-degree burns show full-thickness dermal necrosis with destruction of all cutaneous appendages. The coagulation necrosis may extend to the subcutaneous tissue and to the underlying muscle.

Suction Blisters and Purpura

Negative pressure applied over a circumscribed area may form a subepidermal blister that arises in the lamina lucida. A second reaction, noninflammatory purpura, may also result. The changes may be secondary to overcoming the adhesive forces in the lamina lucida and in vessels (196).

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CHAPTER 10

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Connective Tissue Diseases

LUPUS ERYTHEMATOSUS

Lupus erythematosus is a disease that affects multiple organ systems. Its clinical manifestations range from an isolated cutaneous eruption to fatal systemic illness. Cutaneous forms of lupus erythematosus occur two to three times more commonly than systemic lupus, and they, therefore, represent an important subcategory of the disease. Cutaneous disease is the presenting symptom in 23% to 28% of cases of systemic lupus, and 72% to 82% of systemic lupus patients manifest at least one cutaneous symptom through the course of their illness (1).

A combination of clinical and laboratory data was used to devise the Criteria for the Classification of Systemic Lupus Erythematosus set forth by the American Rheumatism Association (ARA) in 1972. Since then, there have been slight modifications of laboratory criteria to reflect the changes in diagnostic technology (2,3). Recent evaluation of the 1982 revised criteria noted that the current criteria do not include subacute cutaneous lupus erythematosus as a recognized skin manifestation. A recent position paper on the revision of the 1982 criteria for systemic lupus erythematosus recommends skin biopsy, but not of alopecia or oral lesions, and comprehensive antibody studies including SSA and SSB in the workup of lupus erythematosus (1).

The initial ARA criteria were developed primarily for the distinction of patients with systemic lupus erythematosus from those with other rheumatic diseases. Thus, the control populations used were not normal individuals but cohorts of other connective tissue disease patients. Despite this, these criteria are still widely used to diagnose patients with lupus erythematosus. This classification is based on 11 criteria, which are not meant to be either restrictive or exclusive to the diagnosis of systemic lupus erythematosus:

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers, usually painless
5. Arthritis, nonerosive, involving two or more peripheral joints, with tenderness, swelling, or effusion
6. Serositis (pleurisy or pericarditis)
7. Renal disorder (persistent proteinuria exceeding 0.5 g/day or cellular casts)
8. Neurologic disorders (seizures or psychosis)
9. Hematologic disorders (hemolytic anemia; leukopenia of less than 4,000/mm^3; lymphopenia of less than 1,500/mm^3; or thrombocytopenia of less than 100,000/mm^3)
10. Immunologic disorder (positive lupus erythematosus cell preparation; anti-DNA in abnormal titer; antibody to Sm nuclear antigen; or false-positive serologic test for syphilis)
11. Antinuclear antibody

A person is judged to have systemic lupus erythematosus (SLE) if any 4 or more of the 11 criteria are present serially or simultaneously. Furthermore, a diagnosis of SLE is indicated in any patient who has at least three of the following four symptoms: (a) a cutaneous eruption consistent with lupus erythematosus, (b) renal involvement, (c) serositis, or (d) joint involvement (4). Although there is no single serologic gold standard test to detect SLE, the diagnosis does require some serologic abnormality.

Even though the prognosis of SLE has been greatly improved by early diagnosis and current treatment modalities, the mortality rate of the disease is between 15% and 25% (5). Death usually results from infection or severe nephritis (6). A recent meta-analysis of lupus patients showed that patients with systemic lupus erythematosus are at increased risk of lymphomas, specifically non-Hodgkin's lymphoma, independent of the risk associated with chronic immunosuppressive therapy (7).

The importance of adequate laboratory data for evaluation of the seriousness of the illness and its prognosis has long been recognized. Histologic examination of affected tissues in conjunction with serologic and immunofluorescence studies is essential for proper evaluation of a patient with LE.

Cutaneous changes of lupus erythematosus may be subdivided according to the morphology of the clinical lesion and/or its duration (acute, subacute, or chronic). Differentiation between LE subtypes is based on the constellation of clinical, histologic, and immunofluorescence findings (8). Histologic findings alone may not be sufficient to classify correctly the subtype of the eruption (9). Not every case of lupus erythematosus can be assigned with certainty to a category because intermediate forms and transitions from one type to another occur.

Chronic Cutaneous Lupus Erythematosus: Discoid Lupus Erythematosus, Verrucous Lupus Erythematosus, Tumid Lupus Erythematosus, Lupus Erythematosus Panniculitis/Profundus

Discoid Lupus Erythematosus

Characteristically, lesions of discoid lupus erythematosus (DLE) consist of well-demarcated, erythematous, slightly infiltrated, "discoid" plaques that often show adherent thick scales and follicular plugging. Early and active lesions usually display surrounding erythema (Fig. 10-1A). Old lesions often appear atrophic and have hypo- or epidermal hyperplasia. Occasionally lesions may show verrucous epidermal hyperplasia especially at their periphery (10). Hypopigmentation within previously affected areas is frequent. Rarely, neoplasms have been reported in lesions of lupus erythematosus and have included basal cell carcinoma, squamous cell carcinoma, and atypical fibroxanthoma (11).

In many instances, the discoid cutaneous lesions are limited to the face, where the malar areas and the nose are predominantly affected. In addition, the scalp, ears, oral mucosa, and vermilion border of the lips may be involved. In patients with involvement of the head and neck unaccompanied initially by systemic lupus erythematosus, conversion of DLE to SLE is rare (5% to 10%) (12).

In patients with *disseminated discoid lupus erythematosus,* discoid lesions are seen predominantly on the upper trunk and upper limbs, usually, but not always, in association with lesions on the head (13). SLE may eventually develop in up to 20% of these patients (14). Although discoid cutaneous lesions are typical of DLE, they are also seen in as many as 14% of the patients with SLE (15).

Histopathology. In most instances of *discoid lesions*, a diagnosis of lupus erythematosus is possible on the basis of a combination of histologic findings (Fig. 10-1B–E). Changes may be apparent at all levels of the skin, but all need not be present in every case. The findings are summarized as follows:

1. Stratum corneum: hyperkeratosis with follicular plugging
2. Epithelium: thinning and flattening of the stratum malpighii, hydropic degeneration of basal cells, dyskeratosis and squamatization of basilar keratinocytes
3. Basement membrane: thickening and tortuosity, correlating with deposition of immune reactants (Fig. 10-2)
4. Stroma: a predominantly lymphocytic infiltrate arranged along the dermal–epidermal junction, around hair follicles and other appendages, and in an interstitial pattern; interstitial mucin deposition; edema, vasodilation, slight extravasation of erythrocytes
5. Subcutaneous: possible slight extension of the inflammatory infiltrate

The stratum corneum is usually hyperkeratotic. Parakeratosis is not conspicuous, and it may be absent. Keratotic plugs are found mainly in dilated follicular openings (Fig. 10-1B, C), but they may occur in the openings of eccrine ducts as well. Follicular channels in the dermis may contain concentric layers of keratin instead of hairs.

The most significant histologic change in lupus erythematosus is hydropic degeneration of the basal layer, also referred to as liquefaction degeneration. This change is characterized by vacuolar spaces beneath and between basilar keratinocytes (Fig. 10-1C). In its absence, a histologic diagnosis of lupus erythematosus should be made with caution and only when other histologic findings greatly favor such a diagnosis. In addition to liquefaction degeneration, basilar keratinocytes may show individual cell necrosis (apoptosis) and acquire elongate contours like their superficial counterparts rather than retain their normal columnar appearance (squamatization). Frequently, the undulating rete ridge pattern is lost and is replaced by a linear array of squamatized keratinocytes (Fig. 10-1C) (9).

The epidermal changes vary with the clinical character of lesions; there may be thinning and flattening of the stratum malpighii. A clinically verrucous lesion shows a hyperplastic, papillomatous epidermis with hyperkeratotic scale that simulates a hypertrophic solar keratosis or even a superficially invading squamous cell carcinoma (Fig. 10-3A, B) (16). In lesions of DLE that clinically do not show adherent scaling or keratotic plugging, the epidermis may show few or no changes and, in particular, no hydropic changes in the basal layer (17).

The basement membrane, normally delicate and inconspicuous, appears thickened and tortuous in longstanding lesions (Fig. 10-1E). This change becomes more apparent with periodic acid- Schiff (PAS) stains (PAS positive, diastase-resistant), and may be found not only at the dermal–epidermal interface, but also along follicular–dermal junctions. These findings correlate with locations of immunoreactant deposits found on direct immunofluorescence testing of affected skin (Fig. 10-2). By contrast, in areas of pronounced hydropic degeneration of the basal cells, the PAS-positive subepidermal basement zone may be fragmented and even absent (18). Capillary walls may also show thickening, homogenization, and an increase in the intensity of the PAS reaction.

The inflammatory infiltrate in the dermis is usually lymphocytic admixed with plasma cells (Fig. 10-1C, D). Its distribution is a clue to the diagnosis of LE. In active lesions, the infiltrate can be found approximating the dermal–epidermal junction associated with hydropic degeneration. In hair-bearing areas, the infiltrate is located around hair follicles and the sebaceous glands (Fig. 10-1C). Frequently, one can observe hydropic changes in the basal layer of the hair follicles, which may be of diagnostic value in the absence of dermal–epidermal changes. By impinging on pilosebaceous units, the infiltrate causes their gradual atrophy and disappearance. A patchy inflammatory infiltrate also may be present in the upper dermis in an interstitial pattern and around eccrine coils. Occasionally, the infiltrate extends into the subcutaneous fat.

The dermis shows edema and often small foci of extravasated erythrocytes. In dark-skinned persons, melanin is frequently seen within melanophages in the upper dermis because hydropic degeneration in the basal cells causes these

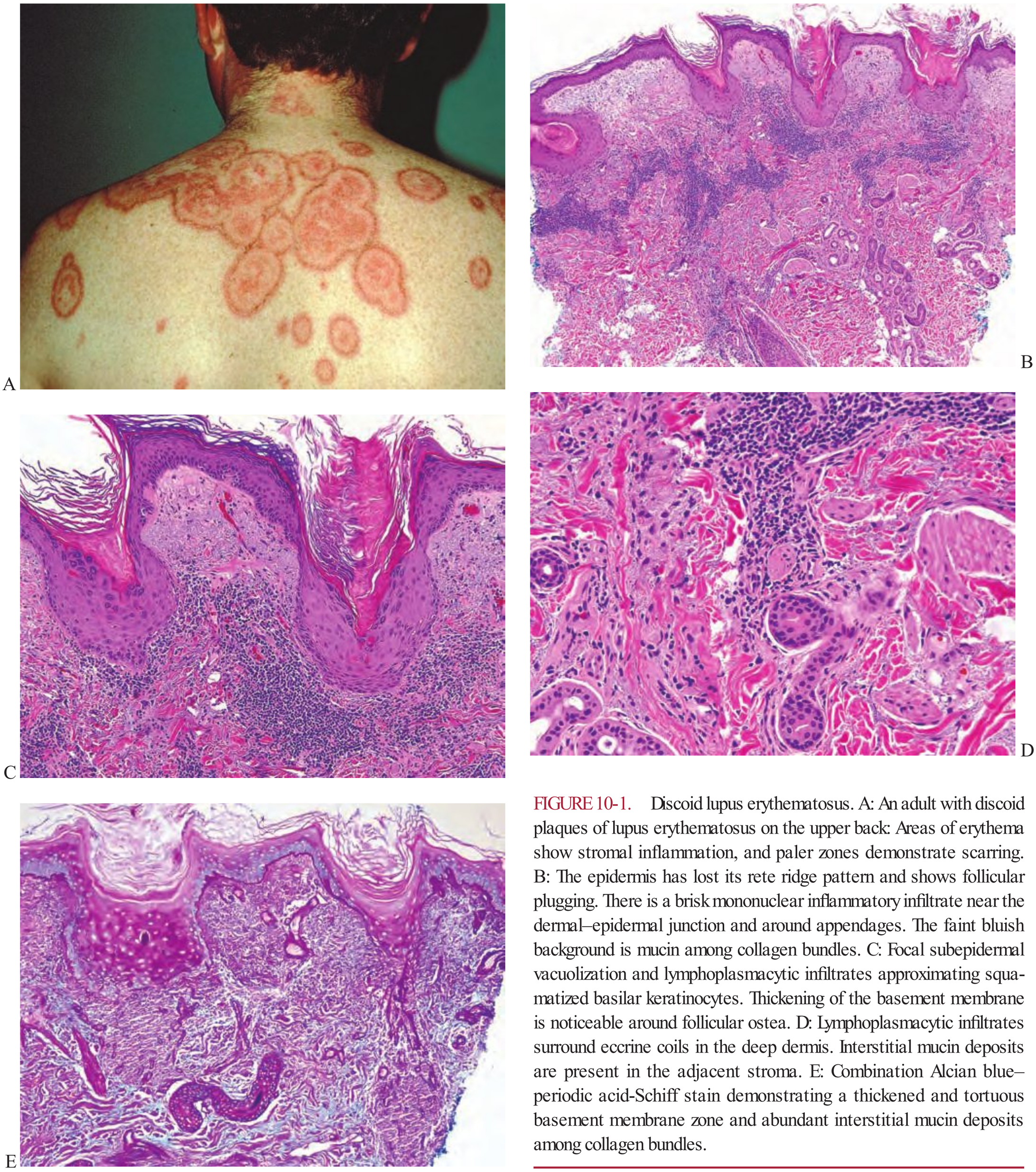


FIGURE 10-1. Discoid lupus erythematosus. A: An adult with discoid plaques of lupus erythematosus on the upper back: Areas of erythema show stromal inflammation, and paler zones demonstrate scarring. B: The epidermis has lost its rete ridge pattern and shows follicular plugging. There is a brisk mononuclear inflammatory infiltrate near the dermal–epidermal junction and around appendages. The faint bluish background is mucin among collagen bundles. C: Focal subepidermal vacuolization and lymphoplasmacytic infiltrates approximating squamatized basilar keratinocytes. Thickening of the basement membrane is noticeable around follicular ostea. D: Lymphoplasmacytic infiltrates surround eccrine coils in the deep dermis. Interstitial mucin deposits are present in the adjacent stroma. E: Combination Alcian blue–periodic acid-Schiff stain demonstrating a thickened and tortuous basement membrane zone and abundant interstitial mucin deposits among collagen bundles.

cells to lose their melanin (pigmentary incontinence). Vascular channels may be dilated and surrounded by edema. Obliterative and proliferative changes are absent. An increase in the ground substance—hyaluronic acid—is common in the middle and lower dermis and is best demonstrated with colloidal iron or Alcian blue stains (Fig 10-1E) (19). Fibrinoid deposits in the dermis are encountered only rarely in discoid lesions, and then only in early discoid lesions.

Colloid bodies, referred to in lichen planus as Civatte bodies, are apoptotic keratinocytes that present as round-to-ovoid, homogeneous, eosinophilic structures. They may be seen in lesions of DLE but also in other inflammatory

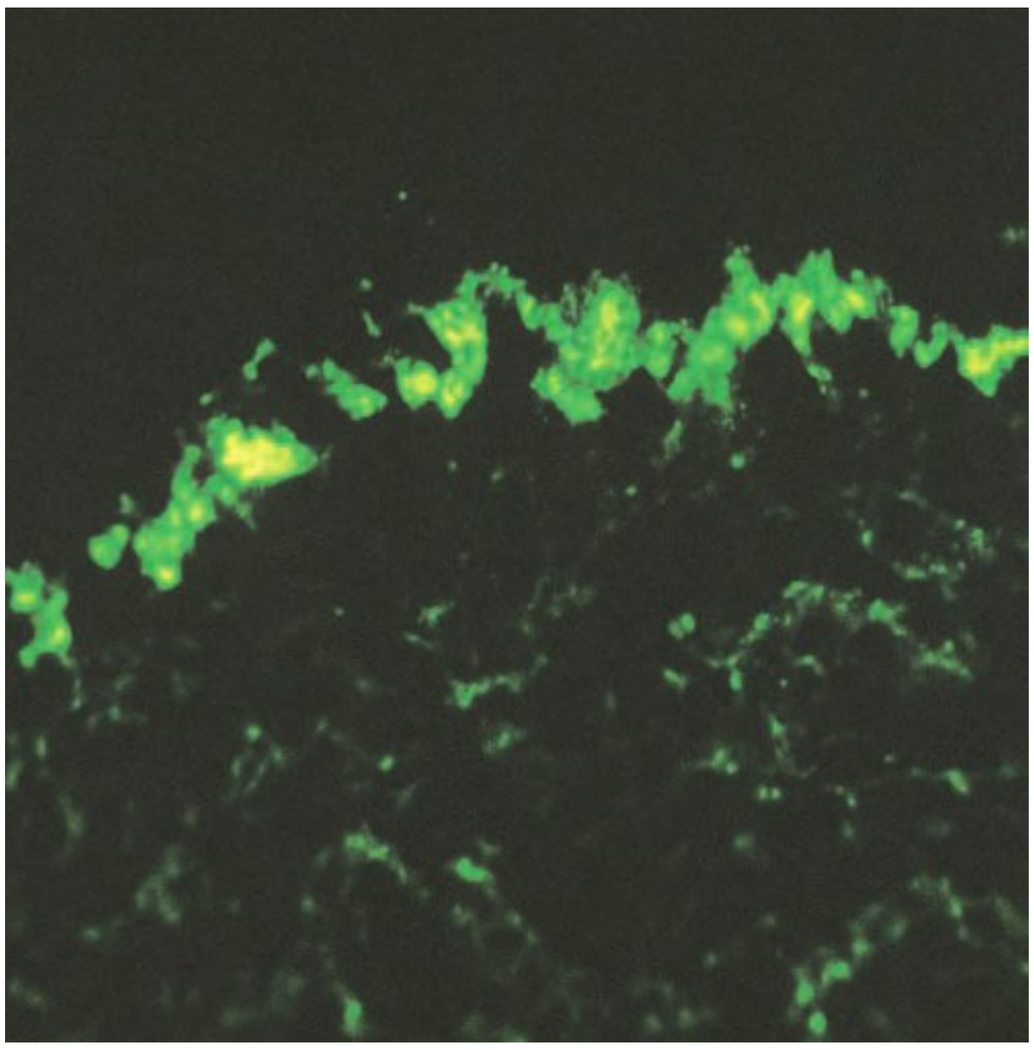


FIGURE 10-2. Positive lupus band test. Granular deposits of immunoglobulin G in the basement membrane zone on direct immunofluorescence of lesional skin.

processes where there is damage to basilar keratinocytes (poikiloderma, lichen planus, fixed drug eruptions, lichenoid keratoses). They measure approximately 10 μm in diameter and are present in the lower epidermis or in the papillary dermis. When located in the dermis, colloid bodies are PAS positive and diastase resistant and, on direct immunofluorescence staining, often are found to contain immunoglobulins (Igs) (IgG, IgM, IgA), complement, and fibrin. This staining does not represent an immunologic phenomenon but is the result of passive absorption.

Differential Diagnosis. The epidermal changes seen in DLE must be differentiated from lichen planus because both diseases may show hydropic degeneration of the basal cell layer. In lichen planus, there is wedge-shaped hypergranulosis and triangular elongation of rete ridges described as "saw-toothing," which are not observed in DLE; in DLE, the epidermis frequently appears flattened. In addition, in lichen planus the infiltrate is superficial (not superficial and deep) and stromal mucin deposition is not seen. (For a discussion of the overlap syndrome lichen planus and lupus erythematosus, see Chapter 7.)

Patchy dermal lymphocytic infiltrates may be seen in five disorders that begin with the letter L (called the five L's). They are lupus erythematosus, lymphocytic lymphoma, lymphocytoma cutis, polymorphous light eruption of the plaque type, and lymphocytic infiltration of the skin of Jessner. Some may also add lues (syphilis) and Lyme disease.

In the absence of significant subepidermal vacuolization, LE must be differentiated from the other six diseases:

- In *lymphocytic lymphoma*, atypical lymphocytes are present, are tightly packed, have an interstitial distribution ("Indian filing"), and do not surround pilosebaceous units as in LE.
- In *lymphocytoma cutis* (see Chapter 31), the infiltrate usually is heavier than in lupus erythematosus, may have an interstitial component, shows no tendency to arrange itself around



A B

FIGURE 10-3. Hypertrophic or verrucous lupus erythematosus. A: A woman with hyperkeratotic scaly plaques on an erythematous base in a photo distribution. B: A hyperplastic epidermis with hypergranulosis and a brisk lichenoid mononuclear infiltrate, histologically mimicking lichen planus.

pilosebaceous structures, and often contains an admixture of larger, paler lymphocytes arranged in lymphoid follicles, mimicking germinal center formation.

- In the plaque type of *polymorphous light eruption* there is often a prominent band of papillary dermal edema. The infiltrate is more intense in the superficial than deep dermis and is occasionally admixed with neutrophils. It does not have a folliculocentric arrangement and is not usually accompanied by stromal mucin deposition (see Chapter 12).
- In *Jessner's lymphocytic infiltration of the skin*, the dermal infiltrate may be indistinguishable from that seen in early, nonscarring, or purely dermal lesions of lupus erythematosus. The presence of increased numbers of B lymphocytes in the infiltrate may help distinguish this from LE (see later text) (20).
- In *lues*, lichenoid lymphoplasmacytic infiltrates are not associated with mucin deposits. Confirmatory antitreponemal antibody immunohistochemical stains or silver stains, such as a Steiner stain, are positive in lues and negative in lupus. Serologic studies assist in distinguishing the two disorders.
- In *Lyme disease*, there are lymphoplasmacytic infiltrates around dermal vessels. Silver and immunohistochemical stains should reveal spirochetal organisms, although they are sparse and difficult to detect.

Verrucous Lupus Erythematosus

An exaggerated proliferative epithelial response, which occurs in approximately 2% of patients with chronic cutaneous LE, manifests as verrucous-appearing lesions (Fig. 10-3A). Clinically, two types of lesions have been reported in this subset of LE. Lesions may simulate lichen planus or keratoacanthomas. They occur on the face (nose, chin, lips), arms, dorsal aspects of the hands, and occasionally the back. The presence of lesions typical of DLE elsewhere is a helpful clue to the diagnosis.

Histologically, the epidermis is papillomatous, hyperplastic, and surmounted by hyperkeratotic scale. Large numbers of dyskeratotic keratinocytes are usually noted in the lower portion of the epithelium, associated with a bandlike mononuclear infiltrate along the dermal–epidermal junction (Fig. 10-3B). Older lesions display a thickened basement membrane zone. A second pattern consists of a cup-shaped, keratin-filled crater surrounded by an acanthotic epidermis with elongate rete ridges and a sparse mononuclear infiltrate. These changes, in the presence of a deep dermal perivascular, periappendageal, and interstitial infiltrate and mucin deposition, suggest a diagnosis of hypertrophic or verrucous lupus erythematosus.

Tumid Lupus Erythematosus

The dermal form of LE without surface/epithelial changes is known as tumid LE. Clinically, affected patients display indurated papules, plaques, and nodules without erythema, atrophy, or ulceration of the surface (Fig. 10-4A). Histologically, superficial and deep dermal perivascular, interstitial, and periappendageal lymphocytic infiltrates associated with stromal mucin deposits are observed (Fig. 10-4B, C) (21). Unlike discoid lupus, in which discoid lesions may coexist with systemic lupus erythematosus, the diagnosis of tumid lupus typically excludes the presence of systemic lupus erythematosus (22).

Lupus Erythematosus Profundus/Panniculitis

Lupus erythematosus may show changes in adipose tissue associated with the chronic cutaneous or systemic forms. Two thirds of affected patients have discoid LE lesions. Women are affected three to four times more often than men. Typically, multiple discrete, firm, deep nodules arise on the face, arms (particularly the deltoid area), chest, and/or buttocks. The legs and back may be affected as well. The overlying skin may be normal, erythematous, or atrophic. The panniculitis resolves, leaving depressed atrophic scars. Several observers believe that lupus erythematosus profundus may represent a lymphoproliferative disease related to connective tissue disease, which has an indolent biological behavior (23).

Subcutaneous adipose tissue may be involved with or without inflammation in the dermis or dermal–epidermal junction. Salient histologic findings include a predominantly lobular lymphohistiocytic infiltrate often with plasma cells, occasionally forming germinal centers. Vascular changes include endothelial prominence, thrombosis, calcification, or perivascular fibrosis ("onion-skin" appearance). Fat necrosis with fibrin deposition often eventuates in hyalinization of adipose lobules (Fig. 10-5A, B). Stromal mucin deposition may be prominent in well-established lesions. The intensity of the infiltrates may lessen over time as the hyalinization progresses.

Subacute Cutaneous Lupus Erythematosus

Subacute cutaneous lupus erythematosus (SCLE) represents about 9% of all cases of lupus erythematosus. It is characterized by extensive, erythematous, symmetric nonscarring and nonatrophic lesions that arise abruptly on the upper trunk, extensor surfaces of the arms, and dorsa of the hands and fingers. This eruption has two clinical variants: (a) papulosquamous lesions and (b) annular to polycyclic lesions (Fig. 10-6A). Frequently both types of lesions are seen. In some instances, vesicular and discoid lesions with scarring may coexist.

Patients with SCLE may have mild systemic involvement, particularly arthralgias. Approximately 50% fulfill criteria for SLE. Conversely, 10% to 15% of SLE patients exhibit cutaneous lesions of SCLE (24). Severe SLE, with renal or cerebrovascular disease, develops in only 10% of SCLE cases (25,26). Serologic studies show 70% of affected patients to have the anti-Ro (SSA) antibody. Patients with SCLE often bear the HLA-DR2 and HLA-DR3 phenotype. SCLE may occur asynchronously with other connective tissue diseases such as Sjögren's syndrome and morphea.

Histopathology. See the histopathology section of neonatal lupus erythematosus and Fig. 10-6B.

Neonatal Lupus Erythematosus

Neonatal lupus erythematosus has clinical and histologic skin changes and serologic findings similar to those of SCLE.

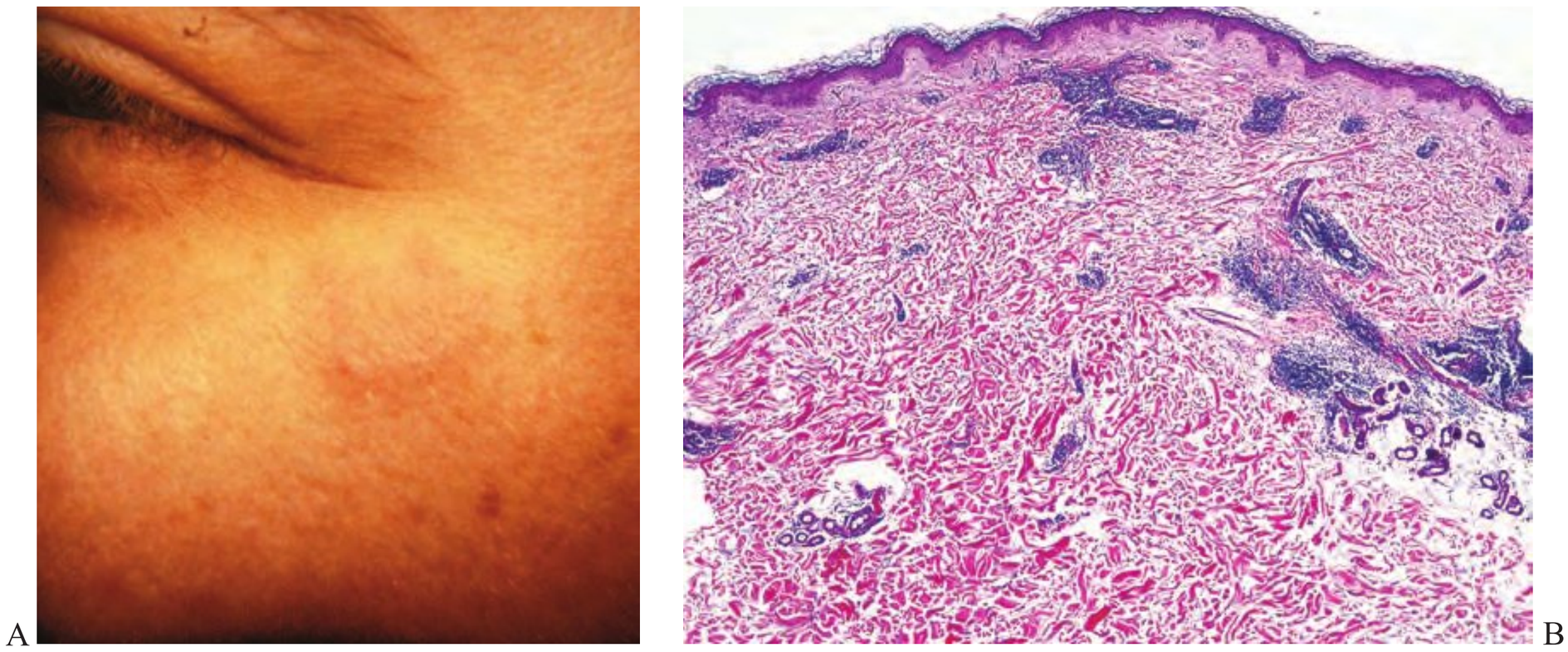


FIGURE 10-4. Tumid lupus erythematosus. A: A barely raised, slightly hyperpigmented plaque on the cheek, without significant scaling, erythema, or atrophy. B: An angiocentric and periappendageal dermal inflammatory infiltrate. The dermal–epidermal junction of this specimen fails to show interface alterations. C: A lymphocytic infiltrate admixed with plasma cells surrounds and separates eccrine glands and adjacent collagen bundles. The faint bluish hue of the matrix is indicative of mucin deposition.

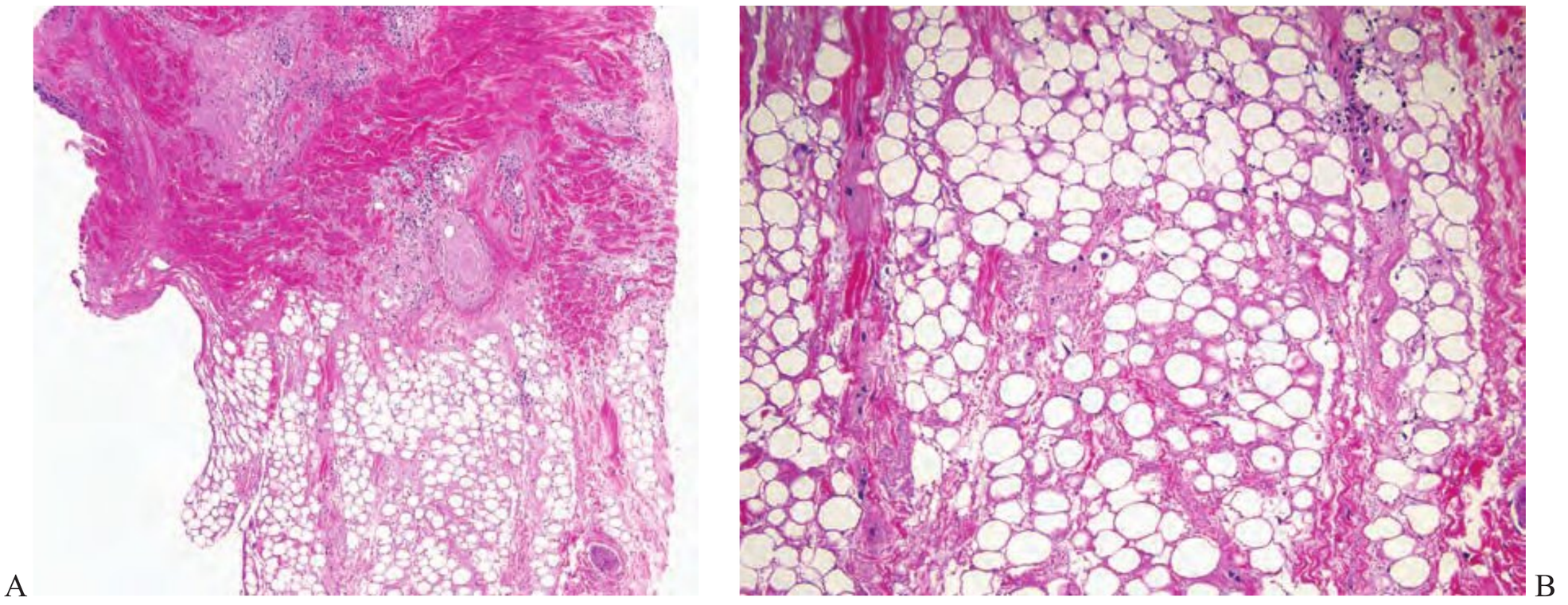


FIGURE 10-5. Lupus panniculitis. A: A perivascular and perifollicular inflammatory infiltrate is present in the deep dermis and extends into adipose tissue in an interstitial pattern. B: Adipocytes vary in size and are embedded in a hyalinized matrix. Longstanding lesions show minimal inflammation and prominent hyalinization.

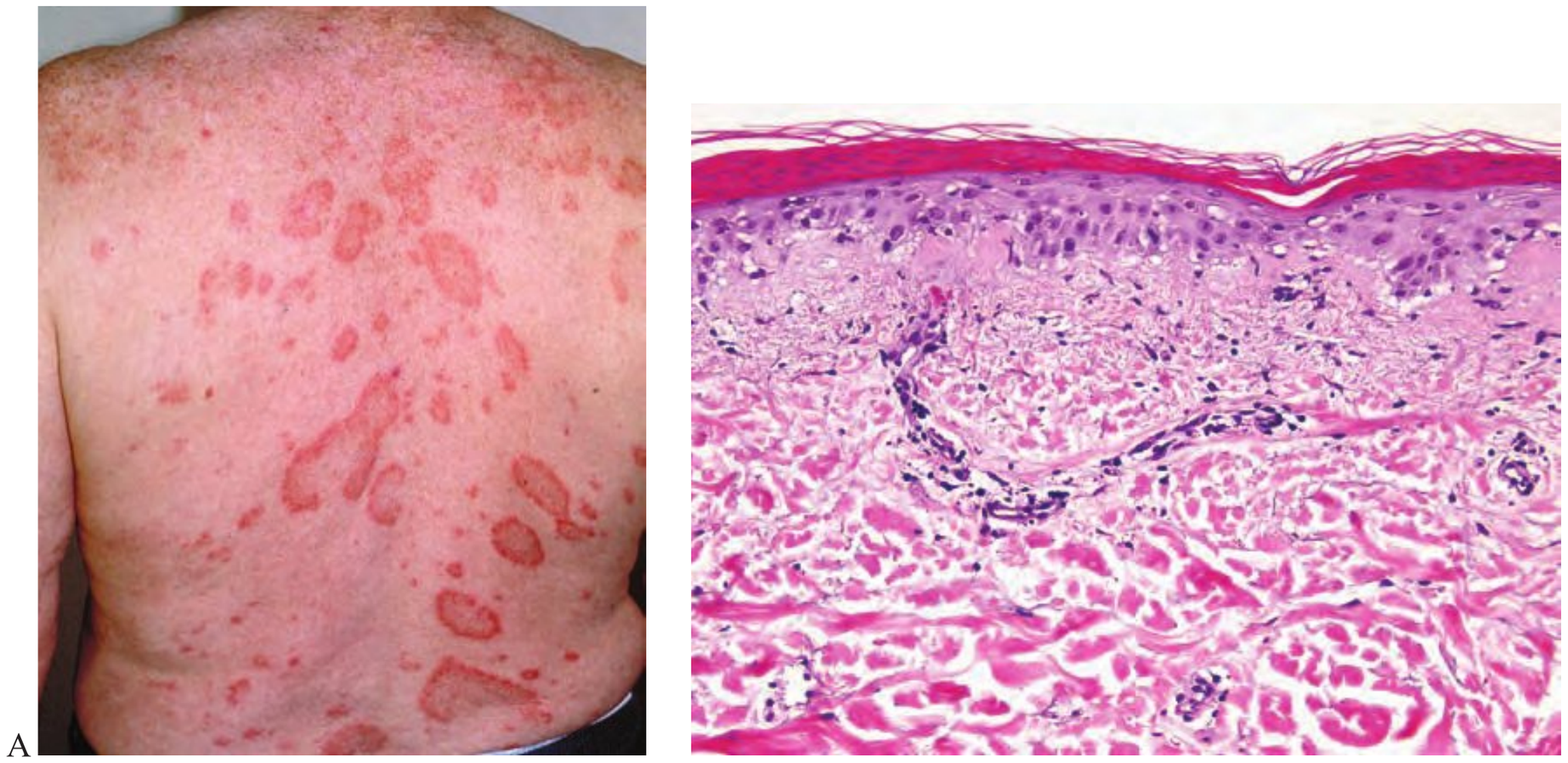


FIGURE 10-6. Subacute lupus erythematosus. A: Variably sized annular scaly patches on the upper back. Scarring and atrophy, as commonly seen in discoid/chronic cutaneous lupus, are uncommon. B: A sparse mononuclear inflammatory infiltrate in the upper dermis associated with pronounced dermal edema. There is continuous subepidermal vacuolization, focal hemorrhage, and slight mucin deposition.

Children of mothers with active SLE may develop LE-like symptoms in the neonatal period related to passage of maternal IgG antinuclear antibodies (particularly anti-Ro/SSA, anti-La/SSB, or anti-U1RNP autoantibodies) through the placenta. Anti-Ro/SSA are the predominant autoantibodies and are found in approximately 95% of cases. This may result in a transient syndrome characterized by widespread polycyclic, annular, usually nonscarring lesions. There is associated photosensitivity, transient thrombocytopenia, mild hemolytic anemia, leukopenia, and congenital heart block. These changes have their onset at birth to 2 months and usually resolve in the first 6 months of life with decreasing levels of maternal antibodies. The heart block occurs in approximately 50% of affected infants, usually without associated skin lesions, and may be fatal. Of interest, individuals affected with transient neonatal LE may develop SLE as young adults (21).

Histopathology. Histologic changes in SCLE (and neonatal LE) differ in degree from those in the discoid lesions and are most intense at the dermal–epidermal interface (Fig 10-6B). They consist of the following:

1. Hydropic degeneration of the basilar epithelial layer, sometimes severe enough to form clefts and subepidermal vesicles
2. Colloid bodies in the lower epidermis and papillary dermis (common)
3. Edema of the dermis, which is more pronounced than in discoid lesions
4. Focal extravasation of erythrocytes and dermal fibrinoid deposits (common)
5. Less prominent hyperkeratosis and inflammatory infiltrate than in discoid lesions (27)

In comparison with chronic, particularly discoid LE, it is not always possible correctly to categorize lesions based on histology alone because there is overlap. Pilosebaceous atrophy is helpful as a discriminating feature and correlates with DLE rather than SCLE.

Systemic Lupus Erythematosus

In SLE, the cutaneous manifestations usually appear less suddenly than in SCLE and are less pronounced, such that the signs and symptoms of systemic disease usually overshadow the often subtle form of skin involvement. Usually systemic manifestations, especially joint manifestations, precede the cutaneous lesions. Only 20% of SLE patients demonstrate prominent cutaneous features at the onset of their disease, but approximately 80% will exhibit cutaneous lesions in the course of their disease (28,29).

The cutaneous manifestations commonly consist of malar erythema, photosensitivity, palmar erythema, periungual telangiectases, diffuse hair loss as a result of telogen effluvium, and urticarial vasculitis and/or bullous lesions. The erythematous lesions of SLE consist of erythematous, slightly edematous patches without significant scaling and without atrophy. As a rule, the patches are not sharply demarcated. The most common site of involvement is the malar region, but any area of the skin may be involved, particularly the palms and fingers. Occasionally, lesions show a petechial, vesicular, or ulcerative component. Rarely, in the late stage, some of the lesions may assume the appearance of poikiloderma atrophicans vasculare.

Well-defined "discoid" lesions with atrophic scarring, as seen typically in DLE, occur in about 15% of the patients with

SLE. They may precede all other clinical manifestations of SLE. A relatively benign course characterizes SLE in most patients with preceding DLE (30); however, many patients usually have had persistent multiple abnormal laboratory findings from the beginning. This is in contrast to cases of simple DLE, in which most abnormal laboratory findings, if present at all, are transient.

Two variants of SLE, *SLE with genetic deficiency of complement components* and *bullous LE*, bear mention. In the former, the onset of SLE occurs in early childhood and often affects several siblings because of the autosomal recessive mode of transmission (31). Deficiencies of C2 and C4 result in strikingly similar clinical pictures of extensive lesions similar to DLE, with marked scaling, atrophy, and scarring associated with sensitivity to sunlight. In addition, there can be central nervous system involvement and glomerulonephritis, which may be fatal (32).

In *bullous SLE* subepidermal blisters may arise in previously involved or uninvolved areas. They may form large hemorrhagic bullae to herpetiform vesicles, arise suddenly, and show clinical resemblance to lesions of bullous pemphigoid or dermatitis herpetiformis.

Rowell's syndrome is a distinct clinical presentation of lupus with erythema multiforme–like lesions. Patients have speckled antinuclear and anti-La antibodies and test positive for rheumatoid factor (33).

The coexistence of SLE and systemic scleroderma or dermatomyositis has been repeatedly described. It is known as overlap syndrome and refers to the coexistence of two related but separate diseases. Similarly, there are reports of systemic lupus and coexistent eosinophilic fasciitis (34,35). Such instances of overlap are in contrast to *mixed connective tissue disease*, which is recognized as a separate disease entity.

Many drugs are associated with induction of lupus erythematosus, the majority of which induce predominantly systemic symptoms such as arthritis, serositis, lymphadenopathy, and fever. A few are associated with specific cutaneous manifestations. They are listed in Table 10-1, and are discussed

TABLE 10-1 Drugs Related to Induction of Lupus Erythematosus

Antiarrhythmics	Procainamide	Anticholesterol	Statins
	Quinidine		Gemfibrozil
	Tocainide	Biological agents	Interleukin-2
Antihypertensive	Hydralazine		Etanercept
	Methyldopa		Infliximab†
	Beta blockers		Interferon-α
	Hydrochlorthiazide*		Efalizumab*
	Calcium channel blockers	Hormones	Estrogen
	Angiotensin-converting enzyme inhibitors		Lefunomide*
		Other	Sulfasalazine
	Clonidine		Penicillamine
Antibiotics	Isoniazid		Fluorouracil agents†
	Minocycline		Gold salts
	Penicillin		Sertraline†
	Streptomycin		Ticlodipine*
	Tetracycline		Buproprione*
	Griseofulvin		Lansoprazole*
	Terbinafine		Doxetacel*
	Ciprofloxin		Reserpine
	Rifampicin		Lithium
Antithyroid	Propylthiouracil		Clonidine
	Methimazole		Hydroxyurea
	Thiamazole		Clozapine
Anticonvulsants	Carbamazepine		Zafirlukast
	Ethosuxamide		
	Phenytoin*		
	Valproate		

*Associated with subacute cutaneous lupus–like syndrome.
†Associated with chronic cutaneous lupus–like syndrome.

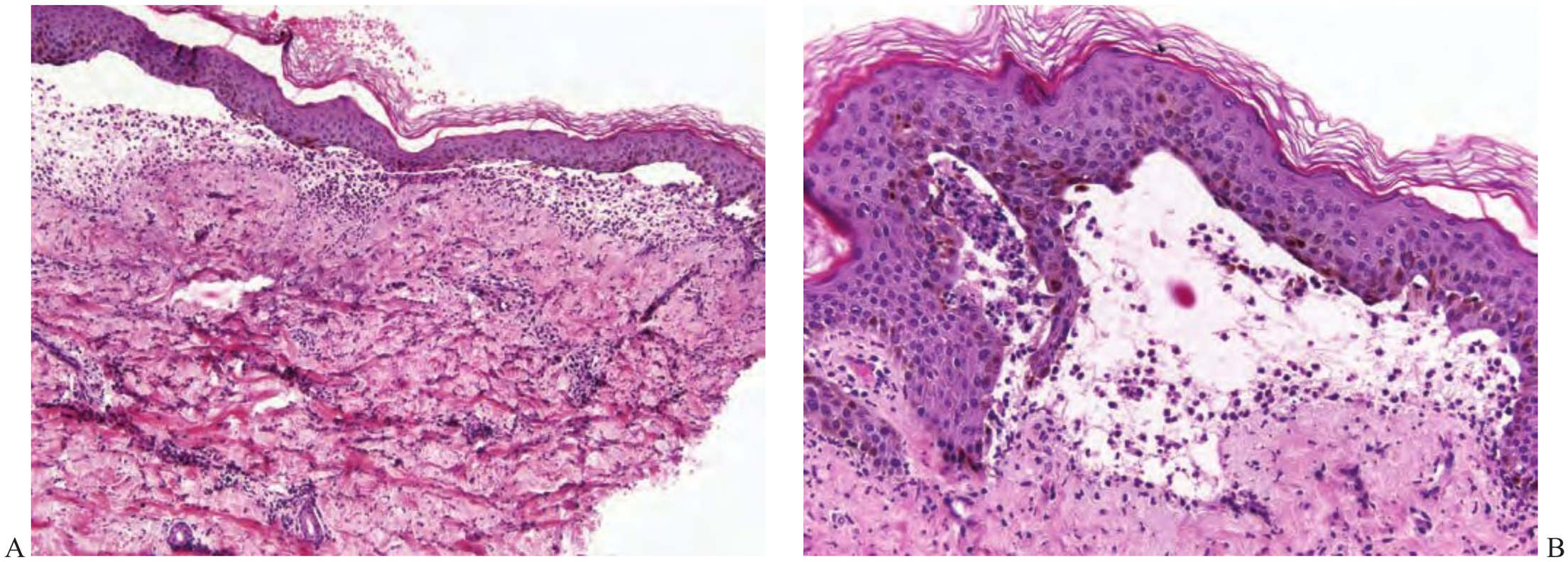


FIGURE 10-7. Bullous lupus erythematosus, neutrophilic. A: There are broad-based subepidermal blisters associated with marked papillary dermal edema and large numbers of neutrophils. Neutrophils are also present around vessels and among collagen bundles throughout the dermis. Faint interstitial mucin deposits and nuclear dust are present. B: The papillary dermal abscesses simulate findings of dermatitis herpetiformis. The dermal changes as noted in panel A, however, would not be seen in dermatitis herpetiformis.

further in the section on drug-induced lupus erythematosus in Chapter 11.

Histopathology. Early lesions of SLE of the erythematous, edematous type may show only mild, nonspecific changes. In well-developed lesions, the histologic changes correspond to those described for subacute cutaneous LE (Fig. 10-6B): Hydropic degeneration of the basal cell layer occurs in association with edema of the upper dermis and extravasation of erythrocytes. Fibrinoid deposits in the connective tissue of the skin are often seen in erythematous, edematous lesions, especially in patients with SLE. Such fibrinoid deposits consist of precipitation of fibrin in the ground substance. They appear as granular, strongly eosinophilic, PAS-positive, diastase-resistant deposits between collagen bundles, in the walls of dermal vessels, in the papillary dermis, or beneath the epidermis in the basement membrane zone. Fibrinoid deposits are not specific for LE. They are seen in association with vascular injury, particularly in leukocytoclastic vasculitis.

Subcutaneous fat is often involved in SLE. Changes similar to those in lupus profundus may be seen but are usually milder: There may be focal mucin deposition associated with a predominantly lymphocytic infiltrate. Adiopocytes may be separated by edema and fibrinoid deposits. These histologic changes in subcutaneous fat produce no clinically apparent lesions.

Occasionally, palpable purpuric lesions in SLE patients show a leukocytoclastic vasculitis histologically indistinguishable from leukocytoclastic vasculitis of other causes: There is endothelial cell swelling, a neutrophilic inflammatory infiltrate, nuclear dust formation, perivenular fibrin deposition, and stromal hemorrhage. Urticaria-like lesions may occur and show either a leukocytoclastic vasculitis or a perivascular mononuclear infiltrate not diagnostic of lupus erythematosus (36). In addition, white atrophic lesions may occur in SLE that both clinically and histologically resemble those of malignant atrophic papulosis of Degos (37).

Bullous SLE shows two histologic inflammatory patterns: One is neutrophilic, and the other is mononuclear. The neutrophilic type simulates dermatitis herpetiformis or linear IgA bullous disease with the formation of papillary microabscesses (Fig. 10-7A, B) (38). Nuclear dust is seen in the papillary microabscesses and in the upper dermis around and within the walls of blood vessels. Direct immunoelectron microscopic studies have localized immunoreactant deposits to beneath the lamina densa; they consist of IgG with or without IgM, and often IgA in a linear or granular pattern. Some patients may also have circulating anti–basement zone antibodies and antibodies directed against type VII collagen. The latter antibodies are similar but not identical to those in epidermolysis bullosa acquisita (39).

The subepidermal blister associated with a mononuclear inflammatory infiltrate arises in longstanding lesions of cutaneous lupus erythematosus (Fig. 10-8A, B). It likely corresponds to an altered dermal–epidermal interface resulting from inflammation and immunocomplex deposition. This type of change is a part of the spectrum of LE rather than a distinct entity.

Systemic Lesions. Although the etiology of SLE is obscure, it is evident that much of the tissue damage results from deposition of antibody–antigen complexes in affected organ systems. These immune complexes are demonstrable in renal glomeruli, blood vessels, skin, and the choroid plexus of the brain.

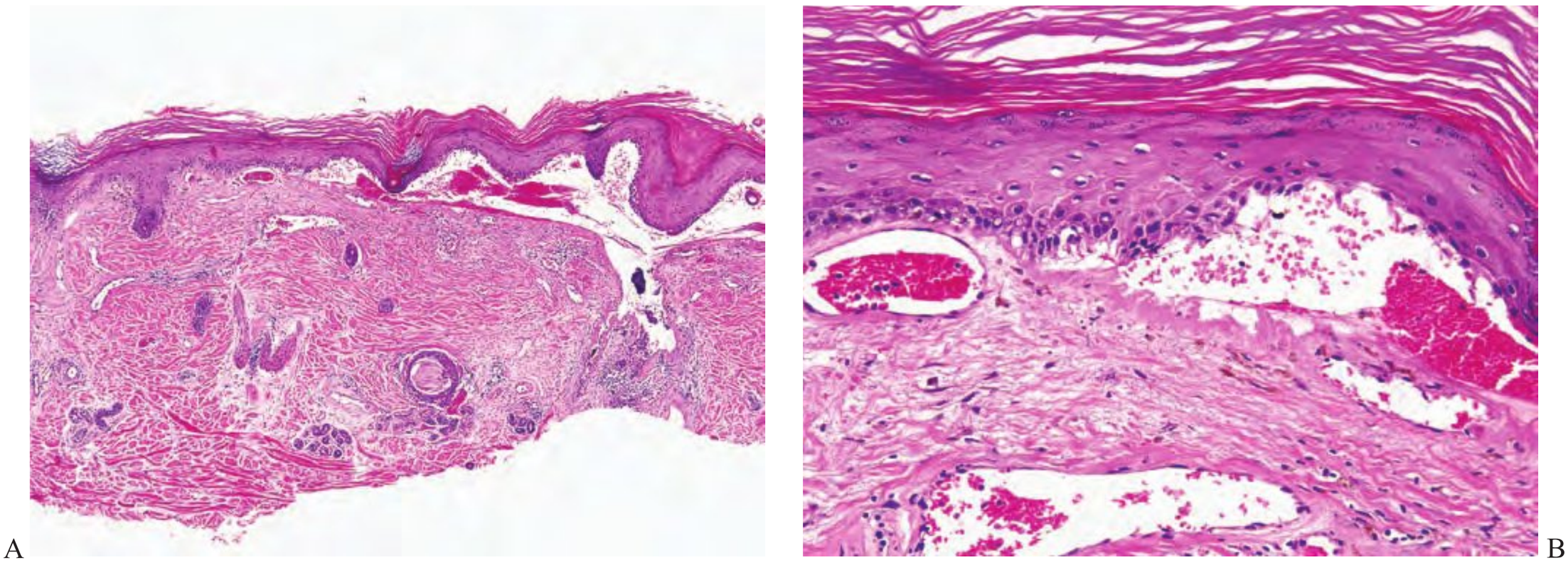


FIGURE 10-8. Bullous lupus erythematosus, mononuclear. A: A broad subepidermal cleft is present beneath an epidermis that has lost its rete ridge pattern and is surmounted by hyperkeratotic scale. The stroma contains perivascular and periappendageal inflammatory infiltrates. B: Adjacent to the zone of dermal–epidermal separation is a thickened eosinophilic basement membrane zone. Melanophages are scattered in the superficial dermis.

Arthritis occurs most often; however, renal changes are the most important because they are the most common cause of death in SLE. Percutaneous renal biopsy allows determination of the type and degree of histologic changes in the kidneys, which are of prognostic significance regardless of the absence or severity of clinical renal disease (40). As in skin, immunoglobulin and complement (immunoreactant) deposits are detectable with immunofluorescence and electron microscopic studies.

A detailed presentation of the classifications of glomerulonephritides is beyond the scope of this section but can be found in the review by Dooley et al. (41).

Serositis involving the pleura, epicardium, and peritoneum may show submucosal mononuclear inflammatory infiltrates associated with fibrinoid deposits. In the spleen, periarterial fibrosis around the follicular arteries is common and is highly characteristic of SLE. Thick, concentrically layered rings of sclerotic collagen fibers surround the arteries.

The *verrucous endocarditis of SLE*, so-called Libman-Sacks endocarditis, occurs mainly on the mitral and tricuspid valves. In the subendothelial connective tissue there are collections of necrotic debris, fibrinoid material, and inflammatory cells forming small vegetations on the valve leaflets (42).

Antiphospholipid syndrome occurs in patients with SLE and other autoimmune diseases who develop immunoglobulins that can prolong phospholipid-dependent coagulation tests. These immunoglobulins occur in association with SLE and other autoimmune diseases but are found unassociated with them as well. One of these is a lupus anticoagulant and occurs in about 10% of SLE patients. Affected patients are at greater risk for thromboembolic disease, including deep venous thrombosis, pulmonary emboli, and other large-vessel thrombosis. Other associated findings are recurrent fetal wastage, renal vascular thrombosis, thrombosis of dermal vessels (Fig. 10-9A, B), and thrombocytopenia. Anticardiolipin antibody, a second type of antiphospholipid antibody, occurs five times more often than lupus anticoagulant antibody. It is associated with recurrent arterial and venous thrombosis, valvular abnormalities, cerebrovascular thromboses, and essential hypertension (Sneddon's syndrome) (43). Other cutaneous findings include livedo reticularis, necrotizing purpura, disseminated intravascular coagulation, and stasis ulcers of the ankles (44).

Pathogenesis and Laboratory Findings. The etiology of lupus erythematosus is considered to be multifactorial (Table 10-2). Studies have demonstrated numerous defects in different arms of the immune system. These abnormalities include but are not limited to abnormal responses to ultraviolet radiation, abnormal antigen-presenting-cell function, numerous HLA associations, polymorphisms in tumor necrosis factor-α promoters, abnormal keratinocyte apoptosis, and polymorphisms in the genes coding for interleukin-1 (IL-1) receptor antagonist and IL-10 promoter sequence (45). In addition, research has shown that aberrant stimulation of Toll-like receptors (TLRs), specifically TLR7 and TLR9, by endogenous antigens may play a crucial role in the autoimmune feedback loop between T cells and B cells (46).

The serologic hallmark of lupus erythematosus is the production of autoantibodies. There are a wide variety of antibodies against different cellular targets. The initial screening test for antinuclear antibodies (ANAs) is indirect immunofluorescence, which provides limited but clinically useful information. Many other assays are available for more specific characterization of ANAs and include immunodiffusion, enzyme-linked immunosorbent assays, immunoprecipitation, and immunoblots.

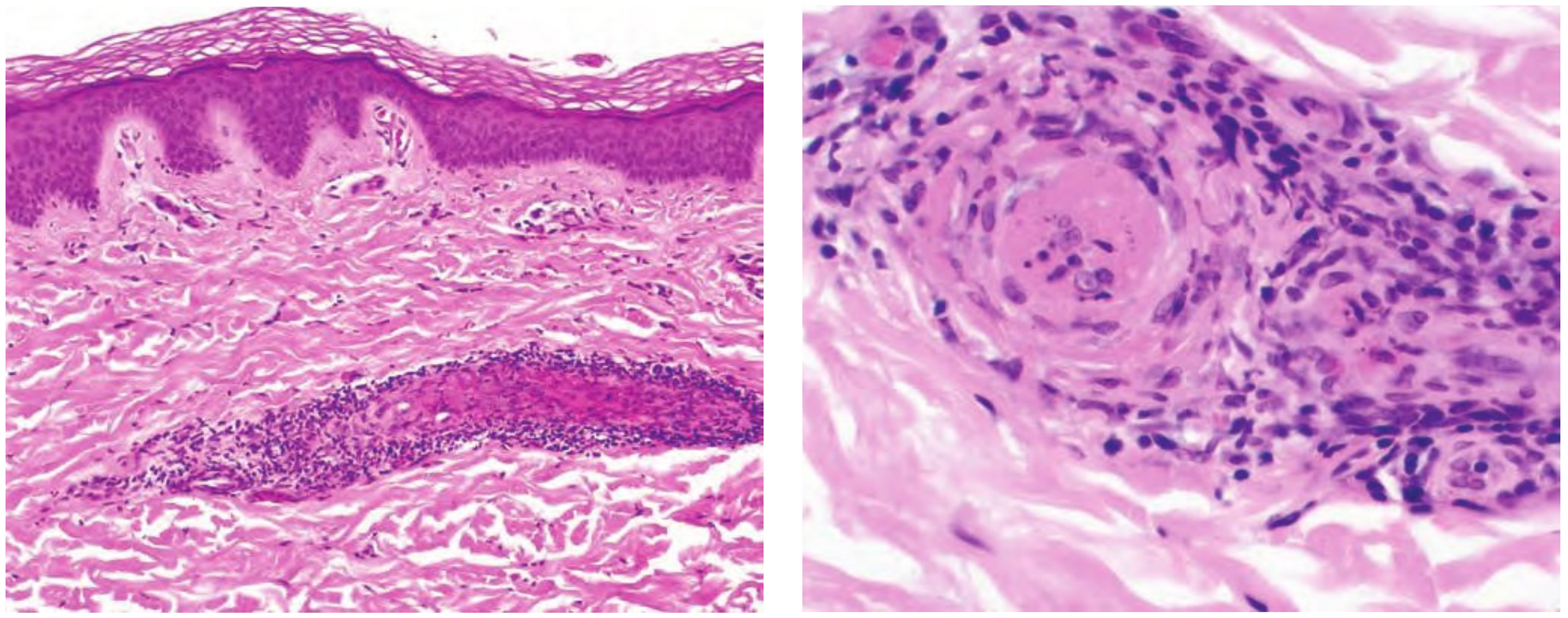


FIGURE 10-9. Lupus anticoagulant syndrome. A: A superficial dermal vessel is surrounded by lymphocytes. B: High magnification of pale eosinophilic intravascular thrombus.

TABLE 10-2 Lupus Erythematosus: Etiologic Factors

Genetic	HLA-DR2	Mothers with newborns with neonatal LE
		Patients positive for anti–Ro/SSA
		Older patients with SLE
	HLA-DR3	Younger SLE patients with anti–native DNA antibodies
	HLA-B8	Increased frequency in:
	HLA-DR3	Mothers with newborns with neonatal LE
	HLA-DQ23	Female patients with primary Sjögren's syndrome
	HLA-DRw52	Female patients with Sjögren's syndrome/LE
Environmental precipitants	Drugs	See Table 10.1
	Ultraviolet light	
	Possibly diet	
Hormonal influences	Predisposition of women in childbearing years	
Autoimmunity	Every aspect of immune system affected:	
	B cells	Abnormal B-lymphocyte maturation and activation
		Hypergammaglobulinemia
	T cells	Decreased peripheral T lymphocytes
		T-cell hyperactivity
		Increased percentage of $CD29^+$ (memory helper) T cells
		Preferential loss of CD4, $CD45R^+$ (suppressor inducer) cells in active LE
		Defective T-suppressor function
	Natural killer (NK) cell	Normal number of NK cells but decreased NK-cell activity (deficient in active cytotoxicity)
	Antilymphocyte antibody	Lymphocytotoxic antibodies in sera of 80% of SLE patients
	Antinuclear antibodies	Nuclear membrane targets
		Chromatin targets
		Ribonucleoprotein targets
	Abnormal feedback loop	Abnormal stimulation of TLR7 and TLR9 by endogenous antigens

TABLE 10-3 Antinuclear Antibodies

Appearance	Pattern	Target site	Associated antibodies	Associated disorder
	Homogeneous	Chromatin	Antihistone	SLE
			Anti-DNA	False + SLE
				Drug-induced LE
	Rim	Chromatin	Anti-DNA	SLE
		Nuclear membrane	Antilaminin (rare)	
	Fine speckled	Nuclear RNP	Anti-Sm	SLE, often with nephritis
			Anti-Ro/SSA	SLE, Sjögren's syndrome
			Anti-La/SSB	
			Anti-U1RNP	SLE, mixed CTD
		Chromatin	Anti-Ku	SLE, scleroderma myositis
			Antitopolsomerase 1 (SCL-70)	Scleroderma
	Discrete speckled	Chromatin	Anticentromere	CREST
	Nucleolar	Nucleolar RNP	Anti-U3RNP	Scleroderma
		Nucleolar components	Anti–RNA polymerase I	
			Anti–Pm-Sci	

CREST, calcinosis cutis, Raynaud's phenomenon, involvement of the esophagus with dysphagia, sclerodactyly, and telangiectases; CTD, connective tissue disease; RNP, ribonucleoprotein.

Indirect immunofluorescence detects nuclear, homogeneous, rim, speckled, and nucleolar patterns (Table 10-3). The fluorescence ANA test can be regarded as a specific marker for SLE in a rim pattern with a titer of 1:160 or higher and is often indicative of the presence of anti–native or double-stranded (ds) DNA antibodies. Although anti-dsDNA has generally been regarded as the most specific marker of SLE, the lack of sensitivity makes a negative test unhelpful. Other markers that have been examined include antinucleosome antibodies, which may be more prevalent in SLE patients and may develop earlier than anti-dsDNA antibodies. This assay, however, is not widely available and has not been rigorously evaluated (47). At a titer of 1:20, about 20% of patients with DLE, most patients with systemic scleroderma, and as many as 5% of normal persons may have a positive reaction. The presence of anti-Sm is indicative of associated lupus nephritis. Antibodies against single-stranded DNA are nonspecific and are found in a variety of diseases. Anti-nRNP antibodies are of diagnostic significance only at high titers because they then indicate mixed connective tissue disease. ANA-negative sera should be examined for the presence of anti-Ro/SSA and La/SSB antibodies, characteristic of subacute and neonatal LE and SLE with genetic deficiency of complement components.

The LE cell test is of historical significance. It consisted of incubating a patient's serum with normal white blood cells. In the presence of antibody to whole nucleoprotein (LE factor), damage to the nuclei of leukocytes incited phagocytosis of affected nuclei by unaffected white blood cells. If a smear of the incubated white blood cells is made and stained with Wright's stain, the phagocytized nuclear material can be observed within some of the neutrophils as a large, round, amorphous, smoky, basophilic body of such a large size that it presses the nucleus of the neutrophil against the cell membrane. This represents the LE cell.

Direct immunofluorescence studies detect immunoreactant deposits in affected tissues, particularly the skin and kidneys. A skin biopsy (3- to 4-mm punch) is submitted in saline-impregnated gauze or phosphate-buffered saline, snap frozen, sectioned, and incubated with fluorescein-conjugated antisera to IgA, IgM, IgG, and the third component of complement (C3). In a positive test there is continuous granular deposition of usually two or more immunoreactants (in a band) along the dermal–epidermal junction (Fig. 10-2). Variables that affect test results are the site of the biopsy (sun exposed vs. sun protected), duration of the lesion (acute, subacute, chronic), and preceding therapy. The frequency and implications of positive results in DLE and SLE are summarized in Table 10-4 (48–50).

Cautious sampling and interpretation of findings are necessary to avoid false-positive and false-negative results. The presence of only one type of immunoreactant, particularly in an intermittent distribution, may be seen in chronically sun-exposed skin or with underlying disorders such as rosacea. False-negative results are often found in acute or subacute lesions and treated lesions. Optimally, an established lesion, present for 3 months or longer, that has not been treated is submitted for study (51).

TABLE 10-4 Direct Immunofluorescence in Lupus Erythematosus

Site		Result: Discoid LE	Result: Systemic LE
Sun exposed (e.g., dorsal forearm)	Involved	Positive in >90% of untreated lesions	Positive in 80%–90% of untreated lesions
Sun exposed (e.g., volar forearm)	Uninvolved	Almost always negative	Positive in >80% of untreated SLE
Non–sun exposed (e.g., buttock)	Uninvolved	Negative	With active LE: positive in >91% With inactive SLE: positive in 33% Positive result may indicate renal involvement

Electron microscopic examination of the cutaneous lesions of both DLE and SLE shows marked changes in the basal cells and the lamina densa. The basal cells show vacuolization of their cytoplasm, which may progress to necrosis and disintegration of the cytoplasm. The colloid or Civatte bodies that may be seen in the epidermis and in the dermis are similar in appearance on electron microscopy to those observed in lichen planus. They are finely filamentous to amorphous granular in appearance and do not possess a delimiting membrane.

The antigen–antibody complexes have been localized with immunoelectron microscopy to beneath the lamina densa. They are seen as irregular aggregates in the uppermost portion of the dermis in the ground substance and occasionally on collagen fibrils. In some instances, small amounts of reaction product are seen within the lamina densa and the lamina lucida. Localization of immune complexes in lupus erythematosus thus differs from their localization in bullous pemphigoid, in which they are situated entirely within the lamina lucida near the basal cells (see Chapter 9). In bullous SLE, direct immunoelectron microscopy of perilesional skin also shows the reaction product in a continuous bandlike distribution below the lamina densa and a separation plane in the dermis below this band, indicating early bulla formation (52).

The presence of intracytoplasmic tubuloreticular structures has been reported in the cutaneous and renal lesions of SLE and in lesions of DLE. They bear a superficial resemblance to tubuloreticular structures and internal nucleoproteins of paramyxovirus. They are a nonspecific result of cell injury related to increased interferon-α levels in lupus patients and are not specific for lupus erythematosus (52).

Jessner's Lymphocytic Infiltration of the Skin

Jessner's lymphocytic infiltration of the skin, first described in 1953 (53), is not a well-understood entity. It is characterized by asymptomatic papules or well-demarcated, slightly infiltrated red plaques, which may develop central clearing. In contrast to lesions of chronic lupus erythematosus, the surface shows no follicular plugging or atrophy. Lesions arise most often on the face but may also involve the neck and upper trunk (54). Although this disorder has been reported to occur in childhood (55), affected patients are usually middle-aged men and women.

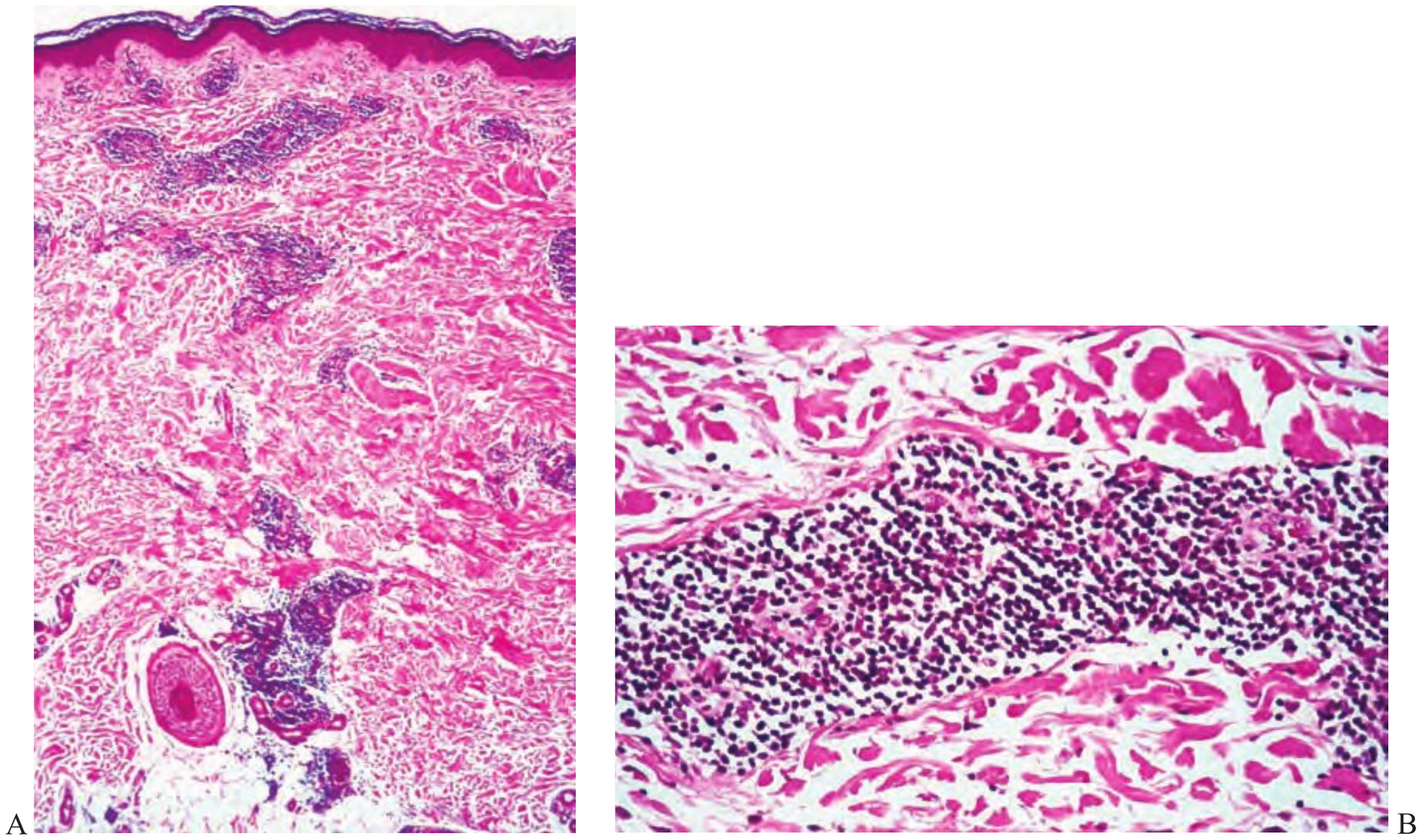
Variable numbers of lesions (one to many) often persist for several months or several years. They may disappear without sequelae or recur at previously involved sites or elsewhere. The eruption may be precipitated or aggravated by sunlight. Antimalarial drugs and/or corticosteroids are useful in controlling this disorder.

Histopathology. The epidermis may be normal but often appears slightly flattened. In the dermis, there are moderately dense perivascular and diffuse infiltrates composed of small, mature lymphocytes admixed with occasional histiocytes and plasma cells (Fig. 10-10A, B). The infiltrate may extend around folliculosebaceous units and into subcutaneous adipose tissue.

The histologic differential diagnosis of lymphocytic infiltration of the skin includes the other six of the seven Ls: lupus erythematosus, polymorphous light eruption, lymphocytoma cutis, lues, Lyme disease, and lymphoma. Jessner's lymphocytic infiltrate is limited to sun-exposed skin and lacks the hyperkeratosis, atrophy, interface changes, mucin, and direct immunofluorescence findings noted in lupus. Therefore, lupus should be excluded with serologic and direct immunofluorescence studies. Serologic studies and the clinical distribution of lesions allow separation of lues and Lyme disease from Jessner's lymphocytic infiltrates.

Approximately 10% of cases of lupus that lack interface alterations and that show negative direct immunofluorescence studies may initially be placed into the holding category of "lymphocytic infiltrates of the skin." Polymorphous light eruptions usually show prominent papillary dermal edema; however, plaque-type polymorphous light eruption may histologically overlap with lymphocytic infiltration of the skin. Clinical features may sometimes separate these two entities.

A poorly understood entity histologically similar to Jessner's lymphocytic infiltrate is palpable migratory arciform erythema. This entity differs clinically in that it is slightly pruritic and tends to involve the trunk and proximal extremities. It waxes and wanes over days to weeks rather than weeks to months. Differences in histology have been reported but have not been thoroughly evaluated by multiple studies (56).



A B

FIGURE 10-10. Jessner's lymphocytic infiltrate. A: The epidermis is normal. The dermis contains tightly cuffed lymphocytic infiltrates following blood vessels and focally surrounding appendages. B: Higher magnification shows a purely lymphocytic infiltrate around vascular channels.

Immunohistochemical cell marker studies indicate that the predominant component of lymphocytic infiltration of the skin is a mature T lymphocyte. Phenotyping studies show predominantly $CD4^+$ T helper cell (57). Other studies have suggested a $CD8^+$ cytotoxic phenotype (58). Rearrangement of the T-cell receptor gene has not been detected in the limited number of cases studied. The relative paucity of B lymphocytes may assist in separation of this entity from lymphocytoma cutis, which usually displays larger B-cell components with or without associated germinal center formation. Lymphoma cutis may be distinguished with cell-marker analysis, which may show a high proportion of B lymphocytes with a less mature phenotype than expected in skin, or cells with aberrant expression of surface antigens.

Pathogenesis. Opinion varies as to whether Jessner's lymphocytic infiltrate of the skin is a distinct entity. The following four views have been expressed: (a) clinical, histologic, and immunohistochemical findings warrant its distinction as a separate entity (59); (b) although some cases represent an entity, others are DLE; (c) all cases are DLE; and (d) it represents an abortive or initial phase of any of the four other diseases with a patchy dermal infiltrate—that is, discoid lupus erythematosus, the plaque type of polymorphous light eruption, lymphocytoma cutis, and lymphocytic lymphoma. The last view appears to be the most likely (60). Isolated reports of Jessner's lymphocytic infiltrate have been reported in association with angiotensin-converting enzyme inhibitor, enalapril, and a synthetic polypeptide, glatiramer acetate, used to treat multiple sclerosis (61,62). Isolated familial cases have also been reported (60).

The diagnosis of lymphocytic infiltration of the skin depends on clinicopathologic correlation and on longitudinal follow-up. It may be used as a preliminary diagnostic term until a more definitive diagnosis is possible.

MIXED CONNECTIVE TISSUE DISEASE

Overlapping findings of SLE, scleroderma, and polymyositis associated with the presence of high titers of anti-U1 ribonucleoprotein (RNP) antibodies have been recognized since 1972 as the syndrome of *mixed connective tissue disease* (MCTD) (63). The first clue to the diagnosis is usually a positive, high-titer speckled ANA. The clinical presentation includes, but is not limited to, edema of the hands, acrosclerosis, Raynaud's phenomenon, synovitis of one or more joints, and myositis that is documented with biopsy or serum elevations of muscle enzymes. Esophageal hypomotility and pulmonary disease may be seen as well. The diagnosis of MCTD may not be made at the outset because symptoms may present in an asynchronous fashion.

Cutaneous lupus erythematosus lesions are found in approximately half of the patients, about as often as "sausage fingers" or sclerodactyly. They cover the entire spectrum of cutaneous lupus erythematosus. Most commonly there are diffuse,

nonscarring, poorly demarcated subacute lesions, but some patients show acute malar eruptions as seen in SLE or persistent scarring lesions as seen in DLE.

Patients with high-titer anti-U1 RNP antibodies have a low prevalence of serious renal disease and life-threatening neurologic complications. Although the prognosis of MCTD compares favorably to that of SLE, death may occur from progressive pulmonary hypertension and cardiac complications (64).

Histopathology. If cutaneous lesions of lupus erythematosus are present, the histologic findings correspond to the type of lesion described in the section on DLE and SLE.

Histogenesis. MCTD, in contrast with most cases of SLE, has no antibodies to DNA. The absence of such antibodies accounts for the rarity of renal disease.

Indirect immunofluorescence studies show the presence of very high titers of serum antibodies directed against extractable ribonuclease-sensitive antigens known as small nuclear ribonucleoproteins (snRNPs). They characterize MCTD but are not specific for it. They produce a fine speckled ANA pattern at high dilutions. This speckled pattern corresponds to the widespread distribution of snRNP in the nucleus at sites of active gene transcription, where messenger RNA is being processed.

Direct immunofluorescence staining of normal skin shows deposition of IgG in a speckled (particulate) pattern in epidermal nuclei. Although this finding is typical of MCTD, it is found occasionally also in patients with SLE and other connective tissue diseases (65). In addition, patients with MCTD may show a subepidermal lupus band in normal skin. Such a band has been observed in normal sun-exposed skin in about 20% of the cases.

DERMATOMYOSITIS

Dermatomyositis manifests as an inflammatory myopathy with characteristic cutaneous findings. In the absence of cutaneous findings, the diagnosis of polymyositis is applied. Cutaneous findings alone, without muscular involvement, have been termed *amyopathic dermatomyositis* or *dermatomyositis sine myositis* (66).

Both dermatomyositis and polymyositis are uncommon diseases that have a similar incidence. Both have two peaks of occurrence: one in childhood and one between the ages of 45 and 65 years (51). In some instances, the cutaneous eruption precedes the development of muscular weakness by many months or even several years.

The four systemic and single cutaneous diagnostic criteria for dermatomyositis are symmetric proximal muscle weakness, elevated muscle enzymes, an abnormal electromyelogram in the absence of neuropathy, consistent muscle biopsy changes, and cutaneous findings (67). Involvement of the skeletal muscles causes progressive weakness, vague muscular pain, and, later, muscle atrophy. The proximal muscles of the extremities and the anterior neck muscles often are the first to be involved. Involvement of the pharynx may result in dysphagia and aspiration of food, and involvement of the diaphragm and the intercostal muscles may lead to respiratory failure. Arthritis and arthralgias may occur in up to 25% of cases. Other, less common systemic manifestations, such as interstitial pneumonitis, dysphagia, dysphonia, and cardiac conduction abnormalities, portend a worse prognosis.

Two distinctive cutaneous lesions are found in dermatomyositis. One is violaceous, slightly edematous periorbital patches that primarily involve the eyelids, known as the *heliotrope rash*. The other is discrete red-purple papules over the bony prominences, particularly the knuckles, knees, and elbows, known as *Gottron's papules*. These may evolve into atrophic plaques with pigmentary alterations and telangiectasia and are then known as *Gottron's sign*.

Other cutaneous findings include periungual telangiectasia, hypertrophy of cuticular tissues associated with splinter hemorrhages, photosensitivity, and poikiloderma. Often lesions resembling the erythematous-edematous lesions seen in subacute cutaneous or systemic lupus erythematosus may be found. Subcutaneous and periarticular calcification may be found, particularly in affected children. Calcinosis is usually seen centered in the proximal muscles of the shoulders and pelvic girdle. Childhood onset may also be associated with lipodystrophy and insulin resistance (68). Other uncommonly reported cutaneous findings include gingival telangiectasia, angiokeratomas, panniculitis, flagellate erythema, scleromyxedematous lesions, and pityriasis rubra pilaris–like lesions (69–72).

Controversy exists over the association of dermatomyositis with malignancy (73). Interpretation of reports with incidences of 6% to 50% is hampered by the asynchronous development of malignancy in relation to the dermatomyositis. Some series fail to show a significant difference between affected patients and the control population. If malignancy arises with dermatomyositis, it usually occurs in the adult form. Some sources indicate that this association is also present in the childhood form, whereas others view such reports with skepticism. Various tumors have been reported, with ovarian carcinoma perhaps being most frequent (74). Larger population-based studies have suggested an incidence of carcinoma at between 20% and 25% (75). Although ovarian carcinoma is still considered the most common associated malignancy, other tumors reported include lung, prostatic, pancreatic, and gastrointestinal carcinomas. In younger males, testicular carcinoma is more prevalent. In Asians, there is an increased association with nasopharyngeal carcinoma (76).

As with lupus erythematosus, the pathogenesis of the disease is uncertain. Associated antibodies include PM1, Jo1 (correlates with pulmonary fibrosis), Ku (associated with sclerodermatomyositis), and M2. Other recently reported markers include autoantibodies to 155kd, and Se antigens have been reported to be associated with amyopathic dermatomyosis. (77). A single case of a cutaneous eruption mimicking dermatomyositis after treatment with imatinib mesylate has

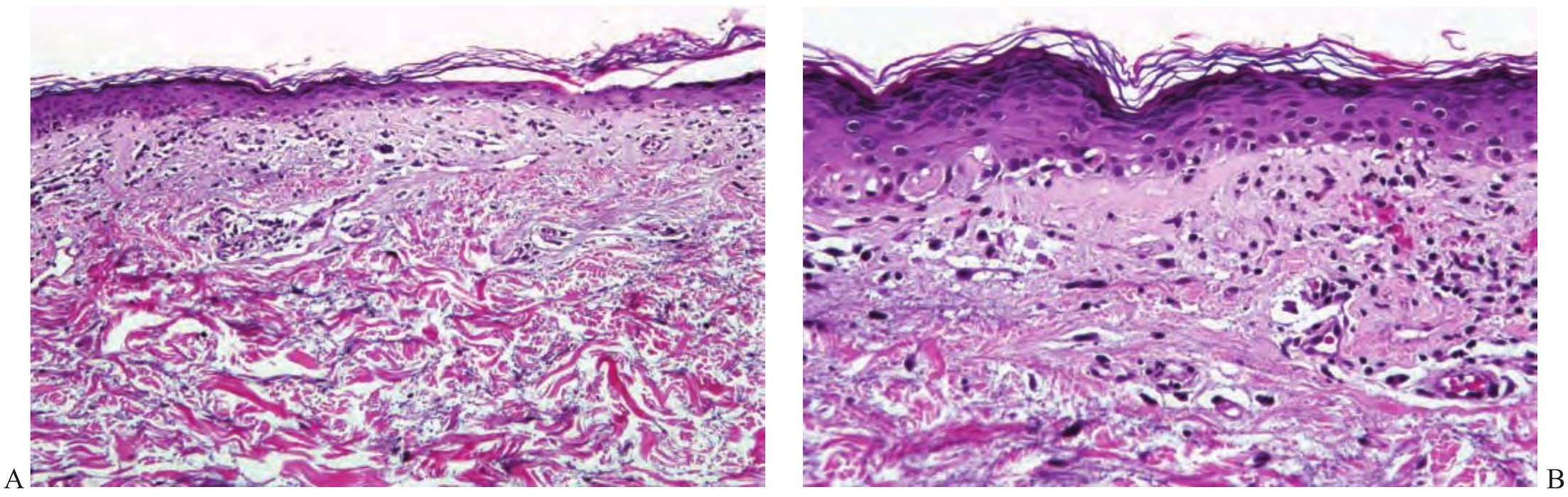


FIGURE 10-11. Dermatomyositis. A: An atrophic epidermis shows marked vacuolar alteration of basilar keratinocytes associated with a sparse lymphocytic inflammatory infiltrate around superficial dermal vessels. B: Marked vacuolar alteration of basilar keratinocytes associated with sparse lymphocytic infiltrates and papillary dermal melanophages.

been reported (78). Medications including hydroxyurea, quinidine, nonsteroidal antiinflammatory agents, d-penicillamine, isoniazid, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors have been reported to exacerbate dermatomyositis.

On the whole, the prognosis of dermatomyositis is favorable, especially when treatment with corticosteroids is used. Other therapeutic agents include methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, chlorambucil, and cyclosporine. The mortality has been reported to be approximately 14% in some series, with metastatic malignancy a frequent cause of death (79).

Histopathology. The erythematous-edematous lesions of the skin in dermatomyositis may show only nonspecific inflammation. However, quite frequently the histologic changes are indistinguishable from those seen in SLE. There is epidermal atrophy, basement membrane degeneration, vacuolar alteration of basilar keratinocytes, a sparse lymphocytic inflammatory infiltrate around blood vessels, and interstitial mucin deposition (Fig. 10-11A, B) (80). With severe inflammatory changes, there may be associated subepidermal fibrin deposition. Although immune complexes are not detected at the dermal–epidermal junction as in lupus erythematosus, it should be remembered that up to 50% of subacute cutaneous lupus biopsies can also have a negative direct immunofluorescence.

Old cutaneous lesions with the clinical appearance of poikiloderma atrophicans vasculare usually show a bandlike infiltrate under an atrophic epidermis with hydropic degeneration of the basal cell layer (see also the section on poikiloderma atrophicans vasculare). The Gottron's papules overlying the knuckles also show vacuolization of the basal cell layer but acanthosis rather than epidermal atrophy (81). Subcutaneous tissue may show focal areas of panniculitis associated with mucoid degeneration of fat cells in early lesions. Extensive areas of calcification may be present in the subcutis at a later stage (see calcinosis cutis, Chapter 17).

Magnetic resonance imaging permits noninvasive assessment of muscle inflammation and may serve as a guide in locating a site for muscle biopsy. Tender proximal muscles of an extremity yield more useful information than atrophic, weak muscles, which show end-stage changes. Three types of changes may be observed in active disease: (a) interstitial inflammatory infiltrates composed of lymphocytes and macrophages, (b) segmental muscle fiber necrosis (loss of skeletal muscle transverse striation, hyalinization of the sarcoplasm, fragmentation and/or phagocytosis of degenerated muscle fragments), or (c) vasculopathy (82). The latter entity may be seen in the childhood form and shows immunocomplex deposition in vessel walls (83). Old lesions usually show a rather nonspecific picture of atrophy of the muscle fibers and diffuse interstitial fibrosis with relatively little inflammation.

Systemic Lesions. Changes in organs other than the skin and the striated muscles occur only rarely in dermatomyositis, in contrast to SLE and systemic scleroderma. The myocardium may show changes identical to those in the skeletal muscle but less severe. Ulcerative lesions in the gastrointestinal tract, caused by vascular occlusions, have also been described (84).

Histogenesis. On electron microscopic examination the degenerative changes include focal disintegration of myofilaments and myofibrils, vacuolization, and accumulation of lipid and lysosomes within muscle fibers. As in lupus erythematosus, nonspecific intracytoplasmic tubuloreticular structures may be found in skin and muscles.

Differential Diagnosis. Differentiation of the cutaneous lesions of dermatomyositis from those of subacute cutaneous or systemic lupus erythematosus may be impossible on a histologic basis. It may also be impossible on clinical grounds in cases in which muscular weakness is mild or absent, as it may be in the early stage of dermatomyositis. In such cases, laboratory tests are of great value. The most important is the

lupus band test, which is always negative in lesions of dermatomyositis (85), whereas in lesions of lupus erythematosus it is positive in 90% of the cases. Other tests that are usually negative in dermatomyositis and often positive in lupus erythematosus include urinalysis and renal function tests, as well as tests for antinuclear antibodies, anti–native DNA antibodies, and antibodies to ribonucleoprotein. Rarely, patients with dermatomyositis demonstrate a positive Ro antibody titer. Patients with active myositis show an elevation of serum creatine kinase and aldolase.

POIKILODERMA ATROPHICANS VASCULARE

Poikiloderma atrophicans vasculare may be seen in three different settings: (a) in association with three genodermatoses, (b) as an early stage of mycosis fungoides, and (c) in association with dermatomyositis and, less commonly, lupus erythematosus.

The three genodermatoses in which the cutaneous lesions have the appearance of poikiloderma atrophicans vasculare are (a) poikiloderma congenitale of Rothmund-Thomson (see Chapter 6), with the lesions of poikiloderma present largely on the face, hands, and feet, and occasionally also on the arms, legs, and buttocks; (b) Bloom's syndrome (see Chapter 6), with poikiloderma-like lesions on the face, hands, and forearms; and (c) dyskeratosis congenita (see Chapter 6), in which there may be extensive netlike pigmentation of the skin suggestive of poikiloderma atrophicans vasculare.

Poikiloderma-like lesions as features of early mycosis fungoides may be seen in one of two clinical forms: either as the large plaque type of parapsoriasis en plaques, also known as poikilodermatous parapsoriasis (see Chapter 7), or as parapsoriasis variegata, also called parakeratosis variegata, which, in its early state, shows papules arranged in a netlike pattern (see Chapter 7). Although these two types of parapsoriasis represent an early stage of mycosis fungoides, not all cases progress clinically into fully developed mycosis fungoides (86). Cases in which no progression toward mycosis fungoides is observed have been described also as *idiopathic poikiloderma atrophicans vasculare* (87).

The third group of diseases in which lesions of poikiloderma atrophicans vasculare occur are represented by dermatomyositis and SLE. Dermatomyositis is much more commonly seen as the primary disease than lupus erythematosus, and the association with dermatomyositis often is referred to as poikilodermatomyositis. In contrast to mycosis fungoides, in which poikilodermatous lesions are seen in the early stage, the lesions found in dermatomyositis and SLE generally represent a late stage.

Clinically, the term poikiloderma atrophicans vasculare is applied to lesions that, in the early stage, show erythema with slight, superficial scaling, a mottled pigmentation, and telangiectases. In the late stage the skin appears atrophic and the erythema is less pronounced than in the early stage, but the mottled pigmentation and the telangiectases are more pronounced. The clinical picture then resembles that of chronic radiodermatitis.

Histopathology. In its early stage poikiloderma atrophicans vasculare, without respect to its cause, shows moderate thinning of the stratum malpighii, effacement of the rete ridges, and hydropic degeneration of the basal cells. In the upper dermis there is a bandlike infiltrate, which in places invades the epidermis. The infiltrate consists mainly of lymphoid cells, but it also contains a few histiocytes. Melanophages filled with melanin as a result of pigmentary incontinence are found in varying numbers within the infiltrate. In addition, there is edema in the upper dermis, and the superficial capillaries are often dilated. In the late stage the epidermis is apt to be markedly thinned and flattened, but the basal cells still show hydropic degeneration. Melanophages and edema of the upper dermis are still present, and telangiectasia may be pronounced.

The amount and type of dermal infiltrate vary with the underlying cause. In poikiloderma atrophicans vasculare associated with one of the genodermatoses the mononuclear infiltrate is mild and may be absent in the late stage (88). Similarly, in the late stage of poikiloderma seen in association with dermatomyositis or SLE there is only slight dermal inflammation (80). In contrast, the amount of inflammatory infiltrate seen in poikiloderma associated with early mycosis fungoides increases rather than decreases with time (Fig. 10-12). In addition, cells with large, hyperchromatic nuclei, so-called mycosis cells, are likely to be present, and there is often marked epidermotropism of the infiltrate, which may result in Pautrier microabscesses. Cell-marker analysis of such cases has shown most cells to be T-helper/inducer ($CD4^+$) lymphocytes that lack Leu-8 (CD7) and/or Leu-9 expression, as seen in cutaneous T-cell lymphoma (89).

SCLERODERMA

Scleroderma (from the Greek *skleros*, hard, and *derma*, skin) is a connective tissue disorder characterized by thickening and fibrosis of the skin. Two types of scleroderma exist: circumscribed scleroderma (*morphea*) and systemic scleroderma (*progressive systemic sclerosis*). They are somewhat analogous to the purely cutaneous form of lupus erythematosus (DLE) and the cutaneous plus visceral involvement in systemic lupus erythematosus. Rarely, morphea and systemic scleroderma may coexist. In such instances, the manifestations of morphea arise first and are extensive, whereas those of systemic scleroderma are mild and nonprogressive (90). Rarely, the manifestations of systemic scleroderma precede those of morphea (91).

There are also two variants of morphea: (a) atrophoderma of Pasini and Pierini and (b) eosinophilic fasciitis of Shulman. The latter disease differs sufficiently from morphea, and so it will be discussed separately.

Hardening of the skin (sclerodermoid changes) may also arise in association with genetic, metabolic, neurologic, and immunologic disorders, with occupational or chemical exposures, in association with malignancy, or as a sequela of infection (92). Genetic disorders that may show sclerodermatous

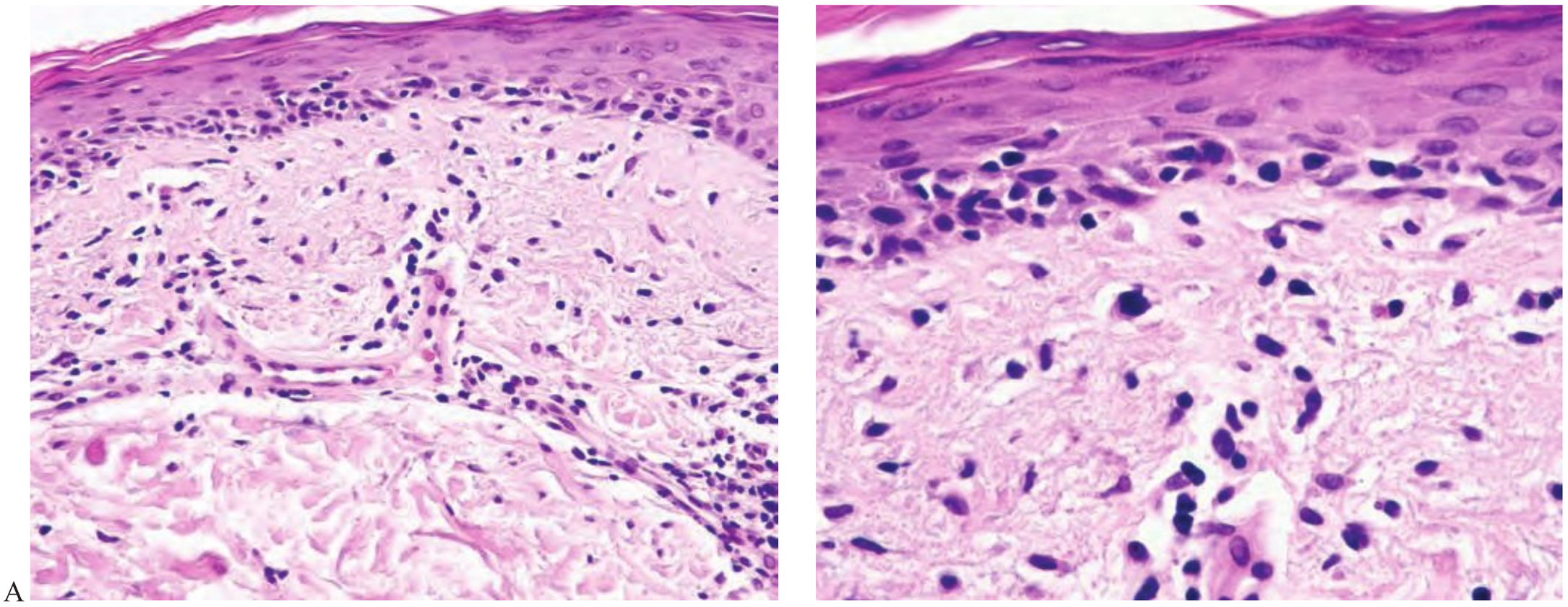


FIGURE 10-12. Poikiloderma. A: The epidermis appears flattened and shows hydropic degeneration of basal cells. B: The upper superficial contains a bandlike infiltrate, which in places extends into the epidermis.

cutaneous changes include phenylketonuria, progeria, Rothmund-Thomson syndrome, and Werner's syndrome. Individuals at risk are jackhammer and chain saw operators and those exposed to polyvinyl chloride, silica, and epoxy resins. Patients with metabolic disorders such as porphyria cutanea tarda, primary systemic amyloidosis, Hashimoto's disease, carcinoid syndrome, and childhood diabetes mellitus may show similar cutaneous changes. Chronic graft-versus-host disease frequently shows sclerodermatous changes, and scattered reports in the literature indicate such changes may arise subsequent to silicone and paraffin injections for cosmetic procedures (93). Chemical agents have been known to induce thickening and hardening of the skin. Specific compounds include polyvinyl chloride, bleomycin, pentazocine, L-5 hydroxytryptophan and carbidopa (94), Spanish rapeseed oil (95), and L-tryptophan (eosinophilia-myalgia syndrome) (96).

Morphea

In morphea, or circumscribed scleroderma, the lesions usually are limited to the skin and to the subcutaneous tissue beneath the cutaneous lesions. Occasionally, however, the underlying muscles and rarely the underlying bones are also affected.

Morphea may be divided according to morphology and distribution of lesions into six types: guttate, plaque, linear, segmental, subcutaneous, and generalized. Eosinophilic fasciitis, even though it is the fascial component of subcutaneous morphea, is discussed separately because of its somewhat different clinical and histologic appearance.

Guttate lesions occur almost always in association with lesions of the plaque type. Guttate lesions are small and superficial; they resemble the lesions of lichen sclerosus et atrophicus but do not show hyperkeratosis or follicular plugging.

Lesions of the plaque type—the most common manifestation of morphea—are round or oval but through coalescence may assume an irregular configuration. They are indurated, have a smooth surface, and show an ivory color. As long as they are enlarging, they may show a violaceous border, the so-called lilac ring.

Lesions of the linear type occur predominantly on the extremities and on the anterior scalp. When one or several extremities are involved, there is often, in addition to induration of the skin, marked atrophy of the subcutaneous fat and of the muscles, resulting in contractures of muscles and tendons and ankyloses of joints. In children it may result in impaired growth of the affected limb (97). On the anterior portion of the scalp and on the forehead, linear morphea often has the configuration of the stroke of a saber (*coup de sabre*) (72).

Segmental morphea occurs on one side of the face, resulting in hemiatrophy. Occasionally, morphea en coup de sabre and facial hemiatrophy occur together (98). This manifestation of morphea typically occurs in children and can often be associated with neurologic deficits (99). Due to a high incidence of overlap between the two conditions and the similar histopathology, some authors feel that they represent slightly different manifestations of the same process. Retrospective studies have estimated the coincidence of the conditions at between 36% and 42% (100,101).

In subcutaneous morphea (morphea profunda) the involved skin feels thickened and bound to the underlying fascia and muscle. The involved plaques are ill defined, and the skin of these plaques is smooth and shiny (102).

Generalized morphea comprises very extensive cases showing a combination of several of the five types just described. Although it is seen mainly in children, in whom it has been described as disabling pansclerotic morphea (90), it

can also occur in adults. Rarely, bullous lesions are seen in patients with generalized morphea (103).

There are several reported cases of morphea that involve the superficial reticular dermis (superficial morphea) as contrasted with its usual involvement of the deep reticular dermis (104). The clinical impact of the depth of involvement is unclear. The coexistence of lesions of morphea and lichen sclerosus et atrophicus is worthy of note.

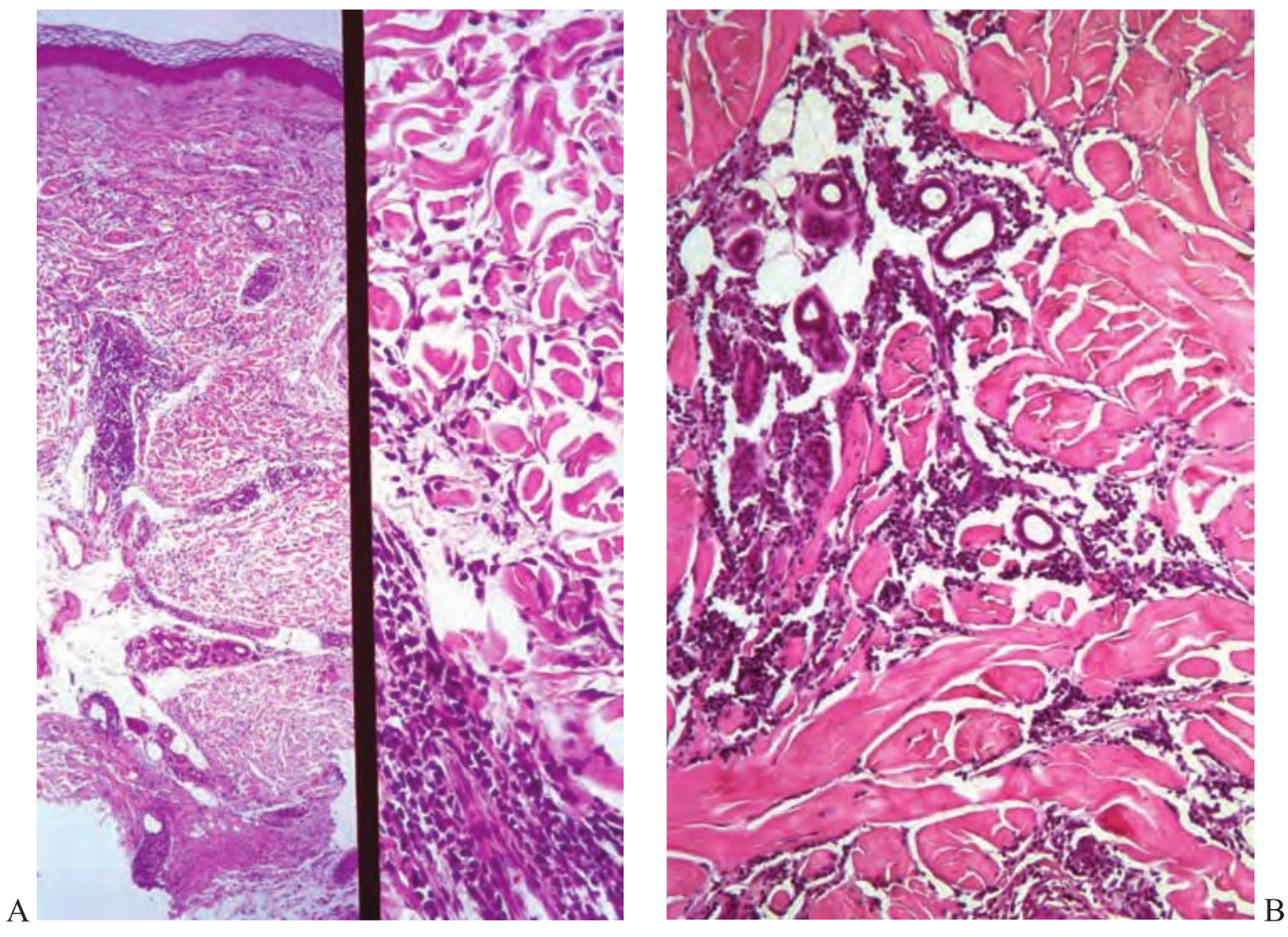
There is conflicting data regarding *Borrelia burgdorferi* infection in cases of morphea. Studies indicating that such a relationship exists are primarily from Europe (105). Studies in North America and some from Europe have resulted in negative findings (106).

Histopathology. The different types of morphea cannot be differentiated histologically. Rather, they differ in regard to severity and depth of involvement of the skin. Therefore, it is of great importance that the biopsy specimen include adequate subcutaneous tissue because most of the diagnostic alterations are seen in the lower dermis and in the subcutis.

Early inflammatory, intermediate, and late sclerotic stages exist. In the early inflammatory stage, found particularly at the violaceous border of enlarging lesions, the reticular dermis shows interstitial lymphoplasmacytic infiltrates with or without eosinophils among slightly thickened collagen bundles (Fig. 10-13A). As lesions become established, the inflammatory infiltrates surround eccrine coils and are associated with hypocellular collagen bundles and reduced numbers of surrounding adipocytes (Fig. 10-13B). A much more pronounced inflammatory infiltrate than that seen in the dermis often involves the subcutaneous fat and extends upward toward the eccrine glands. Trabeculae subdividing the subcutaneous fat are thickened because of the presence of an inflammatory infiltrate and deposition of new collagen. Large areas of subcutaneous fat are replaced by newly formed collagen, which is composed of fine, wavy fibers rather than bundles and stains only faintly with hematoxylin-eosin (107). Vascular changes in the early inflammatory stage generally are mild both in the dermis and in the subcutaneous tissue. They may consist of endothelial swelling and edema of the walls of the vessels (108).

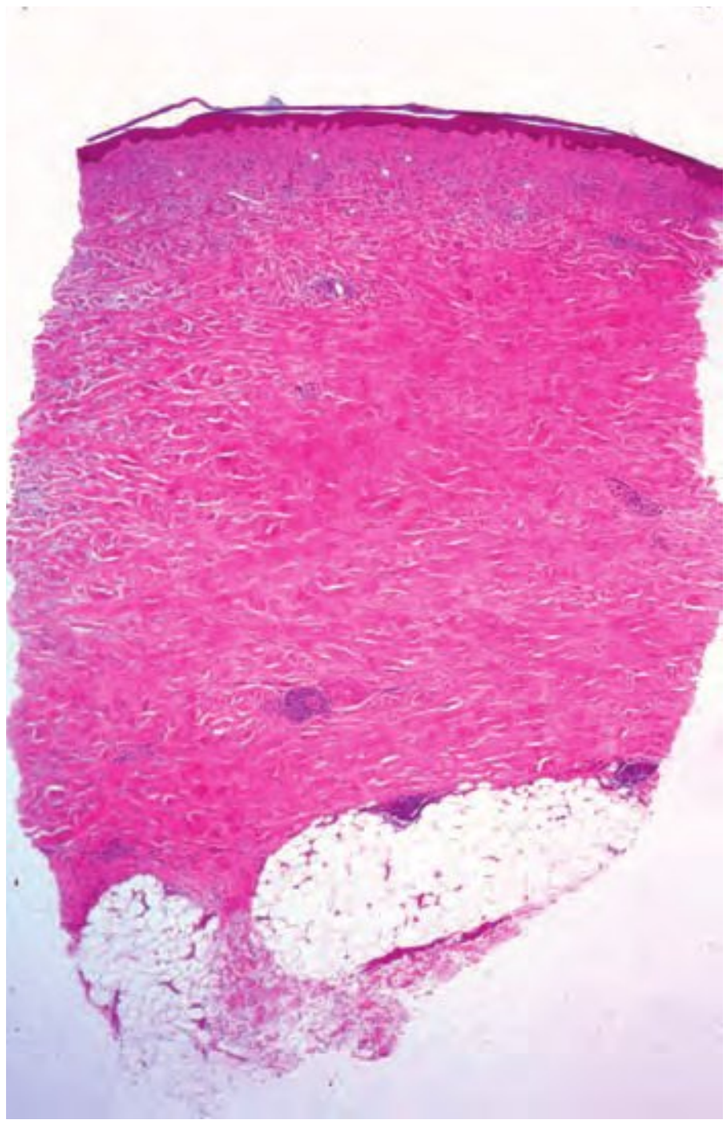
In the late sclerotic stage, as seen in the center of old lesions, the inflammatory infiltrate has disappeared almost completely, except in some areas of the subcutis. The epidermis is normal. The collagen bundles in the reticular dermis often appear thickened, closely packed, and hypocellular and stain more deeply eosinophilic than in normal skin (Fig. 10-13C, D). In the papillary dermis, where the collagen normally consists of loosely arranged fibers, the collagen may appear homogeneous.

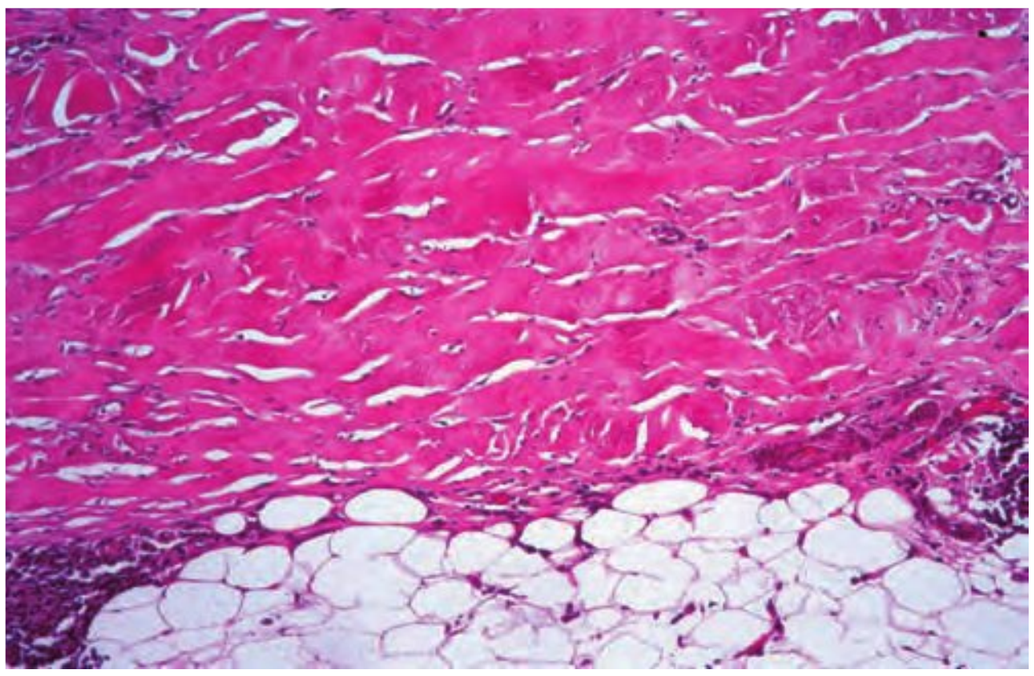
The eccrine glands appear markedly atrophic, have few or no adipocytes surrounding them, and appear surrounded by newly formed collagen (Fig. 10-13B). In addition, instead of



A B

FIGURE 10-13. Morphea. A: The early inflammatory phase of morphea, where there is an interstitial lymphoplasmacytic infiltrate distributed among deep dermal collagen bundles. Collagen bundles are minimally swollen. B: Over time, collagen bundles become thickened, hypocellular, and swollen. Lymphoplasmacytic inflammatory infiltrates separate such collagen strands, surround eccrine coils in the deep dermis, and are associated with loss of adipocytes around eccrine apparatus. (continued)

C 


D

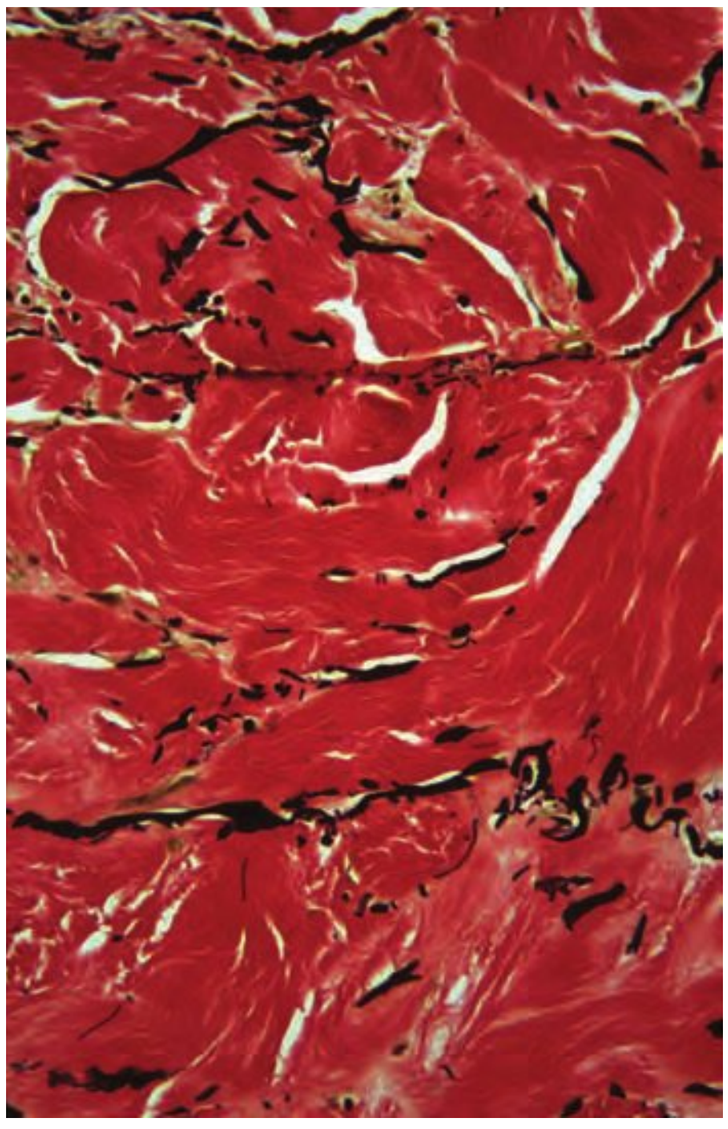

E

FIGURE 10-13. (continued) C: An established lesion of morphea: a "square" appearance in a punch biopsy. Note that appendages such as pilar apparatus are absent. Inflammation is sparse and localized at the dermal–subcutaneous interface. D: The trabeculae subdividing the subcutaneous fat are thickened and there is a patchy lymphoplasmacytic infiltrate. Pale, thickened collagen bundles appear arranged parallel to each other. E: Elastic stains demonstrate thick, coarse elastic fibers separated by collagen. They have a somewhat parallel array.

lying near the dermal–subcutaneous junction as in normal skin, they seem to lie higher in the dermis as a result of the replacement of most of the subcutaneous fat by newly formed collagen. This collagen consists of thick, pale, sclerotic, homogeneous, or hyalinized bundles with only few fibroblasts (hypocellular). Few blood vessels are seen within the sclerotic collagen; they often have a fibrotic wall and a narrowed lumen. Elastic stains show thick elastic fibers arranged parallel to hypocellular collagen strands and parallel to the epidermal surface (Fig. 10-13E) (109).

The fascia and striated muscles underlying lesions of morphea may be affected in the linear, segmental, subcutaneous, and generalized types. The fascia shows fibrosis and sclerosis similar to that seen in subcutaneous tissue. The muscle fibers appear vacuolated and separated from one another by edema and focal collections of inflammatory cells (110).

TABLE 10-5 Contrasting Features of Morphea and Lichen Sclerosus Et Atrophicus

	Morphea	Lichen sclerosus et atrophicus
Epidermis	Relatively normal	Thinning of rete
	No follicular plugging	Follicular plugging
Dermal–epidermal junction	No hydropic degeneration	Hydropic degeneration of basilar cells
	Subepidermal separation infrequent	Often subepidermal bullae
Dermis	Appears homogenized	Marked edema
	Papillary dermal collagen and elastic fibers present	Elastic fibers absent
Subcutis	Inflammation	No inflammation or fibrosis
	Fibrosis	

Bullae, seen only on rare occasions in generalized and in subcutaneous morphea, arise subepidermally, probably as a result of lymphatic obstruction, causing subepidermal edema.

Differential Diagnosis. Contrasting features of morphea and lichen sclerosus et atrophicus are summarized in Table 10-5. They include relatively little epidermal change in morphea, as compared with thinning of the rete ridges, follicular plugging, and interface alterations of lichen sclerosus. The reticular dermal changes of fibrosis and inflammation in morphea contrast with the edema and loss of elastic tissue in lichen sclerosus. Histologic differentiation of the late stage of morphea from lichen sclerosus et atrophicus may cause difficulties, particularly in view of the fact that the two conditions may coexist.

Systemic Scleroderma

In systemic scleroderma, in addition to involvement of the skin and the subcutaneous tissue, visceral lesions are present, leading to death in some patients. The indurated lesions of the skin are not sharply demarcated or "circumscribed," as in morphea, although a few well-demarcated morphea-like patches may occasionally be seen.

Cutaneous involvement usually starts peripherally on the face and hands, gradually extending to the forearms. Facial changes include a masklike, expressionless face, inability to wrinkle the forehead, a beaklike nose, and tightening of the skin around the mouth associated with radial folds. The hands show nonpitting edema involving the dorsa of the fingers, hands, and forearms. Gradually the fingers become tapered, the skin becomes hard, and flexion contractures form. These changes are referred to as acrosclerosis and are associated with Raynaud's phenomenon, which may precede other manifestations by months or even years. Microscopic examination of the nail fold capillary beds shows tortuosity and redundancy of capillary loops with dilation of the arterioles and venules. Such abnormalities may occasionally be seen in patients with localized scleroderma and herald coexisting or evolving systemic sclerosis (111).

Systemic sclerosis with limited scleroderma, known as CREST syndrome, is associated with Raynaud's phenomenon in virtually all affected patients. This variant of acrosclerosis, which frequently but not invariably has a favorable prognosis, consists of several or all of the following manifestations: calcinosis cutis, Raynaud's phenomenon, involvement of the esophagus with dysphagia, sclerodactyly, and telangiectases. Death from visceral lesions is rather infrequent in the CREST syndrome (112).

In about 5% of the cases, the cutaneous lesions first appear on the trunk as so-called *diffuse systemic scleroderma*, often sparing the peripheral portions of the extremities. Raynaud's phenomenon is absent in such patients. There are, however, transitional forms starting out as acrosclerosis with Raynaud's phenomenon but then extending to the proximal portions of the arms and to the trunk. In both forms of systemic scleroderma, the skin in the involved areas is diffusely indurated and, as a result of diffuse fibrosis of the subcutaneous fat, becomes firmly bound to the underlying structures. The skeletal musculature is affected, resulting in weakness and atrophy. Contractures of the muscles and tendons and ankyloses of the joints may develop.

Occasional manifestations pertaining to the skin include diffuse hyperpigmentation, which is seen mainly in diffuse systemic scleroderma. Macular telangiectases on the face and hands, calcinosis cutis located on the extremities, and ulcerations, especially on the tips of the fingers and over the knuckles, occur predominantly in acrosclerosis. In addition, vascular ulcers on the lower extremities resembling those seen in atrophie blanche may occur in patients with acrosclerosis.

Histopathology. The histologic appearance of the skin lesions in systemic scleroderma is similar to that of morphea, so that histologic differentiation of the two types is not possible. One small study stated that the two conditions may be differentiated based upon the pattern of the inflammatory infiltrate and presence or absence of papillary dermal involvement (113). In early lesions of systemic scleroderma the inflammatory reaction is less pronounced than in morphea, so that only a mild inflammatory infiltrate is present around the dermal vessels, around the eccrine coils, and in the subcutaneous tissue. The vascular changes in early lesions are slight, as in morphea (114). In contrast, in the late stage,

systemic scleroderma shows more pronounced vascular changes than morphea, particularly in the subcutis. These changes consist of a paucity of blood vessels, thickening and hyalinization of their walls, and narrowing of the lumen. Even in the late stage of systemic scleroderma, the epidermis appears normal, only occasionally showing disappearance of the rete ridges. Aggregates of calcium may also be seen in the late stage within areas of sclerotic, homogeneous collagen of the subcutaneous tissue (see also calcinosis cutis, Chapter 17).

Systemic Lesions. Internal organs are often affected in scleroderma, but their involvement varies greatly in extent and degree. Involvement does not necessarily imply functional compromise, and in many affected patients systemic scleroderma ultimately comes to a standstill. The clinical symptoms produced by reduced pliability, vascular compromise, and subsequent loss of function can be found in the gastrointestinal tract, lungs, heart, and kidneys, as well as the skin. In the gastrointestinal tract submucosal fibrosis and replacement of the muscularis by fibrosis with intimal thickening of blood vessels give rise to difficulties in swallowing, regurgitation, and malabsorption and eventually ileus. In the lungs interstitial fibrosis, degeneration of alveolar spaces, and intimal thickening of arteries result in dyspnea and cor pulmonale. Cases of pulmonary carcinoma (predominantly bronchoalveolar) have been observed and are associated with the presence of pulmonary fibrosis (115). The most serious consequences arise in the kidneys. Adventitial fibrosis may affect interlobar, arcuate, and interlobular arteries, and mucoid degeneration affects arcuate and interlobular arteries. Uremia occurs more frequently than rapidly evolving renal failure and hypertension. The latter entity, termed scleroderma renal crisis, is associated with "onion-skin" hyperplasia of arterial walls and may be fatal (116).

Pathogenesis and Laboratory Findings. The pathogenesis of systemic scleroderma, as with lupus erythematosus, is uncertain and may be multifactorial. Histogenetic factors are essentially the same in morphea and systemic scleroderma; they differ only in degree and extent.

The triad of vascular compromise, collagen matrix aberrations, and presence of serologic autoimmune indicators contributes in variable degrees to symptoms and clinical findings in scleroderma and morphea (Table 10-6). Although a relationship to retroviral disease has been suggested, it is speculative and may reflect molecular mimicry of viral antigens (117).

Microvascular Changes. Involved vessels are primarily precapillary arterioles. Changes in the microvasculature have been noted in clinically normal skin. Perivascular edema and functional changes in endothelial cells can be detected early (118). Precapillary arterioles then show endothelial proliferation and mononuclear inflammatory infiltrates, followed by intimal proliferation and luminal narrowing (119). Corresponding electron microscopic findings include vacuolization and destruction of endothelial cells, reduplication of the basement membrane, enlargement of the rough endoplasmic reticulum in pericytes and fibroblasts, and perivascular fibrosis. There are some data to suggest that hyperplasia of the pericytic cells at the peripheral superficial aspect of the advancing border of the sclerosis may play an role in the fibrosing process through synthesis of collagenous matrix material and recruitment of fibroblasts through release of cytokines (120). Although widespread arteriolitis may be present in early stages, only rarely does it progress to a necrotizing arteriolitis and eventuate in periarteritis nodosa (121).

A role for adhesion molecules in the evolution of lesions of scleroderma has been suggested: They are believed to bind mononuclear cells to endothelial cells and facilitate diapedesis of inflammatory cells into the connective tissue. Interactions with connective tissue components may lead to the release of cytokines and growth factors, resulting in upregulation of matrix production by fibroblasts and changes in fibroblast phenotype, eventuating in fibrosis (122).

Collagen Matrix Aberrations. Analysis of collagen in affected skin has shown excess production of connective tissue components normally present in the dermis, including types I, III, V, VI, and VII collagen, fibronectin, and proteoglycans (123,124). Other studies suggest that fibroblasts in localized and systemic scleroderma express markers of smooth muscle differentiation (myofibroblasts), which may account for their different biological behavior (125). Some observers have found

TABLE 10-6 Pathogenic Factors in Scleroderma

Vascular aberrations	Raynaud's phenomenon
	Intimal hyperplasia of blood vessels
	Adventitial fibrosis
	Vascular abnormalities in other visceral organs
	Microvascular abnormalities
	Enlargement and tortuosity of capillary loops
	Capillary loop dropout
	Thickened and reduplicated basement membrane
	Loss of endothelium
Immunologic factors	T-helper cell ($CD4^+$) infiltrates
	Reduction in T-suppressor ($CD8^+$) cells
	Increased soluble interleukin-2 receptors correlate with disease progression and mortality
	Decreased interleukin-1 production by peripheral mononuclear cells
Serologic markers	ANA^+ in more than 90% of patients
	Low/absent anti–native (double-stranded) DNA, anti-Sm, rare anti-nRNP
	Speckled ANA pattern correlates with anticentromere antibody on HEp-2 cells and CREST and a relatively favorable prognosis
	Anti–DNA topolsomerase 1 (Sci-70)

ANA, antinuclear antibody; CREST, calcinosis cutis, Raynaud's phenomenon, involvement of the esophagus with dysphagia, sclerodactyly, and telangiectases.

loss of $CD34^+$ dendritic cells in affected areas, a finding of uncertain significance (126).

Serologic/Immunologic Markers. Most patients with systemic sclerosis (greater than 90%) and approximately 50% of those with localized scleroderma (morphea) have a positive ANA. The pattern may be homogeneous, speckled, or nucleolar. When using the human laryngeal carcinoma cell line HEp-2, more than 90% of patients with morphea or acrosclerosis have a detectable anticentromere antibody. In patients with systemic sclerosis this antibody is not usually detected. Instead, 20% to 40% of them have antibodies to Scl-70. This antigen has been identified as DNA topoisomerase I, an intracellular enzyme involved in the uncoiling of DNA before it is transcribed. Antibodies to this enzyme hinder its function. The presence of antibodies to Scl-70 correlates with systemic sclerosis, whereas the presence of anticentromere antibodies correlates with morphea or CREST and suggests a more favorable prognosis (127). Antihistone antibodies have been shown to be positive in cases of morphea, particularly in generalized morphea and linear scleroderma. Although not particularly sensitive, anti–single-stranded DNA is considered very specific for linear scleroderma (128).

In some cases of systemic scleroderma, epidermal nucleolar IgG deposition is seen even in clinically normal skin as a result of high serum concentrations of antibody to nucleolar antigen (129). Although subepidermal and vascular deposits are regularly absent in the skin in scleroderma, kidney biopsies in patients with renal involvement show diffuse vascular deposits of immunoglobulins, predominantly IgM, or of complement in the intima of the interlobular and arcuate arteries, which by light microscopy often exhibit fibromucinous alterations (130).

NEPHROGENIC SYSTEMIC FIBROSIS

Nephrogenic systemic fibrosis, previously referred to as nephrogenic fibrosing dermopathy, is a systemic disorder characterized by symmetric thickening of the skin of the trunk and extremities. It was first recognized in a group of renal transplant patients in 1997 (131). The nomenclature changed when respiratory symptoms and related cardiac changes were recognized. All patients have some degree of renal impairment (132). Initially dialysis was suspected as a predisposing factor; however, up to 10% of patients had never received dialysis (133). There are equal sex and age distributions. The cause has not been established, despite certain correlations, including one with gadolinium exposure reviewed later (see pathogenesis section) (134,135).

Clinically, nephrogenic systemic fibrosis presents as limited or widespread areas of symmetric thickening and hardening of the skin that may resemble scleroderma. The borders of involved areas may be sharply demarcated, serpentine, or ameboid. The skin becomes smooth and shiny or may acquire a peau d'orange appearance. Involvement over joints may lead to contractures. Although typically asymptomatic, patients may complain of muscular weakness, pruritus, and pain (133,135–137). In contrast to scleromyxedema, the face is typically spared. Pulmonary involvement may give rise to respiratory symptoms. Muscle weakness occurs with involvement of skeletal muscles and fascia. Patients with muscle weakness may have sensory motor polyneuropathy by electromyography and nerve conduction studies. Although cardiac fibrosis has been reported, impaired cardiac function has not been documented (137–140).

Histologic findings of nephrogenic systemic fibrosis may be subtle and require incisional biopsies to include fascia (Fig. 10-14A–C). Sections show spindled fibroblasts that extend into subcutaneous septae and subjacent fascia (Fig 10-14B). Collagen bundles are thickened. Cytoplasmic processes of fibrocytes surround collagen bundles. Such areas may demonstrate factor XIIIa–positive stellate fibroblastic cells and CD68-positive multinucleated giant cells. (Fig. 10-14C–E).

Immunohistochemical stains show fibrocyte reactivity with CD34 in a membranous pattern and procollagen I in a cytoplasmic pattern (133,134). Such cells may represent a class of circulating fibrocytes that home to areas of cutaneous injury and play a crucial role in wound healing. One study showed the presence of myofibroblastic cells in early lesions of nephrogenic systemic fibrosis (141).

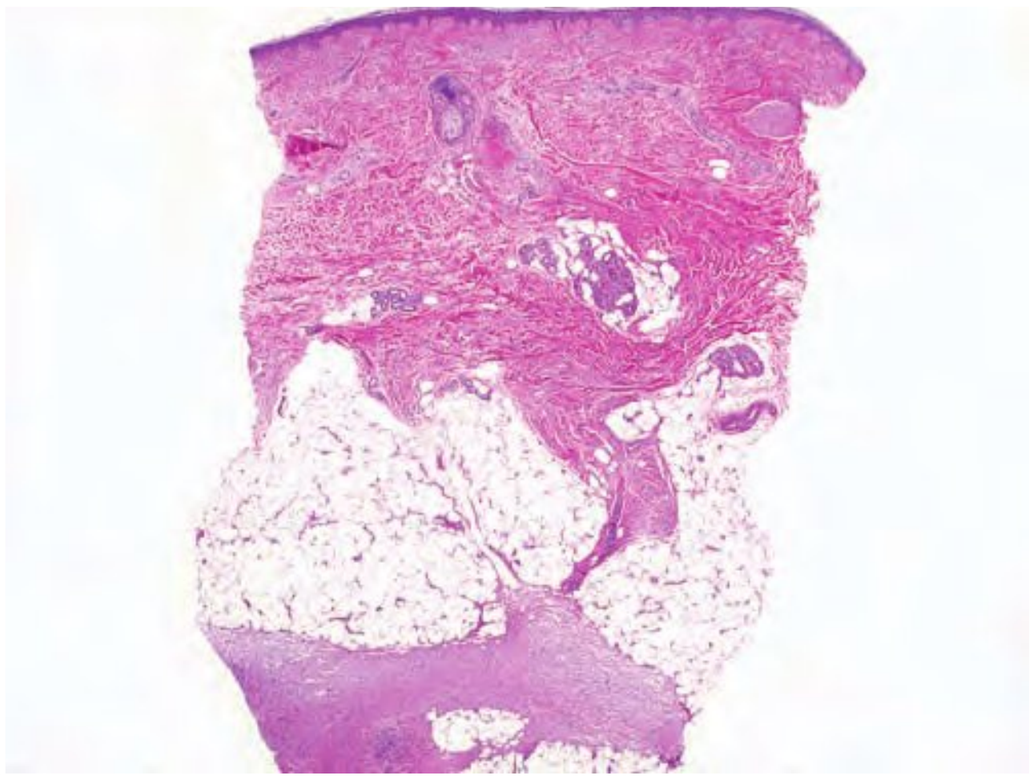
Pathogenesis. Although the diagnosis of nephrogenic systemic fibrosis requires the presence of renal dysfunction, disease onset often correlates closely with acute worsening of kidney function in the setting of chronic disease (135,138). The disease progression can frequently be halted or even reversed if the cause of the worsening can be eliminated and function restored to baseline (132). Other putative factors under scrutiny include procoagulative disorders (including factor V Leiden deficiency, antithrombin III deficiency, protein C and S deficiency and hyperhomocysteinemia), the role of endothelin 1, and gadolinium (137,142,143). The last-named agent is used as a contrast medium in magnetic resonance imaging studies and may trigger development of the disease in acidotic states.

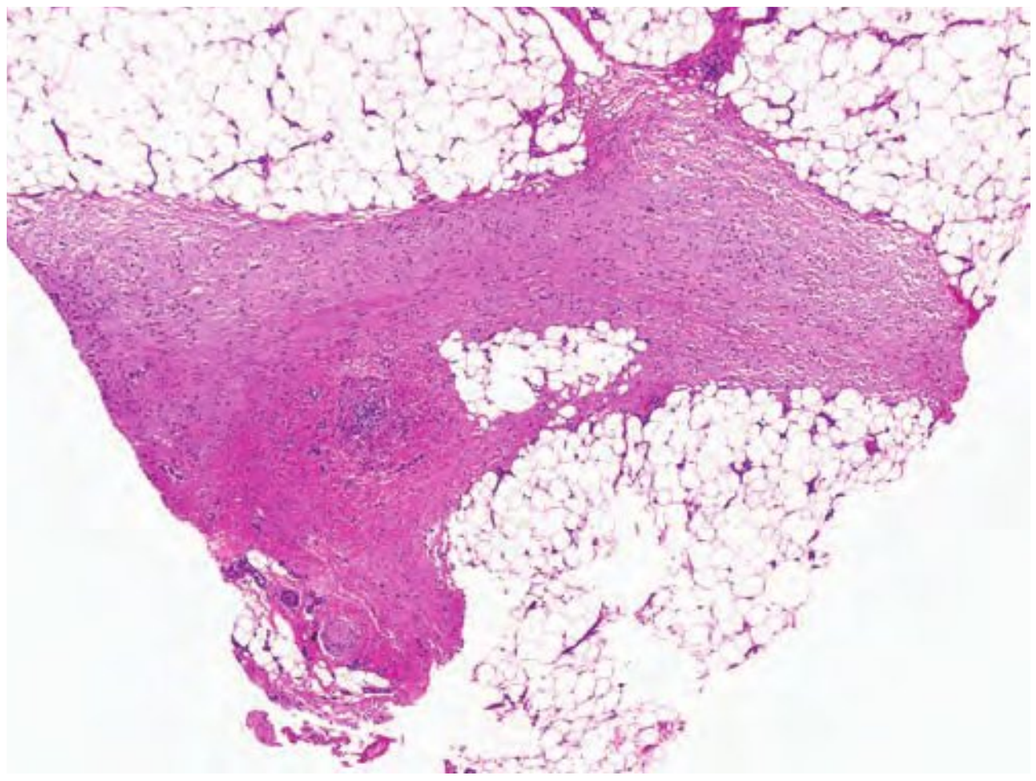
The differential diagnosis includes other fibrosing and sclerodermoid cutaneous disorders. These include scleromyxedema, eosinophilic fasciitis, sclerodermoid graft-versus-host disease, sclerodermoid porphyria cutanea tarda, morphea, and lipodermatosclerosis. Most of these entities can be excluded based on the history and laboratory studies.

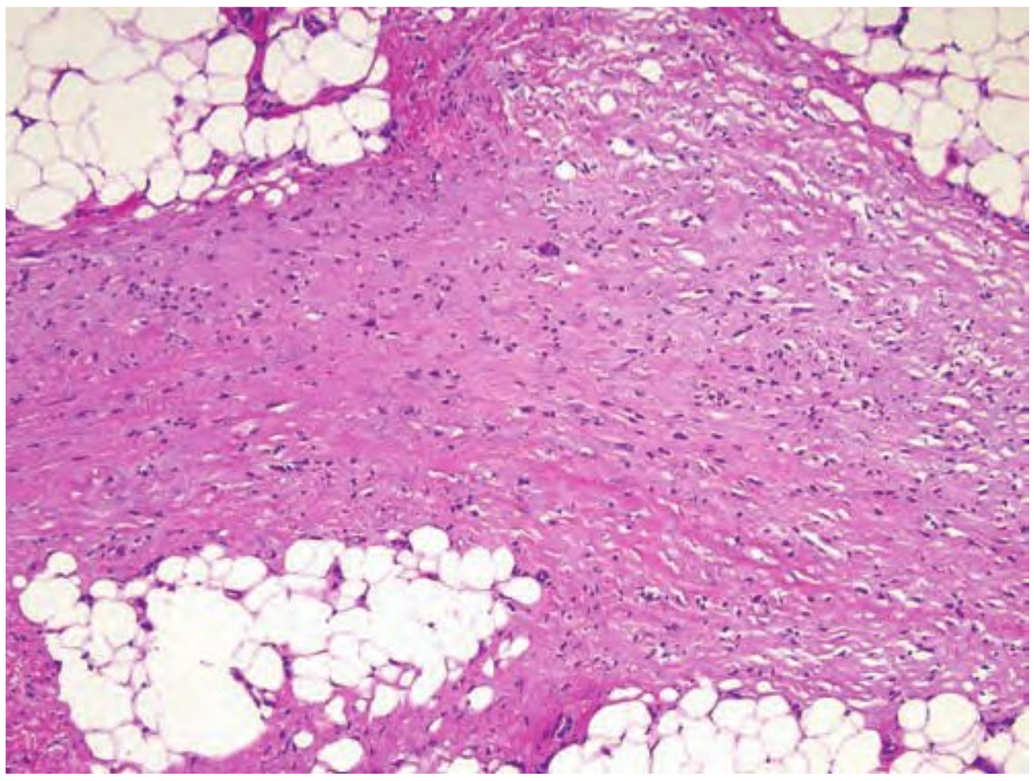
ATROPHODERMA OF PASINI AND PIERINI

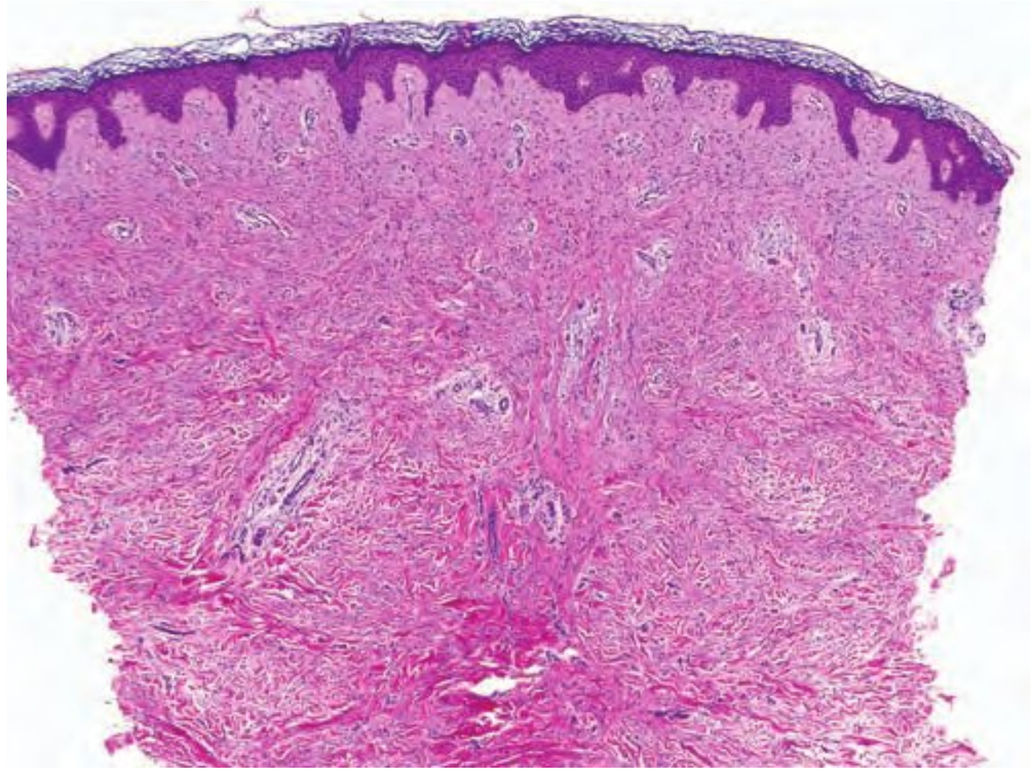
In atrophoderma of Pasini and Pierini there are areas on the trunk, particularly the back, in which the skin appears slightly depressed and has a slate-gray color but shows no other surface changes. The lesions are asymptomatic, bilateral, symmetric, and sharply but often irregularly demarcated, measuring from 1 to 10 cm in diameter. They often show a "cliff-drop" border, which is largely an optical effect of the slate-gray discoloration. In old lesions, the center of the depressed area may feel slightly indurated.

Histopathology. The histologic changes in early lesions usually are slight and nonspecific, consisting of some thickening of the


A


B


C


D

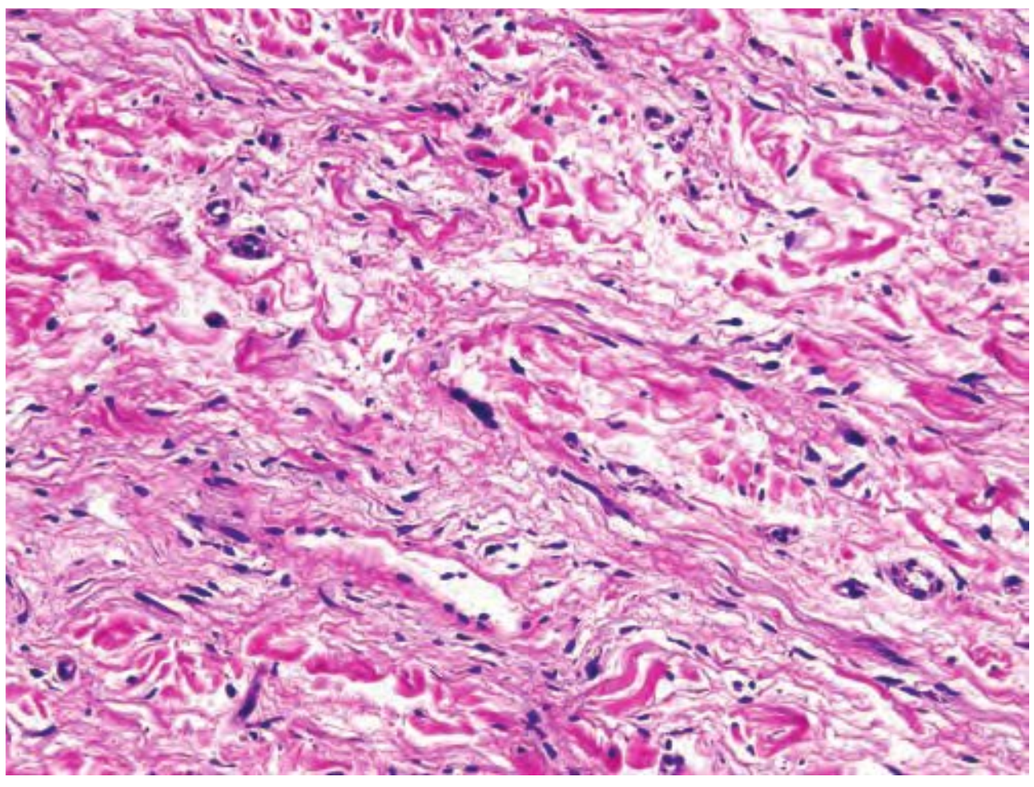

E

FIGURE 10-14. Nephrogenic systemic fibrosis. A: An incisional specimen that shows deep dermal thickening and septal widening. B: Subcutaneous septae are widened by many spindle-shaped fibroblasts. C: High magnification of spindle-shaped fibrocytes, some of which are multinucleated in a thickened subcutaneous septum. Note little residual normal collagen. D: A different example of nephrogenic systemic fibrosis in which fibrocytes are distributed diffusely throughout the dermis. E: High magnification shows multinucleated fibroblastic cells. Note the difference between the spindle-shaped fibrocytes (lower half) and normal collagen bundles (upper half).

collagen bundles and a mild, scattered, chronic inflammatory infiltrate (144). Older lesions show no inflammatory infiltrate, but in the deeper layers of the dermis they may show collagen bundles that not only are thickened, but also appear tightly packed. In addition, indurated areas may show homogeneous, hyalinized collagen bundles (145).

Because the collagen bundles in the skin of the back normally are rather thick, it may be difficult to determine whether the collagen shows any changes. It is therefore desirable to take a biopsy specimen not only from the lesion, but also from normal skin, either from an area nearby or from the opposite side with subcutaneous fat for comparison.

Pathogenesis. Some authors believe that atrophoderma of Pasini and Pierini is a disease entity, as suggested by the original describers. In favor of this view is the observation that in atrophoderma, the atrophy comes first and the sclerosis possibly appears later, whereas in morphea, the sclerosis comes first and the atrophy appears later (146).

Most observers view the clinical presentation of atrophoderma to be distinct from that of morphea: Atrophoderma has an earlier onset (second to third decade) and protracted course of 10 to 20 years, and lesions lack a violaceous ring, which characteristically surrounds lesions of morphea. Microscopic findings show similarities to morphea, however, suggesting that atrophoderma of Pasini and Pierini may be a distinct, abortive variant of morphea (147). To support this view there are instances of coexistent morphea and atrophoderma, as well as reports of transformation of lesions of morphea into atrophoderma. A relationship of this disorder to *B. burgdorferi* infection has been reported but needs more studies to be confirmed (148).

EOSINOPHILIC FASCIITIS (SHULMAN'S SYNDROME)

First described in 1974 (149), eosinophilic fasciitis is a scleroderma-like disorder characterized by inflammation and thickening of the deep fascia. It has a rapid onset associated with pain, swelling, and progressive induration of the skin leading to exaggerated deep grooving of the skin around superficial veins. This disorder is often accompanied by a peripheral eosinophilia, hypergammaglobulinemia, and elevated erythrocyte sedimentation rate and has been associated with aplastic anemia. Other rare associations include polycythemia rubra vera, cutaneous T-cell lymphoma, borreliosis, and autoimmune thyroid disease (150). Simvistatin and phenytoin have been reported to cause eosinophilic fasciitis (151). Eosinophilic fasciitis may have its onset with unusual physical exertion; however, more recently it has been reported in association with L-tryptophan ingestion (152). The latter association is known as eosinophilia-myalgia syndrome, which is clinically and histologically similar to eosinophilic fasciitis.

Eosinophilic fasciitis often involves one or more extremities. The induration may cause a decreased range of motion and, in severe cases, even joint contractures (153). In only a few cases are there lesions on the trunk, and the face is almost invariably spared. In nearly all reported cases, Raynaud's phenomenon and visceral lesions of scleroderma have been absent. Only very few instances of incontestable eosinophilic fasciitis have shown evidence of Raynaud's phenomenon (154) or mild pulmonary fibrosis (155). The disorder has a varied course: Some patients improve spontaneously, others improve with corticosteroids, and still others may have relapses and remissions.

Histopathology. A deep wedge biopsy to skeletal muscle including fascia is essential to making the diagnosis of eosinophilic fasciitis. The fascia is markedly thickened, appears homogeneous, and is permeated by a mononuclear inflammatory infiltrate (Fig. 10-15A–C). In some instances the infiltrate in the fascia contains an admixture of eosinophils (156). The underlying skeletal muscle in some cases shows myofiber degeneration, severe inflammation with a component of eosinophils, and focal scarring; in other cases, however, it is not involved.

In most cases the adipose tissue shows no significant changes, except that the fibrous septa separating deeply located fat lobules are thicker, paler staining, and more homogeneous and hyalinized than normal dermal connective tissue. In other cases, however, the collagen in the lower reticular dermis appears pale and homogeneous, and the entire subcutaneous fat is replaced by horizontally oriented, thick, homogeneous collagen containing only few fibroblasts and merging with the fascia (157).

Pathogenesis. Whereas at first the impression prevailed that eosinophilic fasciitis was a new syndrome, it soon became apparent that the disorder represents a variant of morphea (139). Eosinophilic fasciitis may share features with generalized morphea, including inflammation and fibrosis of the fascia, peripheral eosinophilia, and hypergammaglobulinemia (158). Antinuclear antibodies are present in a significant number of cases (159). The term morphea profunda, analogous to lupus erythematosus profundus, has been applied to this disorder (160). Nevertheless, because of its acute onset in most cases, its usual limitation to the structures underlying the skin, and its tendency to resolve, eosinophilic fasciitis deserves recognition as a distinct variant of morphea (161).

LICHEN SCLEROSUS ET ATROPHICUS

Lichen sclerosus (LS) encompasses the disorders known as *lichen sclerosus et atrophicus*, *balanitis xerotica obliterans* (LS of the male glans and prepuce), and *kraurosis vulvae* (LS of the female labia majora, labia minora, perineum, and perianal region) (162). Lichen sclerosus is an inflammatory disorder of unknown etiology that affects patients 6 months of age to late adulthood. In both male and female patients genital involvement is the most frequent, and often the only, site of involvement. Extragenital lesions may occur with or without coexisting genital lesions.

Lesions of LS are characterized by white polygonal papules that coalesce to form plaques. Comedo-like plugs on the surface of the plaque correspond to dilated appendageal ostia. The plugs may disappear as the lesion ages, leaving a smooth, porcelain-white plaque. Solitary or generalized lesions may become bullous and hemorrhagic.

In male patients, involvement of the glans and prepuce often results in phimosis. Although the literature is dominated by reports of LS in incompletely or uncircumcised men (163), occurrences in circumcised men are reported as well (164). Neoplasms have been infrequently documented in association with LS; however, a cause-and-effect relationship has not been established (149).

In female patients, contiguous involvement of the labial, perineal, and anal areas has been described clinically as "figure 8"

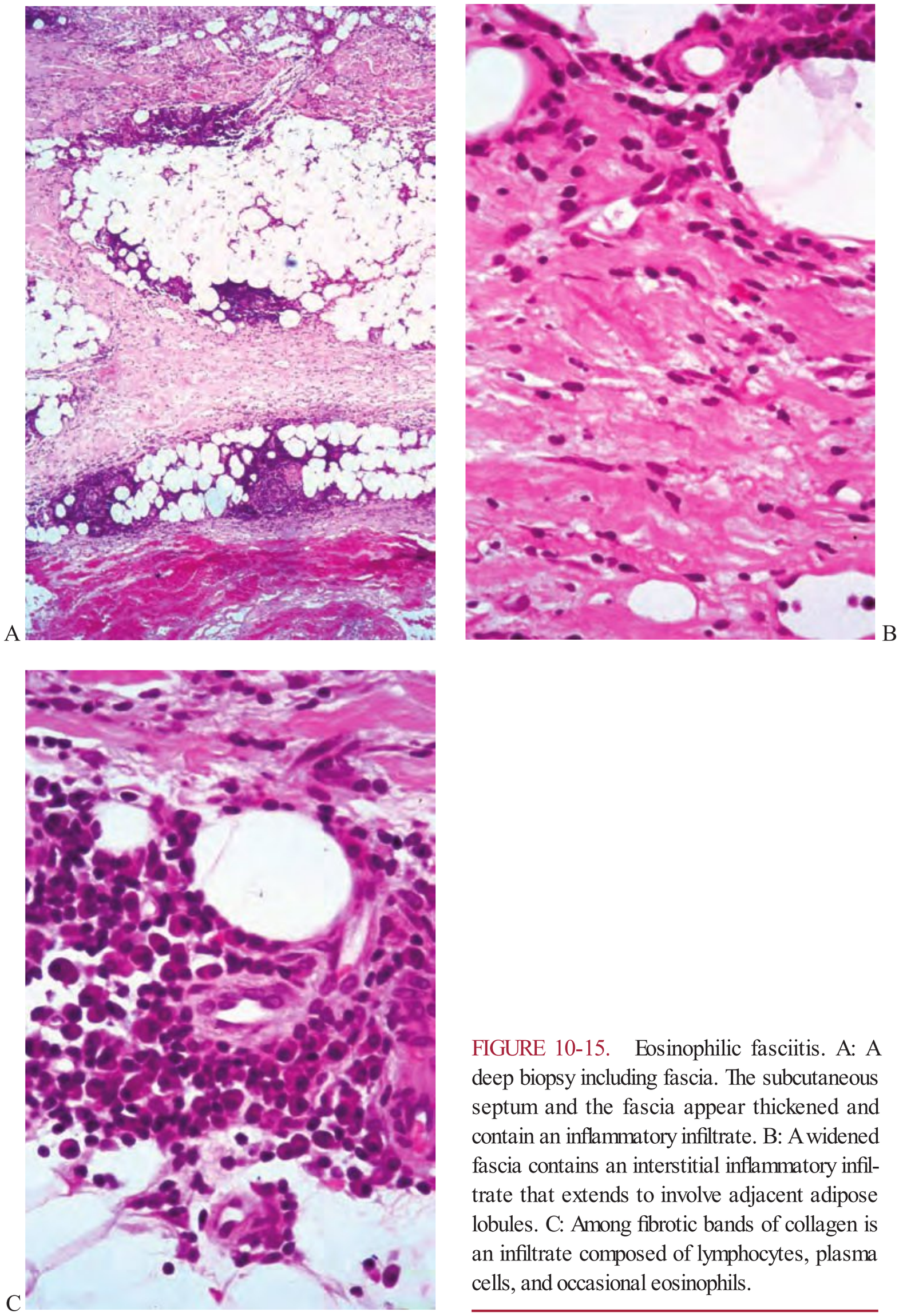


FIGURE 10-15. Eosinophilic fasciitis. A: A deep biopsy including fascia. The subcutaneous septum and the fascia appear thickened and contain an inflammatory infiltrate. B: A widened fascia contains an interstitial inflammatory infiltrate that extends to involve adjacent adipose lobules. C: Among fibrotic bands of collagen is an infiltrate composed of lymphocytes, plasma cells, and occasional eosinophils.

or "keyhole" lesions (165). Many cases of childhood LS in girls resolve by menarche (166). If lesions persist, atrophy of the labia and narrowing of the vaginal orifice may ensue. In contrast to lichen sclerosus et atrophicus of the skin, which rarely itches, there is often severe pruritus in the vulvar region.

The premalignant potential in LS has been debated extensively and remains ill defined. The most recent large population-based study detected a small increased risk of squamous cell carcinoma in patients with LS. Because neoplasms have arisen in areas adjacent to lesions of LS, long-term follow-up of patients with lichen sclerosus et atrophicus of the vulva is advisable.

Of interest, lesions of LS may koebnerize (be provoked by trauma) as well as coexist with morphea (167,168). In extensive cases of morphea, lichen sclerosus et atrophicus may become superimposed on some of the lesions. It is then best

recognized by finding pale superficial dermal collagen, as compared with hypocellular compacted deep dermal collagen, and the presence of follicular plugging (123). Cases of both extragenital and genital LS have also been reported in the setting of graft-versus-host disease (169).

Histopathology. The salient histologic findings in cutaneous lesions of lichen sclerosus et atrophicus are (a) hyperkeratosis with follicular plugging, (b) atrophy of the stratum malpighii with hydropic degeneration of basal cells, (c) pronounced edema and homogenization of the collagen in the upper dermis, and (d) an inflammatory infiltrate in the mid-dermis.

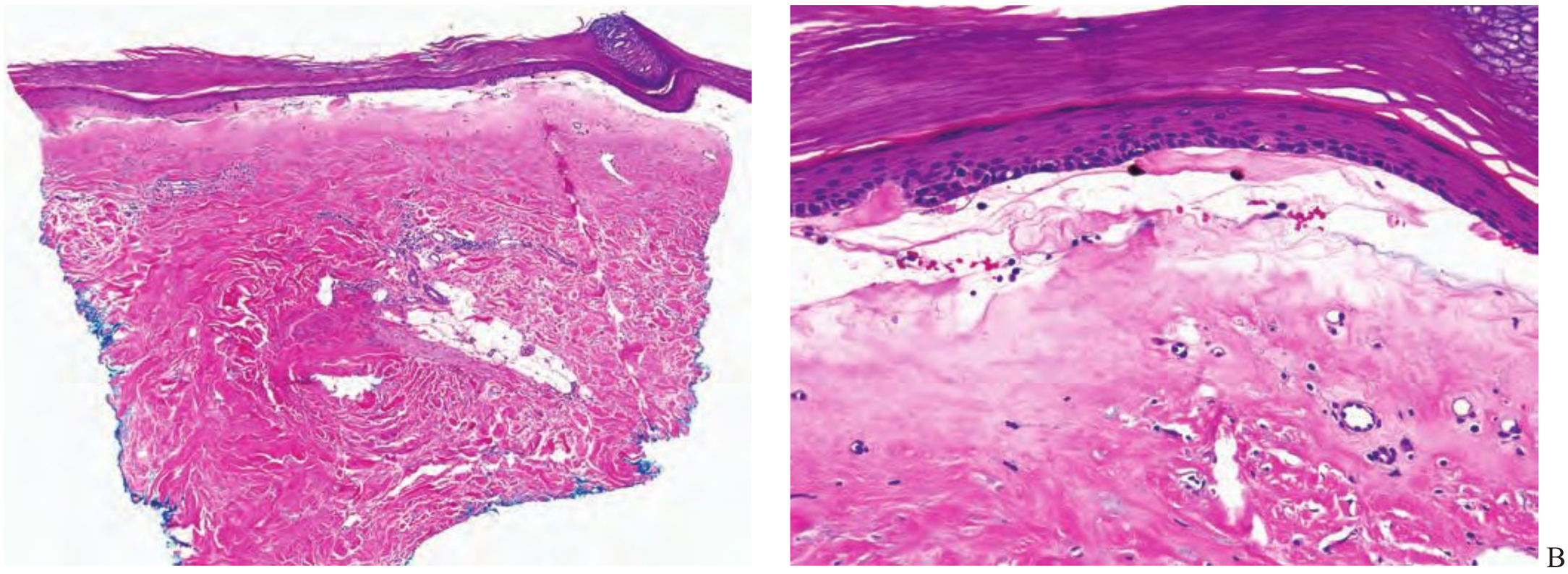
The hyperkeratosis is so marked that the horny layer is often thicker than the atrophic stratum malpighii, which may be reduced to a few layers of flattened cells (Fig. 10-16A, B). The cells of the basal layer show hydropic degeneration. The rete ridges often are completely absent, although they may persist in a few areas and show some irregular downward proliferation. In such proliferations, hydropic degeneration of the basal cells usually is pronounced.

Keratotic plugging of appendageal ostia is often associated with atrophy and disappearance of appendageal structures. Keratotic plugging is not apparent in mucosal lesions. In the latter areas, particularly the vulva, squamous hyperplasia adjacent to the atrophic epidermis can be found in about one third of patients with LS. There may be varying degrees of "dysplasia" consisting of disorderly arrangement of the cells and enlarged, hyperchromatic nuclei. Transition into carcinoma, however, is said to be rare (170).

Beneath the epidermis is a broad zone of pronounced lymphedema (Fig. 10-16A, B). Within this zone, the collagenous fibers are swollen and homogeneous and contain only a few nuclei. They stain poorly with eosin and other connective tissue stains. The blood and lymph vessels are dilated, and there may be areas of hemorrhage. Elastic fibers are sparse and, in old lesions, are absent within the area of lymphedema (171). In areas of severe lymphedema, clinically visible bullae may form; they are found in subepidermal locations (172). Shrinkage within the area of lymphedema may occur during the process of dehydration of the specimen, resulting in the formation of pseudobullae, which often are located intradermally.

Except in lesions of long duration, an inflammatory infiltrate is present in the dermis. The younger the lesion, the more superficial is the location of the infiltrate. In very early lesions and at the periphery of somewhat older lesions, the infiltrate may be found in the uppermost dermis, in direct apposition to the basal layer. Soon, however, a narrow zone of edema and homogenization of the collagen displaces the inflammatory infiltrate farther down, so that, in well-developed lesions, the infiltrate is found in the mid-dermis. The infiltrate can be patchy, but it is often bandlike and composed of lymphoid cells admixed with plasma cells and histiocytes. In old lesions in which the infiltrate is slight or absent, the collagen bundles in the midportion and lower dermis may appear swollen, homogeneous, and eosinophilic, thus appearing sclerotic (hence lichen *sclerosus*). Cases of overlap of morphea and LS may be seen and demonstrate the histologic changes of both disorders in their respective locations of the dermis (Fig. 10-17A–C).

Pathogenesis. Changes in the dermal matrix have been detected in LS. By electron microscopy, collagen fibrils often



A B

FIGURE 10-16. Lichen sclerosus. A: Lichen sclerosus showing a subepidermal zone of pallor. A "trilayered" or "striped" appearance: compact hyperorthokeratotic scale and atrophic epidermis (dark pink/red), a pale dermis (white), and subjacent, variably dense interstitial lymphocytic inflammatory infiltrate (blue) delineating the depth of this process. B: An established lesion, showing a thick hyperkeratotic scale, an atrophic epidermis, and pale superficial dermal stroma with rare lymphocytes and plasma cells. A cleftlike space separates an atrophic epidermis from a pale dermis.

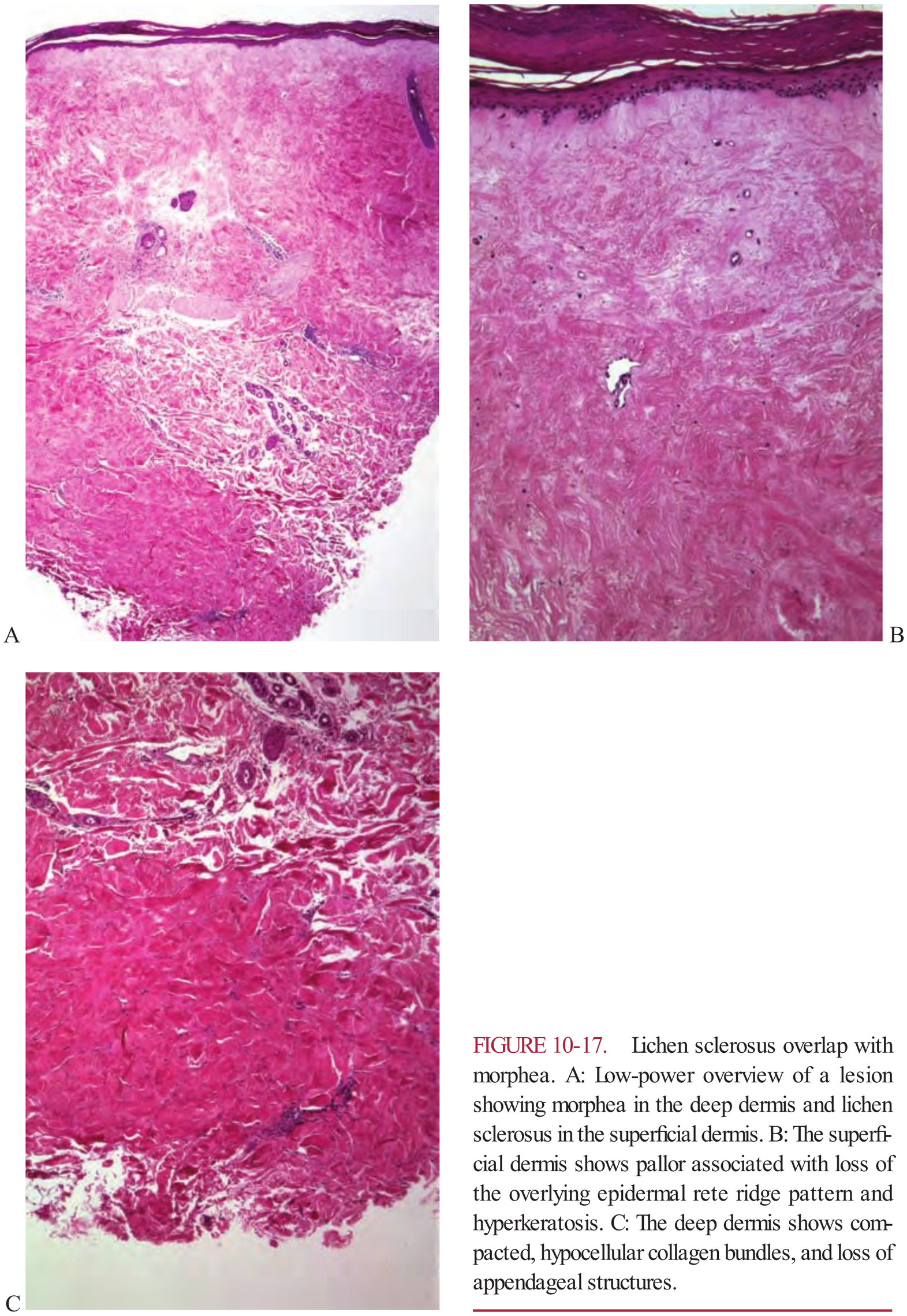


FIGURE 10-17. Lichen sclerosus overlap with morphea. A: Low-power overview of a lesion showing morphea in the deep dermis and lichen sclerosus in the superficial dermis. B: The superficial dermis shows pallor associated with loss of the overlying epidermal rete ridge pattern and hyperkeratosis. C: The deep dermis shows compacted, hypocellular collagen bundles, and loss of appendageal structures.

lack cross-striation, and in cross sections they sometimes have the appearance of empty tubes, suggesting degeneration of collagen fibrils (173). In some areas, new immature collagen of reduced and variable diameter (40 to 80 nm) is seen (174). Ultrastructural studies also have shown degeneration of subepidermal elastin and increases in ground substance (175). The features all suggest an increased rate of matrix turnover or a dysregulated remodeling response. Studies examining the components of the dermal matrix have demonstrated increases in the matrix proteins tenascin and fibrinogen, which serve as scaffold proteins on which new collagen is deposited. Similar increases in tenascin and fibrinogen have been demonstrated in scleroderma and morphea, suggesting that this is may be a nonspecific change (176).

The frequent finding of human papillomavirus alterations in lesions of LS have lead some to consider LS an aberrant immune response to persistent antigenic stimulus. This notion is supported by the presence of LS changes in cases of other

chronic vulvar dermatitides. It has been hypothesized that persistent antigen may lead to the presence of CD8/CD57-positive T cells, which may play a role in tissue remodeling and fibrosis though cytokine elaboration (177).

In the epidermis, intercellular edema separates epidermal cells that show degenerative changes. There is nearly a complete absence of melanosomes within the keratinocytes. Immunoperoxidase and Fontana-Mason stains of melanocytes have shown there is both a loss of melanocytes and decreased transfer of melanosomes to keratinocytes (178).

Differential Diagnosis. Very early lesions may resemble lichen planus because of the apposition of the inflammatory infiltrate to the basal layer. However, the basal cells are not replaced by flattened squamous cells as in lichen planus but appear hydropic, and a subepidermal zone of edema usually has already begun to form in some areas in lichen sclerosus et atrophicus.

Old lesions of lichen sclerosus et atrophicus with thickening and eosinophilia of the collagen bundles in the midportion and lower dermis and only a slight inflammatory infiltrate may resemble morphea. Nevertheless, the epidermis in morphea, although it may be thin, shows neither hydropic degeneration of the basal cells nor follicular plugging, and the upper dermis in morphea has elastic fibers and shows no zone of edema (126). Still, in lesions in which lichen sclerosus et atrophicus develops either secondarily to morphea or simultaneously with it, there are, in addition to the epidermal and subepidermal changes of lichen sclerosus et atrophicus, changes indicative of morphea in the lower dermis and in the subcutaneous fat. A definite diagnosis of both lichen sclerosus et atrophicus and morphea in the same lesion can be made only if the newly formed collagen extends into the subcutaneous fat and consists of faintly staining, homogeneous collagen (179).

FIBROBLASTIC RHEUMATISM

At least 18 cases of this rare condition have been reported according to a recent review (180). It is characterized by a combination of progressive inflammatory arthritis and fibrotic nodules typically involving the skin of the hands, and it may occur in children as well as adults. Patients typically present with the sudden onset of polyarthralgia and develop a progressive inflammatory polyarthritis, with cutaneous nodules typically in the form of periungual papules that may mimic multicentric reticulohistiocytosis. Patches or plaques of erythema, sclerodactyly, and Raynaud's phenomenon may be associated findings. There are no significant laboratory findings. The skin nodules are characterized by mononuclear cell infiltrates, fibroblastic proliferation with myofibroblastic differentiation (181), dermal fibrosis with thickened collagen fibers, and decreased elastic fibers. This condition is variably but often inexorably progressive, but it may be responsive to immunosuppressive therapy, especially in its early stages (182).

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CHAPTER 11

Kim M. Hiatt
Thomas D. Horn

Cutaneous Toxicities of Drugs

Perhaps because of its position of high visibility, the skin is reportedly the most common site of drug reactions (1). Cutaneous eruptions attributed to drugs occur at a rate of 2% to 3% of inpatients, with a higher rate, 12%, reported in the intensive care setting (2,3). Morbilliform and urticarial eruptions are the most common overall, as well as in the intensive care setting. They are most often seen in response to antibiotics, antiepileptics, and, in one study, traditional Chinese herbal medications (3,4). Fortunately, the incidence of severe cutaneous drug reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and drug reaction with eosinophilia and systemic symptoms) is less. These severe reactions are seen in the same general population and are attributed, most commonly, to the same drugs and are reported to affect less than 1 in 10,000 users (1,3). The risk of developing an adverse drug reaction is higher in women, the elderly, patients with Sjögren's syndrome, and those with immune suppression, in particular, patients with systemic lupus erythematosus and acquired immunodeficiency syndrome (4–6). In the intensive care setting, obesity and immune dysfunctions such as antiphospholipid antibody syndrome and dysthyroidism are further risk factors (2).

Drug-related eruptions are attributed to immunologic as well as nonimmunologic mechanisms. Nonimmunologic mechanisms encompass the pharmacokinetics of drugs such as absorption, plasma protein binding, distribution, metabolism, and elimination. Genetic factors influence metabolic pathways, specifically oxidation, hydrolysis, and acetylation and are suggested to be the mechanisms of toxicity reactions such as those that occur in sulfonamide and anticonvulsant toxicities (7). Theories regarding immunologic mechanisms of drug-induced disease include cell-mediated reactions to altered cell surface proteins effecting a lymphocytic response. Molecular mimicry of endogenous peptides modified by binding with ingested drugs has also been suggested (8). In addition, drugs can stimulate an anaphylactic-type reaction by immunoglobulin E (IgE)–mediated or immune complex–mediated pathways. Drug–protein complexes cross-link IgE molecules on sensitized mast cells or basophils, releasing chemical mediators that result in systemic effects, including urticaria, angioedema, anaphylaxis, and anaphylactoid reactions. Immune complex mechanisms rely on persistence of drug antigen in the serum long enough to elicit an antibody response. Finally, antibody-mediated reactions occur as a result of cell-bound drug hapten complexing with IgG antibody, which stimulates complement fixation and cytolysis, as occurs in some cases of drug-associated thrombocytopenic purpura (7). New drug formulations, in particular liposomal and transdermal delivery systems, and the introduction of numerous chemotherapeutic and immune response modulators are accountable for increasing numbers of cutaneous reactions primarily by the nature of their preferential accumulation in target tissues such as skin (9–11). Several medication-related cutaneous eruptions are considered in depth elsewhere in this text but will be mentioned briefly in this context, including urticaria (see Chapter 7), erythema multiforme (see Chapter 9), toxic epidermal necrolysis (see Chapter 9), erythema nodosum (see Chapter 20), erythroderma (see Chapter 9), vasculitis (see Chapter 8), and corticosteroid-induced acne (see Chapter 18).

EXANTHEMIC DRUG ERUPTIONS

Eruptive and efflorescent cutaneous drug reactions are the most common adverse effects of medications (4,5,12–14). Virtually any drug may be associated with a morbilliform rash, which consists of fine blanching papules that appear suddenly, are symmetric, and often are brightly erythematous in white patients. The eruption most commonly starts as erythematous papules on the trunk and becomes confluent with time (Fig. 11-1). The mucous membranes are characteristically not involved. The nonspecific clinical and histologic changes make definitive implication of a specific agent difficult. The most common medications causing morbilliform eruptions are amoxicillin clavulanate, amphotericin B, and metamizole (5,14). The presence of facial edema and systemic hypereosinophilia in conjunction with the morbilliform eruption is a signal for a serious drug eruption: drug rash with eosinophilia and systemic symptoms (DRESS), which reportedly occurs most commonly after exposure to minocycline but has also been reported with exposure to other drugs, including sulfasalazine, carbamazepine, nevirapine, and allopurinol (1,15–20).

Histopathology. The typical morbilliform drug eruption displays a variable, often sparse, mainly perivascular infiltrate of lymphocytes and eosinophils. Eosinophils may be absent. Some vacuolization of the dermal–epidermal junction with



FIGURE 11-1. Morbilliform drug eruption. This eruption occurred in a patient with systemic symptoms (drug rash with eosinophilia and systemic symptoms). (Courtesy of Frances Ramos-Ceballos, MD.)

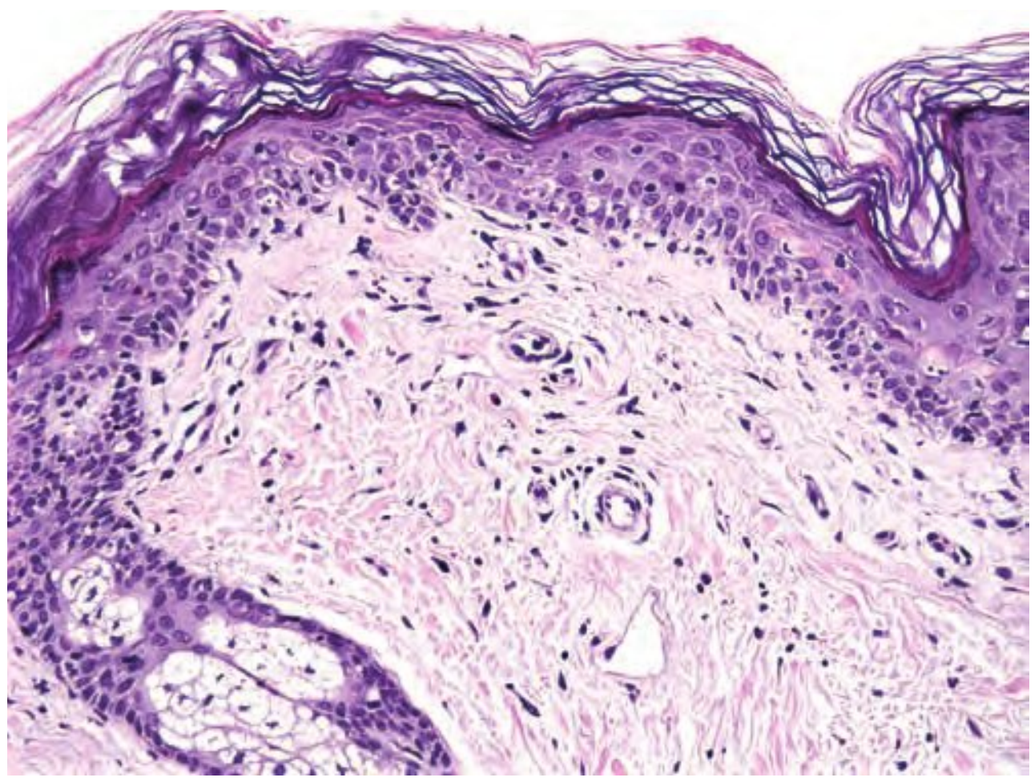


FIGURE 11-2. Drug-induced erythema multiforme. The epidermis has necrotic keratinocytes at all levels of the epidermis and a minimal dermal inflammatory infiltrate. The eosinophils suggest the drug-induced etiology.

few apoptotic epidermal cells may be observed but not to the degree typical of erythema multiforme or toxic epidermal necrolysis. There are no specific histologic features of morbilliform eruption presenting in DRESS.

Differential Diagnosis. Distinction of morbilliform drug eruption from viral exanthem in the absence of eosinophils is generally not possible. More than occasional dyskeratotic epidermal cells should prompt consideration of erythema multiforme, toxic epidermal necrolysis, or fixed drug eruption.

DRUG ERUPTIONS PRIMARILY CHARACTERIZED BY INTERFACE DERMATITIS

The histologic features comprising interface dermatitis (see Chapter 9) include vacuolar alteration of the basilar epidermis, necrotic keratinocytes, flattening of basilar keratinocytes, variable infiltration of the upper dermis by lymphocytes and histiocytes, variable exocytosis, and melanophages. These findings may be induced by drugs in several different but reproducible patterns, including erythema multiforme, toxic epidermal necrolysis, lichenoid drug eruption, and fixed drug eruption.

ERYTHEMA MULTIFORME

Erythema multiforme (EM) is characterized by an abrupt onset of self-limited and occasionally recurring papules and erythematous, edematous macules with concentric zones of color change described as targetoid or "bull's eye." The distribution varies but shows a predilection for the palms and soles. As in the other drug-related cutaneous eruptions, the list of offending agents continues to expand, but it is most commonly attributed to sulfonamides and their derivatives such as the cyclooxygenase-2 inhibitor celecoxib (21); and includes diverse agents such as selective serotonin reuptake inhibitors, 5-fluorouracil, and sestamibi (22–24).

Histopathology. In EM, there is a mild lichenoid infiltrate with dyskeratotic keratinocytes in EM than in others. These necrotic keratinocytes are characteristically found at all epidermal levels in the fully evolved lesion and may become confluent to form a thoroughly necrotic blister roof (Fig. 11-2). (see Chapter 9). In addition, exocytosis of lymphocytes is present. The dermis shows a mild perivascular inflammatory cell infiltrate. The etiology of the process often cannot be determined by the histology; however, a dermal inflammatory infiltrate containing eosinophils and acrosyringeal keratinocyte necrosis would suggest a drug-mediated process (25).

TOXIC EPIDERMAL NECROLYSIS AND STEVENS-JOHNSON SYNDROME

At the other end of the interface dermatitis spectrum, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are both severe cutaneous eruptions that display diffuse, tender erythema. Blisters may develop in both disorders, as well as mucosal and conjunctival involvement (Fig. 11-3). Fortunately, their incidence is low: 1.2 to 6 cases per million persons per year for SJS and 0.4 to 1.2 cases per million persons per year for TEN (26). TEN is associated with therapeutic drugs in 95% of cases and with immunizations and infections in the other instances. SJS, on the other hand, is only associated with

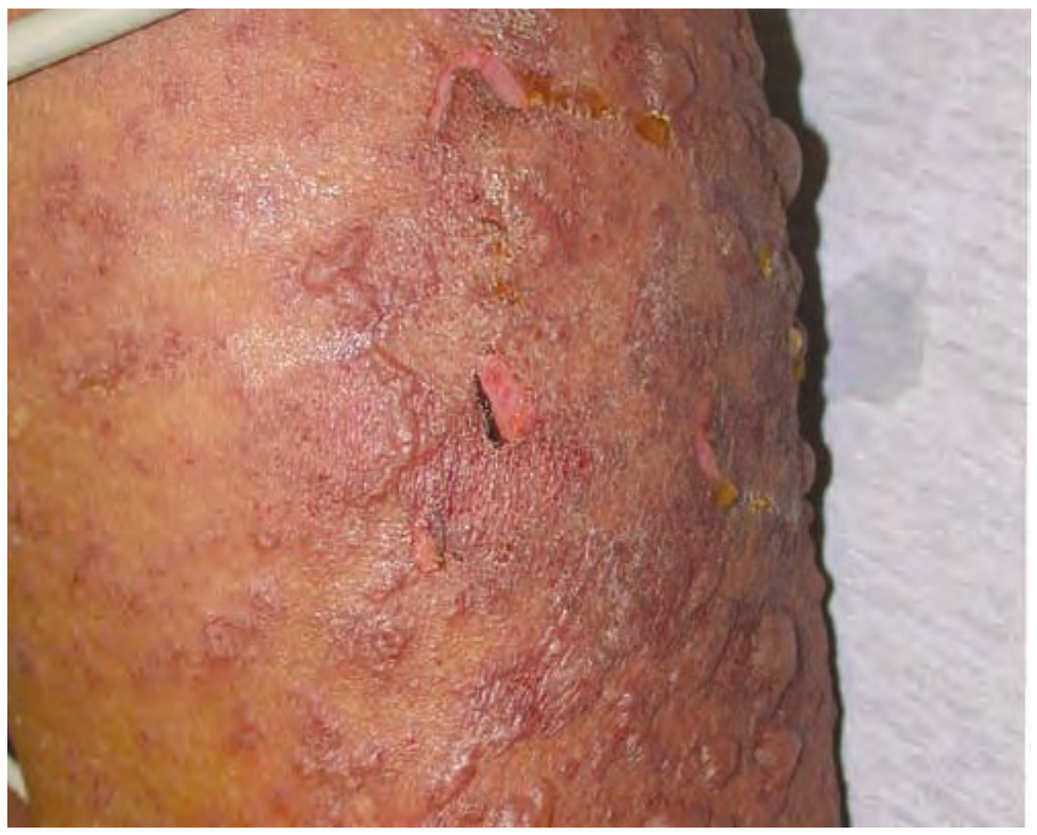


FIGURE 11-3. Toxic epidermal necrolysis. Diffuse blisters with sloughing skin secondary to Dilantin. (Courtesy of Cheryl Hull, MD.)

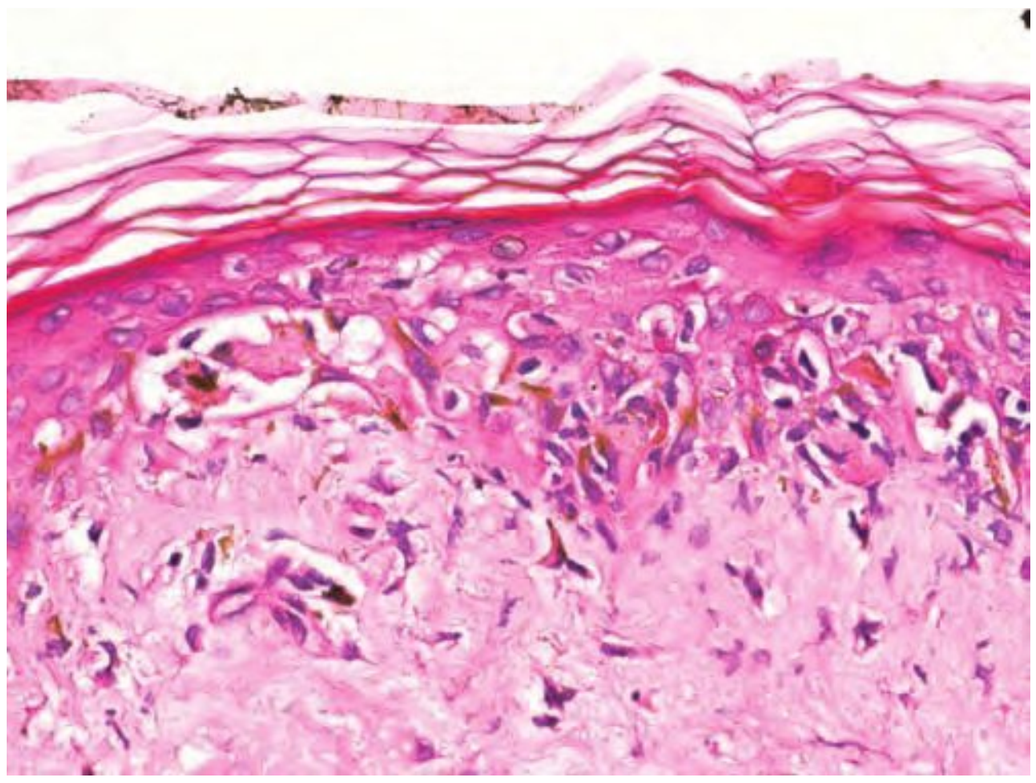


FIGURE 11-4. Toxic epidermal necrolysis. There is extensive dyskeratosis of the epidermis with early blister formation. A mild perivascular lymphocytic infiltrate is seen in the superficial dermis

drugs in 50% of cases (26). The mechanism of epithelial destruction is not clearly defined. However, drug-specific, $CD8^+$ lymphocytes with granzyme-mediated cytotoxicity are suggested to have a role in TEN pathogenesis (27). An overwhelming number of drugs have been associated with SJS and TEN, most commonly antibiotics, nonsteroidal anti-inflammatory drugs, and anticonvulsants. Allopurinol was the drug most commonly associated with SJS and TEN in one study of 379 patients with these two severe cutaneous eruptions (28). Medications associated with increased risk for these entities include sulfonamides, trimethoprim-sulfamethoxazole, phenobarbital, carbamazepine, phenytoin, oxicam, nonsteroidal antiinflammatory agents, allopurinol, doxycycline (29), corticosteroids (30), cyclooxygenase inhibitors (31,32), sustained-release bupropion, nitroglycerine patch, griseofulvin (33), and nucleoside reverse-transcriptase inhibitor (abacavir) (34).

Histopathology. In the spectrum of interface dermatitides, erythema multiforme and toxic epidermal necrolysis display greater keratinocyte necrosis and less inflammation than other disorders. Necrotic keratinocytes are found at all epidermal levels and, as in EM, may become confluent to form a thoroughly necrotic blister roof (Fig. 11-4). Eventual subepidermal bullae may form (see Chapter 9). The etiology of the process often cannot be determined by the histology; however, a dermal inflammatory infiltrate containing eosinophils and acrosyringeal keratinocyte necrosis would suggest a drug-mediated process (25).

LICHENOID DRUG ERUPTION

Lichenoid drug eruption has clinical similarity to lichen planus. Erythematous to violaceous papules and plaques develop on the trunk and extremities in association with drug ingestion. Implicated agents most commonly include quinacrine, quinidine, and gold but also include nonsteroidal antiinflammatory drugs, antihypertensive medications (especially captopril), penicillamine, chloroquine, etanercept, imatinib, sildenafil, terazosin, infliximab, and hepatitis B vaccine (35–41).

Histopathology. Lichenoid drug eruption is similar to lichen planus histologically (Fig. 11-5). In comparison with erythema multiforme and toxic epidermal necrolysis, lichenoid drug eruptions are more heavily inflamed, with a more prominent

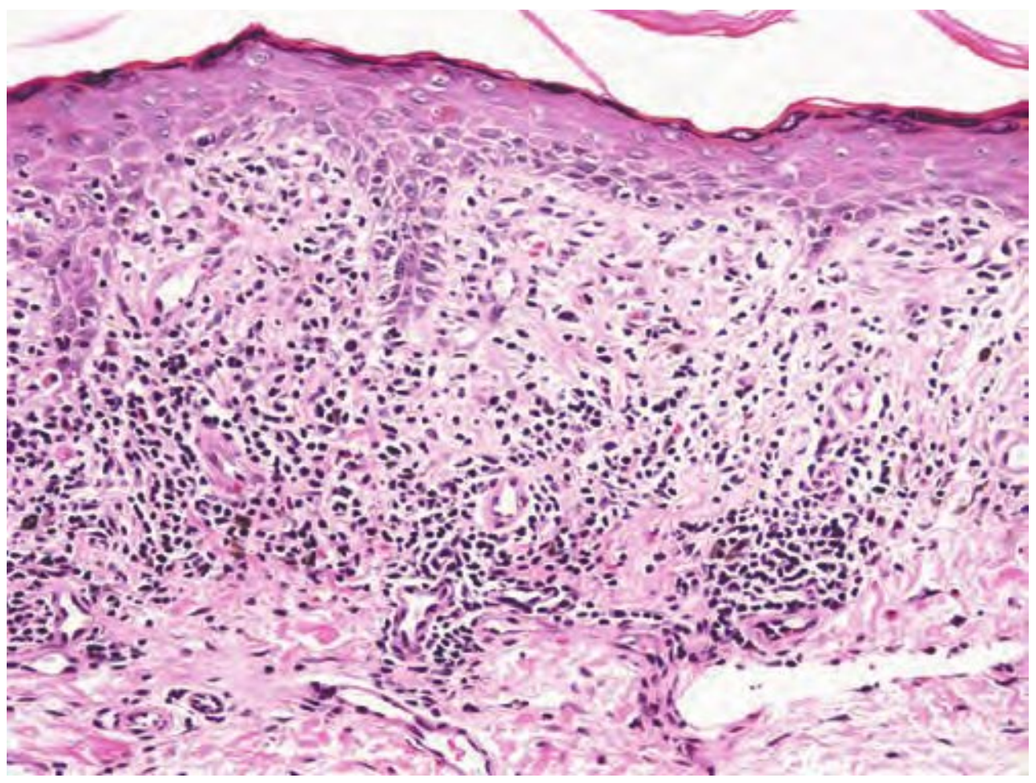


FIGURE 11-5. Lichenoid drug reaction. There is vacuolar change of the basilar layer and scattered apoptotic keratinocytes. Eosinophils in the dermal infiltrate and melanin incontinence are not characteristically seen in the clinically and histologically similar lichen planus.

interstitial pattern. Differentiation from lichen planus may not be possible. Numerous eosinophils, parakeratosis, and perivascular inflammation around the mid and deep dermal plexuses are generally absent in lichen planus.

FIXED DRUG ERUPTION

Fixed drug eruptions (FDEs) show circumscribed erythematous patches that recur persistently at the same site with each administration of the implicated drug. Increasing numbers of lesions may occur with each successive administration. The most common type of FDE consists of one or several slightly edematous, erythematous patches that may develop dusky centers, become bullous, and, on healing, leave pigmented macules. FDEs occur most commonly after the ingestion of trimethoprim-sulfamethoxazole, acetylsalicylic acid, phenolphthalein, tetracycline, barbiturates, and phenylbutazone, but they also occur after ingestion of various other drugs (42).

Histopathology. The histologic changes observed in FDE resemble those of erythema multiforme and toxic epidermal necrolysis. The frequent presence of hydropic degeneration of the basal cell layer leads to "pigmentary incontinence," which is characterized by the presence of melanin within macrophages in the upper dermis (Fig. 11-6). Scattered necrotic keratinocytes with eosinophilic cytoplasm and pyknotic nuclei (often referred to as Civatte bodies, colloid bodies, or dyskeratotic cells) are frequently seen in the epidermis and represent apoptosis. Bullae form by detachment of the epidermis from the underlying dermis. Not infrequently, the epidermis shows extensive confluent necrosis, even in areas in which it has not yet become detached. Confident distinction among fixed drug eruption, erythema multiforme, and toxic epidermal necrolysis based on examination of a skin biopsy specimen alone is not always possible. The inflammatory infiltrate may be composed purely of mononuclear cells or may be polymorphous.

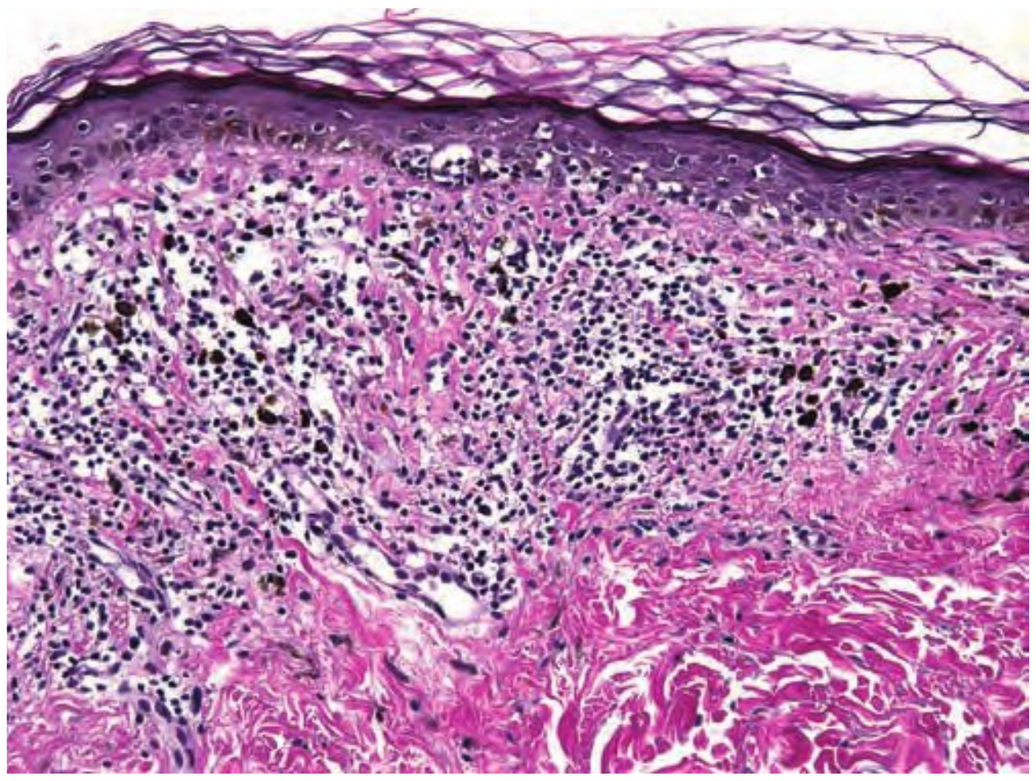


FIGURE 11-6. Fixed drug eruption. This section shows the characteristic lichenoid lymphocytic infiltrate and abundant pigment incontinence with scattered melanophages. In addition, basal vacuolar alteration and dyskeratotic cells occur in the epidermis.

Pathogenesis. On electron microscopic examination, the necrotic keratinocytes are filled with thick, homogenized keratin tonofilaments and show only sparse remnants of organelles and nuclei. Keratinocytes located in the basal cell layer are often the most severely affected cells. The pigmentary incontinence develops when (a) lymphocytes migrate into the epidermis and cause damage to keratinocytes, which become necrotic; (b) macrophages invade the epidermis and phagocytize the necrotic keratinocytes together with their melanosomes; and (c) the macrophages return to the dermis, where they are able to digest all cellular remnants except for the melanosomes, which are resistant to digestion. The intraepidermal lymphocytes are largely represented by $CD8^+$ T cells, whereas the dermal perivascular and interstitial lymphocytes are predominantly $CD4^+$, phenotypically resembling effector memory cells (43). In addition, these $CD8^+$ intraepidermal lymphocytes demonstrate keratinocyte cytolytic activity, indicating their role in the pathogenesis of FDE lesions (44). The process of pigmentary incontinence in FDE is similar to that occurring in incontinentia pigmenti (see Chapter 6). Expression of keratinocyte intercellular adhesion molecule-1 (CD54) is sharply limited to lesional epidermis in fixed drug eruption. Localized induction of this adhesion molecule by drugs may explain the sharply circumscribed clinical lesions (45).

NEUTROPHILIC DRUG ERUPTIONS

Drugs have been implicated in cutaneous eruptions with a neutrophilic infiltrate; these conditions include acneiform eruptions, neutrophilic fixed drug eruption, neutrophilic eccrine hidradenitis, acute generalized exanthematous pustulosis, Sweet's syndrome, and dermatitis herpetiformis–like eruption (46–50). The neutrophilic dermatitis seen as a result of granulocyte repopulation due to exogenous granulocyte colony stimulating factor (G-CSF) is described in the section of this chapter pertaining to eruptions resulting from human recombinant proteins.

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

In acute generalized exanthematous pustulosis (AGEP), widespread nonfollicular, sterile pustules develop within a period of hours after administration of the offending agent. Although enteroviral infection and mercury exposure are cited as causes, antibacterial antibiotics, most commonly pristinamycin and ampicillin/amoxicillin, are most often implicated, with a broad range of other medications as well, including acetaminophen, quinolones, hydroxychloroquine, alphonamides, terbinafine, and diltiazem (51). Fever, leukocytosis, purpura, and clinical

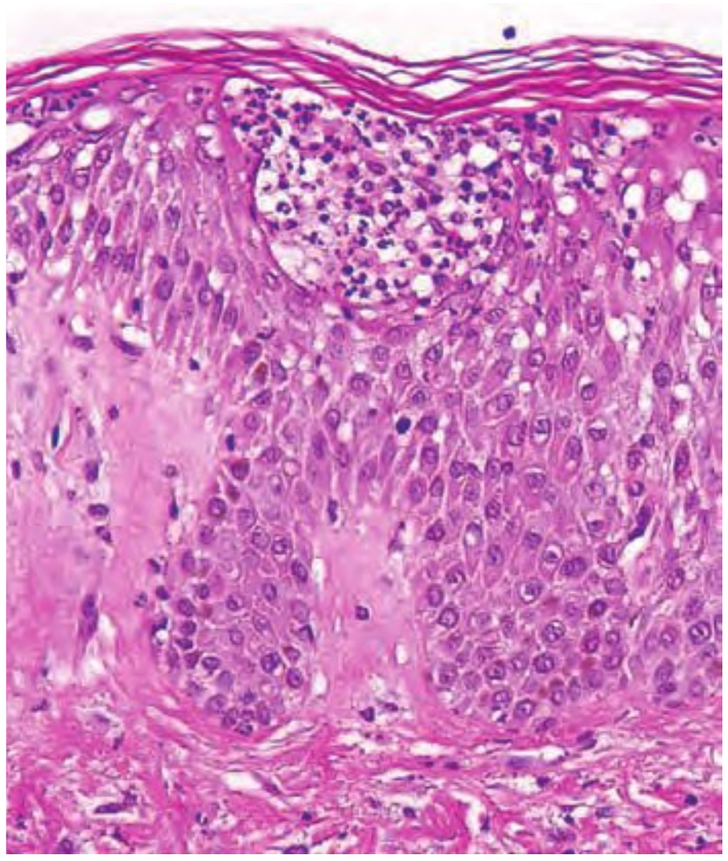


FIGURE 11-7. Acute generalized exanthematous pustulosis. A subcorneal and intraspinous collection of neutrophils is present in the background of mild epidermal edema (spongiosis).

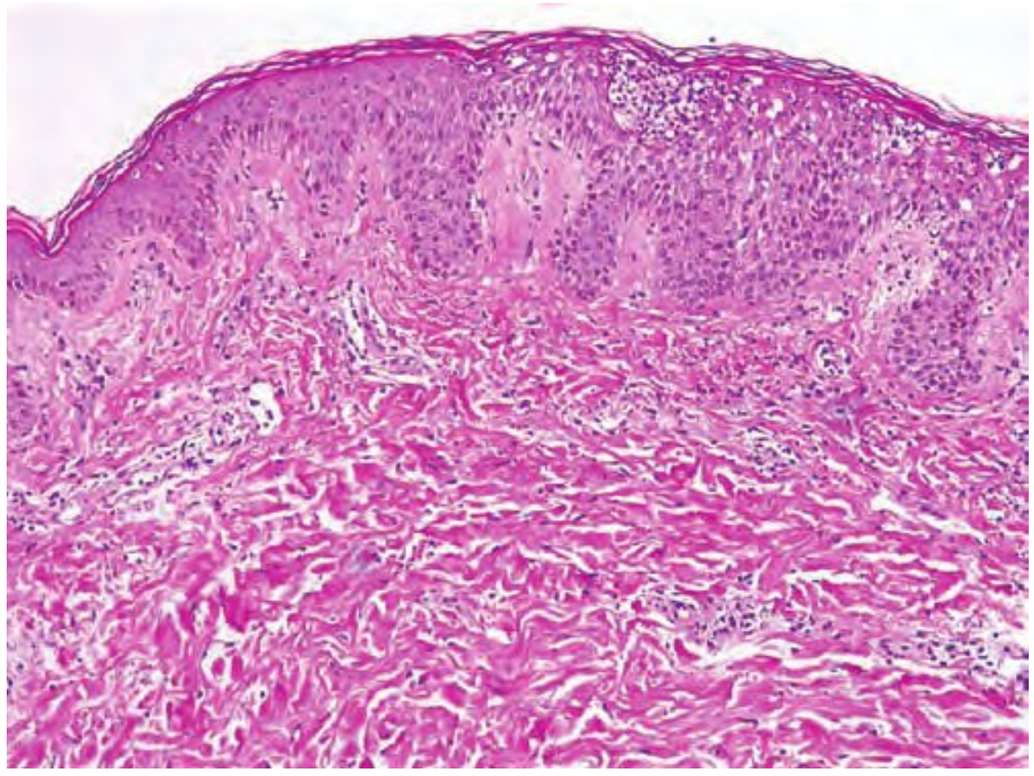


FIGURE 11-8. Acute generalized exanthematous pustulosis. Diffuse spongiosis and a mild upper dermal perivascular inflammatory infiltrate are seen in this case caused by amoxicillin.

features suggesting erythema multiforme accompany the pustules. *In vitro* studies have shown this to be a drug-specific process effected by $CD4^+$ T-cell–mediated release of the neutrophil chemoattractant interleukin-8 (IL-8) (52). T cells from patients with AGEP secrete high levels of IL-8/CXCL8, a potent neutrophil attractant chemokine. In addition, these T cells produce large quantities of granulocyte-macrophage colony stimulating factor (GM-CSF) (53). Unlike drug-induced macular and papular eruptions, there is no upregulation of major histocompatibility complex (MHC) class II expression on keratinocytes.

Histopathology. Biopsies of AGEP have subcorneal or intraepidermal pustules, papillary dermal edema, and a lymphohistiocytic perivascular infiltrate with some eosinophils and neutrophils (Figs. 11-7 and 11.8). Vasculitis and/or single-cell keratinocyte necrosis may be present.

Differential Diagnosis. Based strictly on histologic descriptions, distinction of AGEP from pustular psoriasis, subcorneal pustular dermatosis, and, in some instances, leukocytoclastic vasculitis cannot be made.

DRUG-INDUCED SWEET'S SYNDROME–LIKE ERUPTION

This neutrophilic dermatosis is clinically identical to the non–drug-induced variant of Sweet's syndrome (see Chapter 9). As such, it presents with tender erythematous plaques. Implicated drugs include furosemide, oral contraceptive, and nitrofurantoin (49,54). A localized variation of this is neutrophilic dermatosis of the dorsal hands (NDDH), which presents as pustules and ulcerative plaques on the dorsal hands. Some patients have lesions limited to the dorsal hands, whereas others have additional skin changes elsewhere (55).

Histopathology. A biopsy shows a dermal neutrophilic infiltrate identical to non–drug-induced Sweet's syndrome (see Chapter 9). In NDDH, leukocytoclastic vasculitis is seen on biopsy (56).

TOXIC ACRAL ERYTHEMA

Hand-foot syndrome, palmar-plantar erythrodysethesia syndrome, or toxic acral erythema refers to a transient painful erythema of the palms and soles that becomes edematous and ultimately desquamates. Blisters may form, leaving ulcerated epithelium. Numerous chemotherapeutic agents, including cytarabine, docetaxel, and 5-fluorouracil, have been implicated. The cutaneous lesions attributable to docetaxel—an antineoplastic agent that interferes with normal microtubule function—are not limited to acral sites (57).

Histopathology. Histologically, the skin displays vacuolar degeneration of basilar keratinocytes with eventual cleft formation. Mild epidermal dysmaturation may be seen. Keratinocyte necrosis is also present in the lower third of the epidermis. In the dermis, there is a mild perivascular infiltrate of lymphocytes with few eosinophils.

DRUG-INDUCED SCLERODERMA-LIKE CONDITIONS

Scleroderma-like conditions have been attributed to numerous exogenous agents. Although the pathophysiology is unclear, disturbances in the vasculature and immune system leading to

fibroblastic dysregulation and subsequent deposition of intercellular matrix proteins have been proposed, and telomerase activity appears to serve a protective role (58). Bleomycin, an antitumor agent, is known to cause similar changes in a reversible, dose-dependent fashion in both the skin and the lung due to drug accumulation in these organs deficient in specific metabolic enzymes (59). Multiple cycles of docetaxel are also associated with rapid development of transient scleroderma-like features in dependent areas (60) . Scleroderma-like changes have also been associated with other agents, including phytonadione (vitamin K_1), L-tryptophan, pentazocine, paclitaxel, penicillamine, ergot, bromocriptine, ketobemidone, morphine, cocaine, and appetite suppressants (61,62).

Histopathology. The features are those of idiopathic scleroderma (see Chapter 10), including fibrosis of the dermis and subcutis, adnexal structure entrapment, and atrophy and mild vascular dilation with minimal to no inflammatory infiltrate.

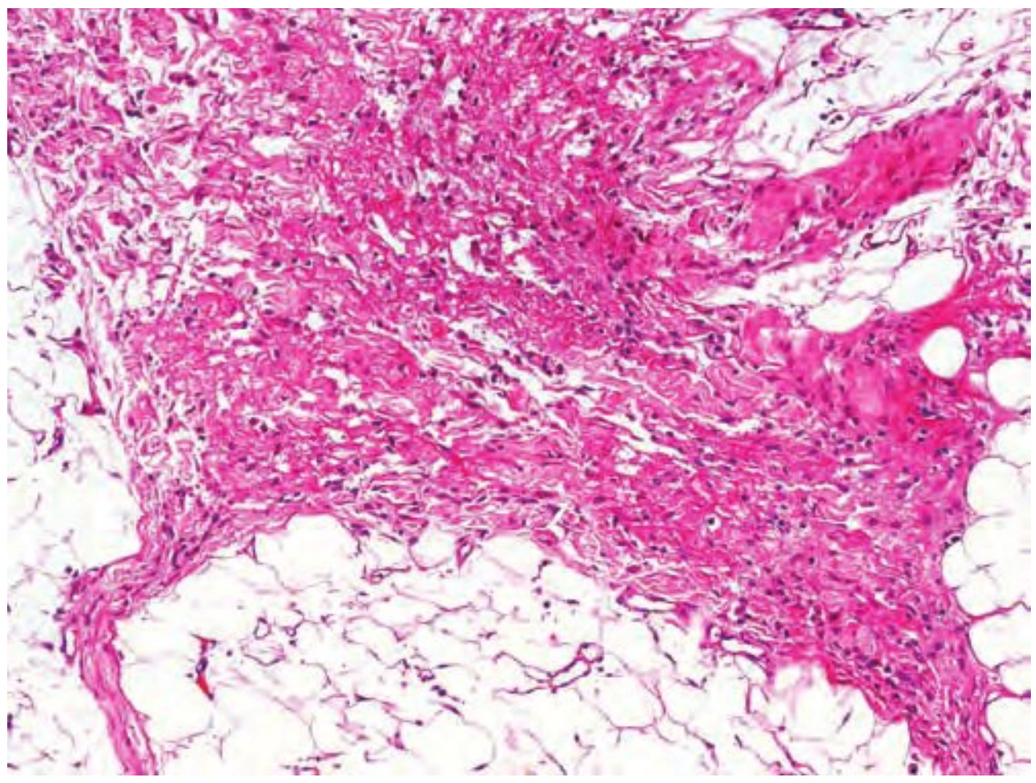


FIGURE 11-9. Nephrogenic systemic fibrosis. The deep dermis shows increased cellularity composed of activated fibroblasts with stellate morphology and occasional multinucleation. Increased collagen and dermal mucin are also present.

NEPHROGENIC SYSTEMIC FIBROSIS

Nephrogenic systemic fibrosis (NSF), previously referred to as nephrogenic fibrosing dermopathy, is a progressive multiorgan fibrosing disorder. Although the cause and pathogenesis remain elusive, it has been closely linked to patients with compromised renal function and gadolinium exposure. High morbidity and mortality are associated with NFD. The fibrosis most commonly affects the lower extremities and manifests as dense induration, papules, or plaques. A role for gadolinium in routing the collagen-producing circulating fibrocyte has been proposed (63). A gadolinium-associated systemic inflammatory process that results in mobilization of iron and subsequent tissue injury also has been proposed (63). NSF is covered in detail in the chapter of this book pertaining to cutaneous fibrosing disorders (see Chapter 10).

Histopathology. The biopsy specimen shows mild to moderate increased cellularity in the mid to deep reticular dermis. The cellularity is composed of fibroblasts with activated morphology, large nuclei, occasional multinucleation, and abundant angulated cytoplasm (Fig. 11-9). Increased collagen and dermal mucin are also characteristically seen. The cellularity and collagen deposition may extend along the subcutaneous septae and fascia.

BULLAE AND SWEAT GLAND NECROSIS IN DRUG-INDUCED COMA

A patient who is in a coma as a result of an accident, illness, or a large dose of a narcotic drug may show, within a few hours, areas of erythema at sites of pressure. Usually within 24 hours, vesicles and bullae develop in the erythematous patches. The incidence of bullae depends on the severity of the coma and is highest in patients who subsequently die. Coma caused by carbon monoxide poisoning can also produce the lesions (32). The bullae are located at sites subjected to pressure, such as the hands, wrists, scapulae, sacrum, knees, legs, ankles, and heels.

Histopathology. The epidermis shows varying degrees of necrosis. In areas of complete necrosis of the epidermis, the bullae arise subepidermally, but small intraepidermal vesicles may be seen in areas of only diminished viability showing eosinophilia of the cytoplasm and decreased staining of the nuclei. Where the epidermis is necrotic in its upper layers but not in its lower layers, even large bullae can form intraepidermally.

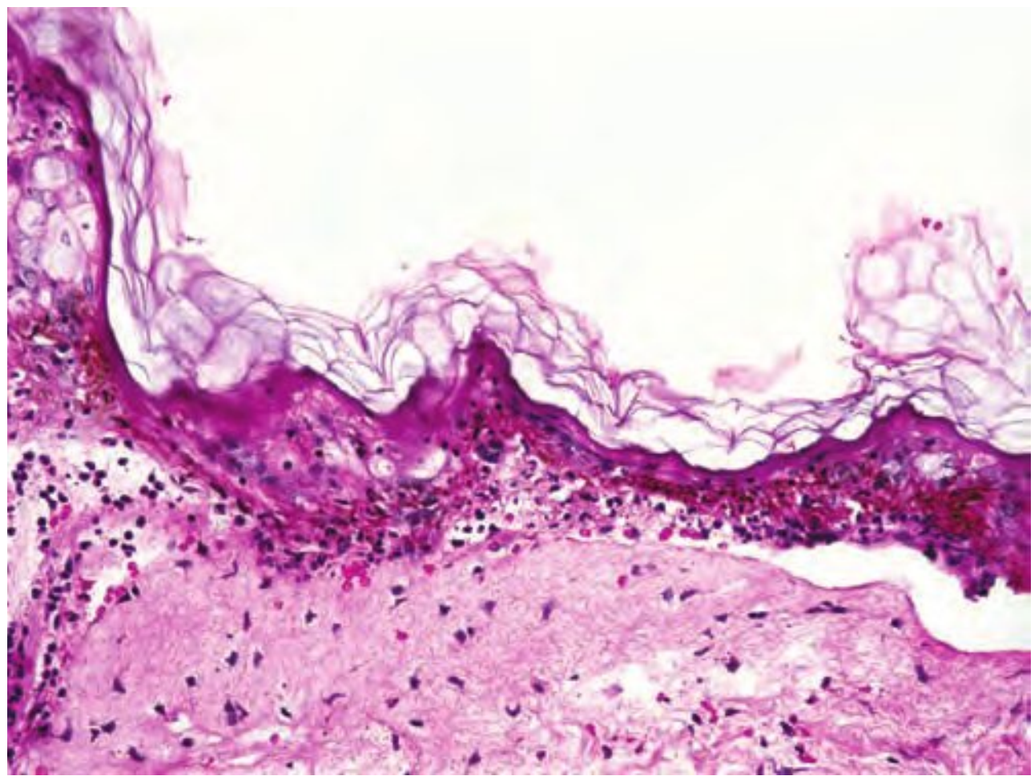


FIGURE 11-10. Drug-induced coma bulla. There is extensive necrosis of the epidermis with subepidermal blister formation. Inflammation in the blister cavity is secondary to adjacent ulceration. The dermis shows only a mild inflammatory infiltrate.

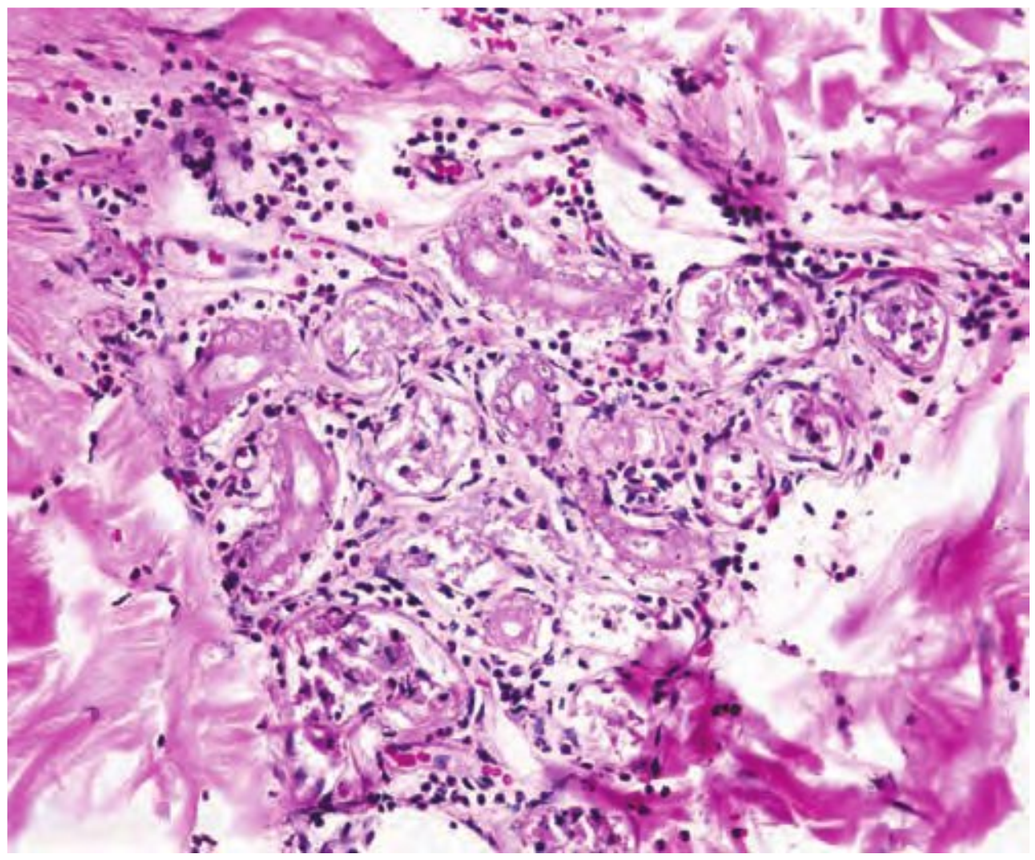


FIGURE 11-11. Coma bulla and sweat gland necrosis. This image shows necrosis of the eccrine coil with cytoplasmic eosinophilia along with absent and pyknotic nuclei.

Blisters may also form in a suprabasal location and may contain some acantholytic cells (Fig. 11-10) (64).

The secretory cells of the sweat coil are the most susceptible to necrosis, which is characterized by eosinophilic homogenization of their cytoplasm and pyknosis or absence of their nuclei. The sweat ducts usually appear less severely damaged but may also show pale staining or necrosis similar to that of the secretory cells (Fig. 11-11) (64). Necrosis may also be seen in the hair follicle, sebaceous gland, and, as mentioned, the epidermis (64). It is of interest that the sweat gland necrosis is limited to areas in which there are skin lesions. In patients who survive, the necrotic sweat gland epithelium is replaced by normal-appearing epithelial cells within about 2 weeks. In many instances, the pilosebaceous units are also affected with sebaceous gland necrosis and occasional necrosis of the outer and inner root sheaths.

The dermis beneath the bullae, and occasionally also the dermis around the sweat glands, contains a sparse polymorphous infiltrate composed of neutrophils, eosinophils, lymphocytes, and histiocytes. In addition, some extravasated erythrocytes are often present.

Vascular changes consist of vessel wall damage associated with a neutrophilic infiltrate (64). Lesions due to a non–drug-induced coma characteristically show fibrinoid thrombi in the vascular lumina (65).

Pathogenesis. The necrosis of the epidermis and sweat glands is a result of both generalized and local hypoxia. The bullae, in turn, are the result of epidermal damage. Coma, whether the result of an accident, an illness, or a drug, causes generalized hypoxia by depressing blood circulation and respiration. In the case of poisoning with carbon monoxide, its binding to hemoglobin acts as an additional factor (66) . Pressure causes further local hypoxia by decreasing blood flow.

DRUG-INDUCED BULLOUS DISORDERS

Several medications are linked to the development of antibody-mediated pemphigus (Table 11-1). Among these, penicillamine is perhaps the most common; however, the growing list of implicated agents includes other thiol-, sulfur-, and amide-containing drugs (67). The majority of cases of penicillamine and other thiol-induced pemphigus present as pemphigus foliaceus and have fewer immunofluorescence findings and a more favorable prognosis on drug withdrawal. Those cases attributed to nonthiol drugs, in particular those with an active amide group, may provoke disease indistinguishable from spontaneously occurring pemphigus vulgaris. Drug induction of subepidermal blisters is also recognized, with vancomycin-induced linear IgA dermatosis as a prime example (68–70). Oropharyngeal pemphigus secondary to interferon-α2a has also been reported (71).

Histopathology. Histologic examination reveals a picture identical to that seen in pemphigus vulgaris and/or pemphigus foliaceus not associated with drugs (72) (see Chapter 9). The autoantibody response to desmoglein 1 and desmoglein 3 is similar in both spontaneous and drug-induced disease (73).

Pathogenesis. Both biochemical and immunologic mechanisms, not mutually exclusive, have been proposed. In the subset of patients in which tissue-bound antibodies cannot be found, a biochemical mechanism has been suggested. These drugs directly bind to keratinocyte membranes, forming bonds that interfere with cell–cell adhesion and resulting in acantholysis (67). Predisposition to development of pemphigus vulgaris is linked to MHC II, specifically human leukocyte antigen (HLA) DRB1 and DQB1 (74). It has been postulated that polymorphisms of the DR4 β chain impart T-cell recognition of exogenous peptides that stimulate autoantibody production by B lymphocytes (75). In addition, immunologic

TABLE 11-1 Drugs Causing Pemphigus

Penicillamine	Pyrazolone derivatives
Captopril	Interleukin-2
Piroxicam	α-Interferon
Bucillamine	Propanolol
Penicillin	Phenobarbital
Ampicillin	Levodopa
Rifampin	Nifedipine
Cefadroxil	Glibenclamide
Cephalexin	Cilazapril
Ceftazidime	Lisinopril

acantholysis can be triggered by biochemical events that lead to formation of a neoantigen, with consequent autoantibody production (67). In most thiol-drug–related cases, intercellular antibodies can be demonstrated, indicating that this class of drugs acts primarily through immunologically mediated acantholysis.

DRUG-INDUCED LUPUS ERYTHEMATOSUS

Drug-induced lupus erythematosus resembles mild systemic lupus erythematosus and is characterized by arthralgia or arthritis and myalgia and may be accompanied by serositis, fever, hepatomegaly, splenomegaly, and skin manifestations. The cutaneous lesions are typical of systemic lupus erythematosus with annular erythematous plaques, central clearing, and a peripheral scale (Fig. 11-12) and may erupt days to years after onset of treatment (76,77) . Central nervous system and renal involvement are rare. The drugs most commonly implicated include procainamide, hydralazine, quinidine, chlorpromazine, isoniazid, methyldopa, and propylthiouracil (78). However, the number of medications associated with induction of lupus erythematosus is increasing, with rare reports of terbinafine, docetaxel, anti–tumor necrosis factor-α, adalimumab, and others (60,79–81). It is possible that the development of a systemic lupus erythematosus–like syndrome in a patient under medication with these drugs represents the uncovering of latent systemic lupus erythematosus.

Drug-induced systemic lupus erythematosus can be clinically, pathologically, and serologically indistinguishable from spontaneously arising systemic lupus erythematosus. However, cutaneous and renal manifestations are rare in drug-induced systemic lupus erythematosus, and pleuropulmonary manifestations are somewhat more common than in spontaneous disease. Clinical presentations resembling subacute cutaneous lupus erythematosus secondary to terbinafine have been reported (82,83). Usually, but not always, the clinical and laboratory manifestations subside when the medication is discontinued.



FIGURE 11-12. Drug-induced subacute cutaneous lupus erythematosus. Annular erythematous plaques with mild peripheral scale are seen in this patient on Dilantin. (Courtesy of Donna Pellowski, MD.)

Histopathology. The histologic picture of the cutaneous lesions is the same as in lupus erythematosus (see Chapter 10).

Pathogenesis. As in other autoimmune-related disorders, genetic predisposition, in particular, HLA-DR4, has a role in drug-induced lupus. Antinuclear antibodies are usually present and directed against single-stranded DNA or histones (84). Different drugs appear to be associated with different antihistone profiles (78). Anti–double-stranded DNA antibodies are usually absent. Hypocomplementemia is rare. The occurrence of a lupus band on direct immunofluorescence testing of normal-appearing skin is uncommon (85). The rate of drug acetylation has also been associated with disease onset. Rapid acetylators have a much lower incidence of hydralazine-induced lupus, whereas slow acetylators are at higher risk (86). Additionally, there is evidence that myeloperoxidase produced by neutrophils in conjunction with cells capable of generating superoxides transforms lupus-inducing drugs to cytotoxic products. Elucidation of this process is evolving (78).

DRUG-INDUCED PHOTOSENSITIVITY

Drug-induced photosensitivity can be subdivided into photoallergic and phototoxic drug eruptions. Photoallergic drug eruptions represent a T-cell–mediated reaction.

Photoallergic Drug Eruption

In photoallergy, ultraviolet light alters either the hapten or the avidity with which the hapten combines with the carrier protein to form a complete photoantigen (87). Among the photoallergenic drugs are the sulfonamides; the thiazides, such as chlorothiazide and tolbutamide, both of which are aromatic sulfonamides; griseofulvin; the phenothiazines, such as chlorpromazine; quinine; topical nonsteroidal antiinflammatory medications, including piroxicam; and sunscreens (88,89). A photoallergic drug eruption causes a photocontact dermatitis in all light-exposed areas. Like any allergic contact dermatitis, it causes itching.

Histopathology. The histologic appearance of a photoallergic dermatitis is that of an allergic contact dermatitis and includes spongiosis, mild acanthosis, and a superficial perivascular lymphocytic infiltrate with eosinophils (Fig. 11-13) (90).

Phototoxic Drug Eruption

Certain internally administered drugs, in association with ultraviolet light, may produce a phototoxic dermatitis that resembles intensified sunburn. Among the drugs known to elicit a phototoxic response are all drugs capable of producing a

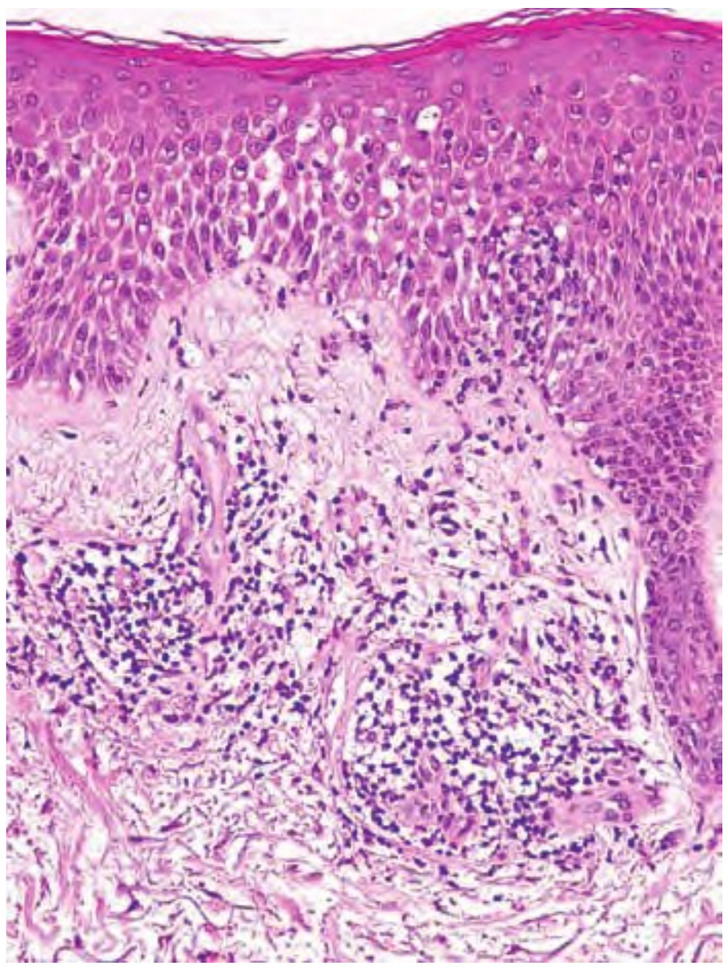


FIGURE 11-13. Photoallergic dermatitis. There is spongiosis with microvesicle formation, exocytosis of lymphocytes, and a perivascular lymphocytic infiltrate admixed with scattered eosinophils.

photoallergic reaction, provided that they are given in sufficiently high concentrations (91). Other commonly prescribed phototoxic drugs are certain tetracyclines, such as demeclocycline hydrochloride and doxycycline, quinolones, and psoralens (3,92).

Histopathology. A phototoxic drug eruption, like a sunburn reaction, shows both vacuolated keratinocytes (sunburn cells) characterized by abundant, pale cytoplasm and apoptotic keratinocytes characterized by reduced, eosinophilic cytoplasm. The dermis shows edema and enlargement of endothelial cells (Fig. 11-14).

PHOTODISTRIBUTED HYPERPIGMENTATION

Certain drugs—in particular, tetracycline, chlorpromazine, diltiazem, amiodarone, imipramine, and desipramine—are known to produce cutaneous discoloration on sun-exposed areas of the skin (94–96). This pigment change results from overproduction of melanin in melanocytes specifically stimulated by the offending drug, lack of melanin clearance due to stable complex formation with the drug, or dermal deposition of the drug, which undergoes an ultraviolet-related change that inhibits clearance (94). In imipramine hyperpigmentation, dispersive spectroscopy studies show that the dermal granules have copper and sulfur, elements normally found in tyrosinase and pheomelanin as well as melanin (97,98). This pigment alteration results in blue, blue-gray, or brown hues. Exposed parts of the bulbar conjunctivae may show brownish pigmentation. Similarly, photodistributed slate-gray, reticulated pigmentation has been described in patients on long-acting diltiazem hydrochloride (94).

Histopathology. In chlorpromazine, amiodarone, imipramine, and desipramine reactions, there is variable amount of melanin in the basal layer of the epidermis. Throughout the dermis, there is considerable accumulation of pigment-laden macrophages, predominantly in a perivascular pattern (Fig. 11-15). The pigment has the staining properties of melanin, in that it stains black with the Fontana-Masson silver stain and is decolorized by hydrogen peroxide. Hyperpigmentation from imipramine results from melanin complexed with drug metabolite, which causes refractile golden-yellow granules that deposit in the superficial and papillary dermis and are visible on light microscopy (Fig. 11-16) (99). In addition, on electron microscopy, electron-dense granules are present within macrophages (98). In patients on long-term chlorpromazine, this melanin-like material is found in many internal organs,

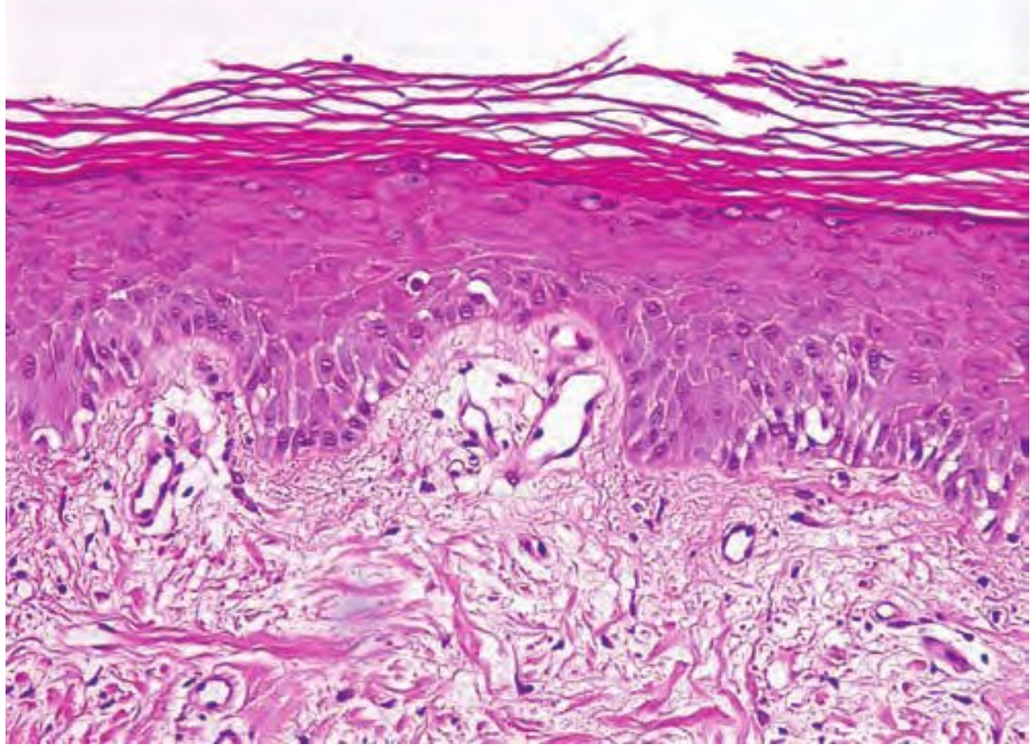


FIGURE 11-14. Phototoxic dermatitis. There are vacuolated keratinocytes and apoptotic keratinocytes in the epidermis. Dermal edema and enlarged endothelial cells are also characteristic.

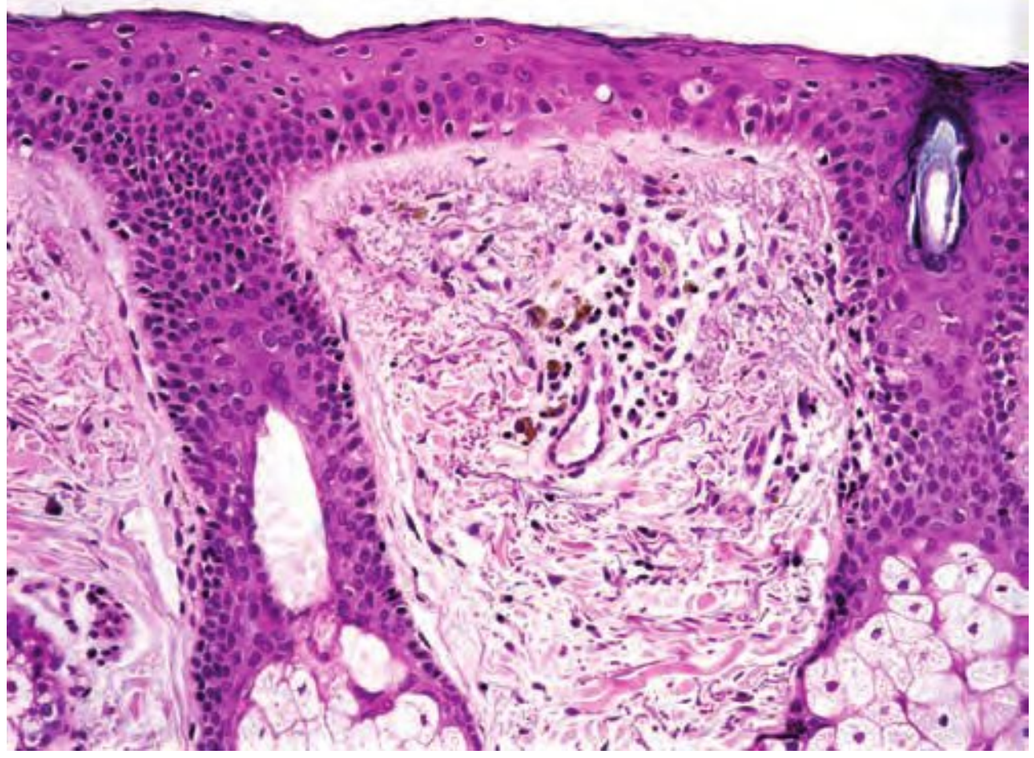


FIGURE 11-15. Chlorpromazine pigmentation. Perivascular pigment-laden macrophages are seen in this case of chlorpromazine pigmentation.

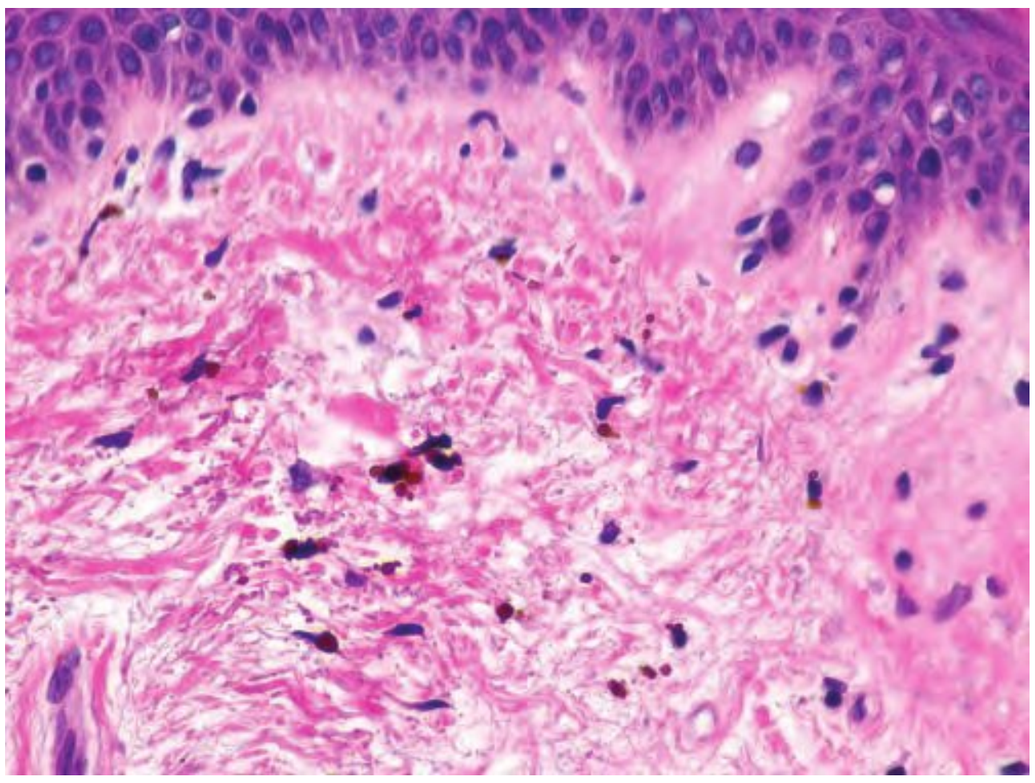


FIGURE 11-16. Imipramine pigmentation. Photodistributed slate gray pigmentation is caused by round, yellow-brown globules in the dermis.

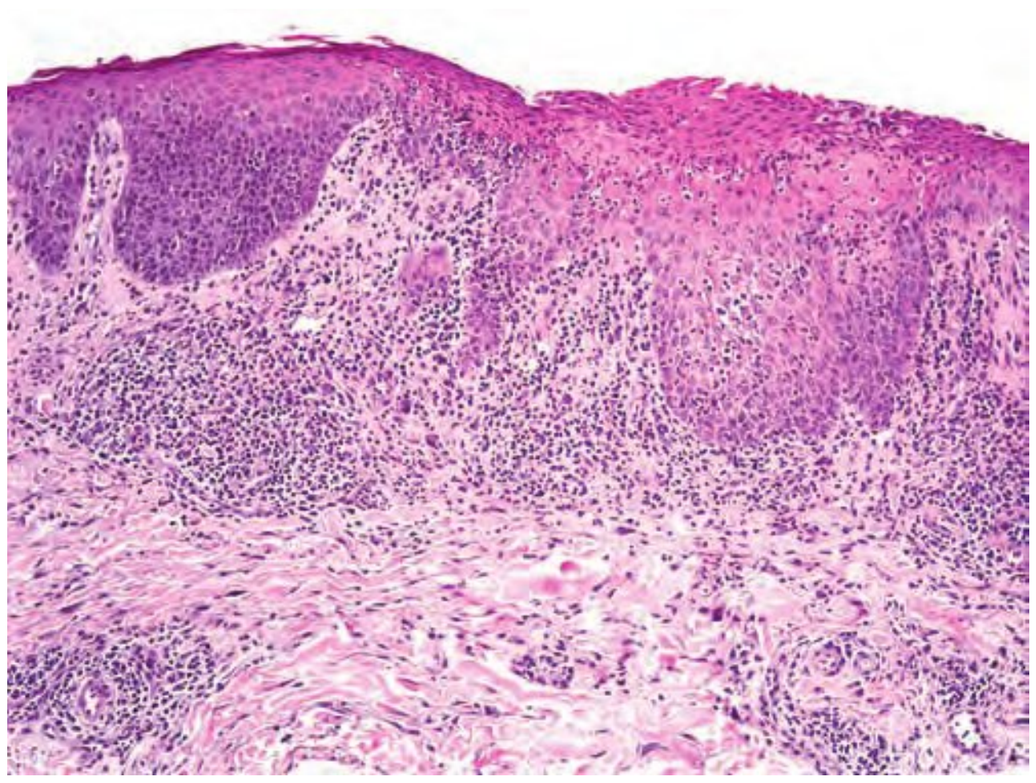


FIGURE 11-17. Cutaneous pseudolymphoma. There is a dense inflammatory infiltrate with exocytosis of atypical-appearing lymphocytes and absence of spongiosis in this Dilantin-induced pseudolymphoma.

throughout the entire mononuclear-phagocyte system, and, to a lesser degree, in the parenchymal cells of the liver, kidneys, and endocrine glands, in myocardial fibers, and in cerebral neurons (100).

In contrast, the diltiazem reactions reveal lichenoid dermatitis with atrophic epidermis and basal vacuolar change. The papillary dermis is expanded with prominent and dilated thin-walled vessels and a sparse perivascular and periadnexal lymphocytic infiltrate (95).

Histogenesis. Electron microscopic examination has confirmed the presence of many melanosome complexes within the lysosomes of dermal macrophages. In addition, 0.2- to 3-μm-diameter, round or bizarrely shaped electron-dense bodies may be seen in macrophages, endothelial cells, pericytes, Schwann cells, and fibroblasts, usually within lysosomes (101,102). Both electron-dense bodies and melanosome complexes may be found within the same lysosome. Although the dense bodies histochemically react like melanin, the striking sulfur peak on microprobe analysis strongly suggests the drug or its metabolite (102) is also present. Because some drugs do bind to melanin (103), it seems likely that the electron-dense bodies represent complexes of melanin with drug. These complexes are subsequently carried from the dermis by way of the circulating blood leukocytes to the various internal organs. In diltiazem-related hyperpigmentation, only melanosomes, without drug or drug metabolite, are seen (104).

DRUG-INDUCED PSEUDOLYMPHOMA SYNDROME

Phenytoin, ethosuxamide, lamotrigine, tattoo, carbamazepine, sodium valproate, gemcitabine, gold, and clonidine patch are among the agents that have been associated with a pseudolymphoma syndrome characterized by generalized lymphadenopathy, hepatosplenomegaly, fever, arthralgia, and eosinophilia (105–107). Cutaneous findings range from a few erythematous plaques or nodules to a generalized macular and papular eruption and generalized exfoliative dermatitis (107). In all cases there is improvement and ultimate clearing when the offending agent is discontinued.

Histopathology. On histologic examination of the skin, the infiltrate is often indistinguishable from that of mycosis fungoides (this syndrome is also known as "pseudo-mycosis fungoides"), in that there are cerebriform nuclei in the dermal infiltrate and Pautrier microabscesses in the epidermis (Fig. 11-17). In cutaneous nodules, the infiltrate may suggest a cutaneous lymphoma of the non-Hodgkin's type because large masses of atypical lymphocytes are present in the dermis and in the subcutaneous tissue. T-cell receptor monoclonality has been demonstrated in some cases (108).

DRUG-INDUCED PSEUDOPORPHYRIA

Ciprofloxacin, voriconazole, nonsteroidal antiinflammatory drugs, and oral contraceptives are among the medications reported to cause cutaneous lesions resembling the blisters of porphyria cutanea tarda (109–113). Unlike porphyria cutanea tarda, other cutaneous manifestations are absent, and no derangement in porphyrin metabolism has been identified. Healing occurs once the medication is discontinued. Implicated drugs include naproxen, furosemide, tetracycline, dapsone, and pyridoxine (114,115).

Histopathology. The blisters resemble the poorly or noninflamed subepidermal bullae of porphyria cutanea tarda (Chapter 17).

Histogenesis. The mechanism by which this reaction occurs is unknown. Unlike porphyria cutanea tarda, no deposits in the skin are revealed by direct immunofluorescence testing (Chapter 17) (115).

CUTANEOUS REACTIONS TO ANTINEOPLASTIC CHEMOTHERAPEUTIC DRUGS

In general, the cutaneous changes brought about by antineoplastic chemotherapeutic agents are the result of their antiproliferative effects disrupting cutaneous cellular metabolism. Clinical manifestations vary.

Hyperpigmentation develops under occluded skin after thiotepa administration. The grouped linear streaks, or "flagellate" hyperpigmentation, on the trunk and extremities are characteristic of bleomycin hyperpigmentation (116,117) (Fig. 11-18). In addition, hyperpigmentation after long-term hydroxyurea therapy is well documented (118,119). Diffuse hyperpigmentation commonly occurs after antineoplastic chemotherapy. Erythema preceding the hyperpigmentation in these settings is minimal or absent.

Inhibitors of the epidermal growth factor receptor have increasing importance in the treatment of solid tumors. These receptors are integral to epidermal development and maintenance. Accordingly, cutaneous reactions due to inhibition is of the receptors are common. In most of these reactions, 85%, occur as an acneiform follicular eruption (120–122).

Anagen effluvium is a well-established effect of the antiproliferative nature of many chemotherapeutic agents. Neutrophilic eccrine hidradenitis presents with erythematous,



FIGURE 11-18. Bleomycin pigmentation. The characteristic linear "flagellate" streaks on the trunk of this patient on bleomycin. (Courtesy of Donna Pellowski, MD.)

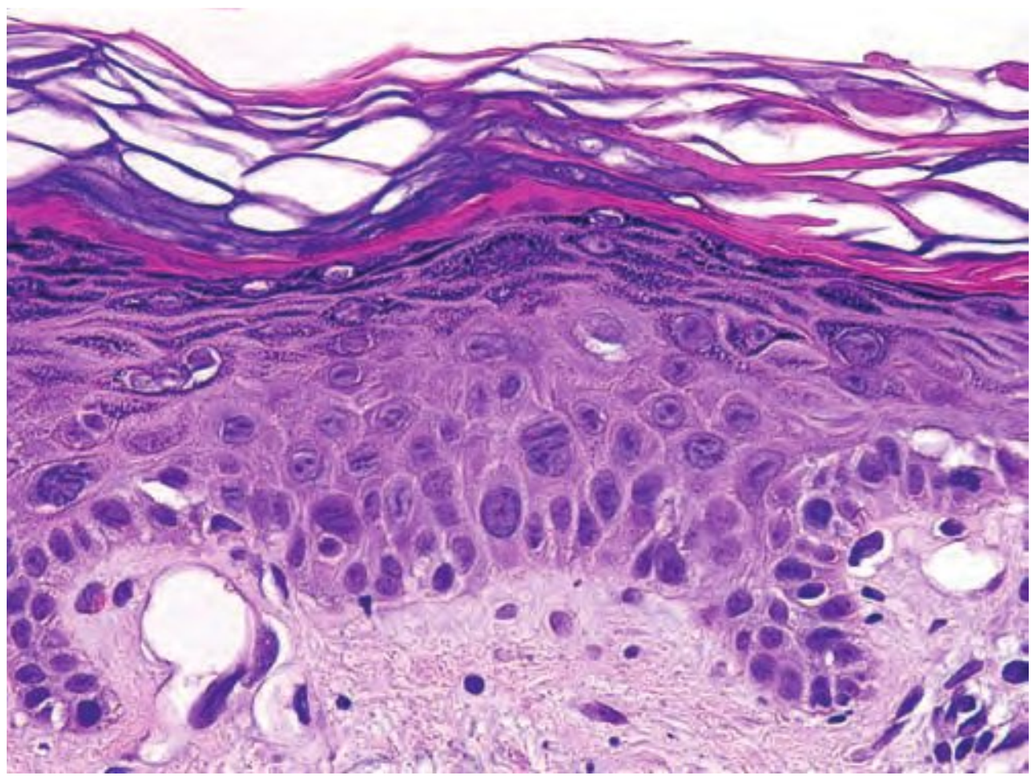


FIGURE 11-19. Mild epidermal dysmaturation due to antineoplastic chemotherapy. Loss of polarity and disorganization of keratinocytes is minimal and confined to the lower epidermal layers in this specimen.

often acral, plaques several days after cytoreductive chemotherapy. Acral erythema unassociated with primary eccrine changes also occurs after chemotherapy (see previous discussion).

Histopathology. Cytoreductive chemotherapy may cause a disruption of the normal pattern of keratinocyte maturation from small cuboidal cells in the basilar epidermis to flattened squamous cells in the stratum corneum. At intervening epidermal levels, keratinocytes are separated by widened intercellular spaces, lose polarity, and display irregular large nuclei, midepidermal mitotic figures, and apoptosis (Figs. 11-19 and 11.20). These changes, referred to as *epidermal dysmaturation*, may be observed in the epidermis after any significant cytoreductive

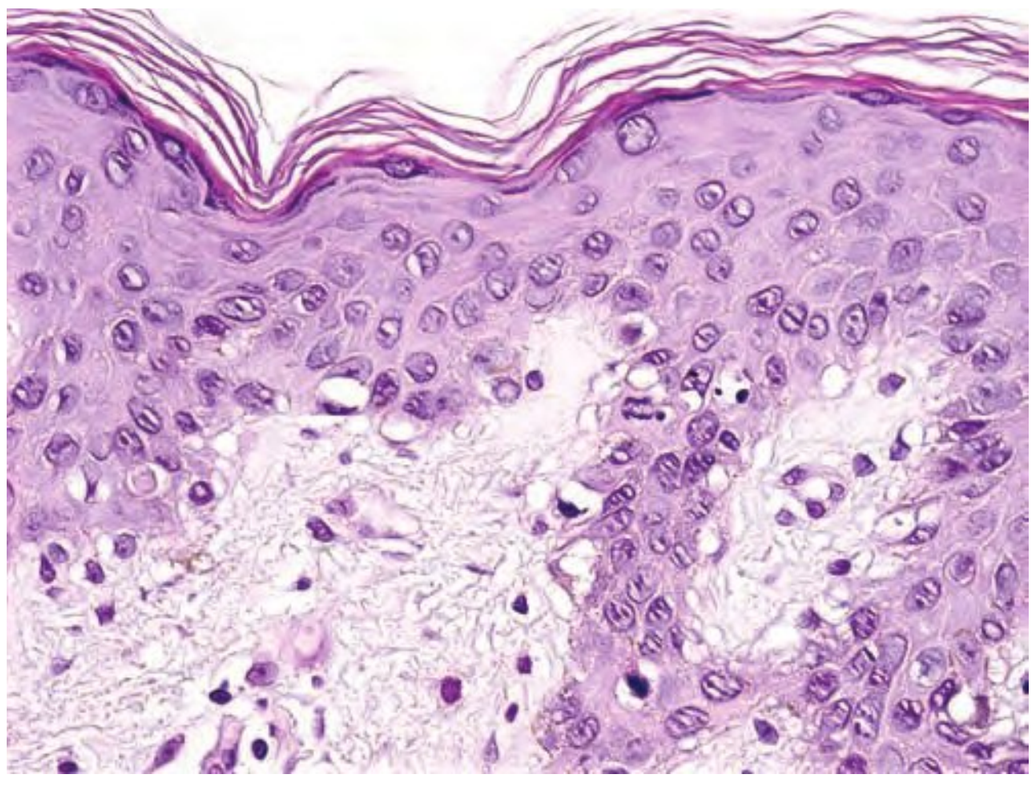


FIGURE 11-20. Severe epidermal dysmaturation due to antineoplastic chemotherapy. Loss of polarity and disorganization of keratinocytes are advanced in this specimen.

therapy and are not necessarily associated with clinical lesions. Upper dermal melanophages often accompany these changes. In this setting, "starburst" mitotic figures are described after systemic etoposide administration (123). Numerous mid- and upper-level mitotic figures (so-called "mitotic arrest") are observed after podophyllotoxin application to condyloma. Etoposide and podophyllotoxin are vinca alkaloid derivatives, disrupting mitotic spindle formation by attaching to microtubule proteins.

Several entities in this section are unified by the theory of drug concentration in eccrine sweat. Specimens from patterned *postchemotherapy hyperpigmentation* show vacuolization of basilar epidermis, melanin incontinence, and apoptosis in occluded skin after administration of alkylating agents (124). Inflammation is sparse or absent. Squamous metaplasia of upper eccrine ducts, *syringosquamous metaplasia*, is described after cytoreductive therapies. The normally cuboidal cells lining the duct display irregularly increased amounts of eosinophilic cytoplasm with associated polymorphous inflammation, fibrosis, and necrosis (Fig. 11-21). *Neutrophilic eccrine hidradenitis* consists of variable infiltration of the eccrine coil by neutrophils and lymphocytes with necrosis of secretory epithelium. Individual cells or whole coils show increased cytoplasmic eosinophilia, degeneration of nuclei, and loss of integrity of cell walls (Fig. 11-22). Edema and mucinous change may be seen in the perieccrine adipose tissue.

Histogenesis. The notion of concentration of antineoplastic chemotherapeutic agents in sweat serves to unify the clinical observation of patterned hyperpigmentation (beneath bandages and electrocardiogram pads in the case of thiotepa) and the histologic observations of neutrophilic eccrine hidradenitis and syringosquamous metaplasia. Changes after antineoplastic chemotherapy likely represent a mix of direct toxic effect on the various constituent cells of the skin with secondary inflammation incited by cell damage. Other chemotherapy-related cutaneous changes may also involve similar mechanisms—namely, intertriginous erosion/ulceration after isophosphamide (125) and flagellate hyperpigmentation after bleomycin. Why specific agents affect specific cell populations in the skin in repeatable fashion is unclear. It is important to note that identification of epidermal dysmaturation assumes considerable importance in establishing the diagnosis of acute graft-versus-host reaction (126). When possible, the inflammation and apoptosis of a graft-versus-host reaction should be sought in areas unaffected or less affected by dysmaturation.

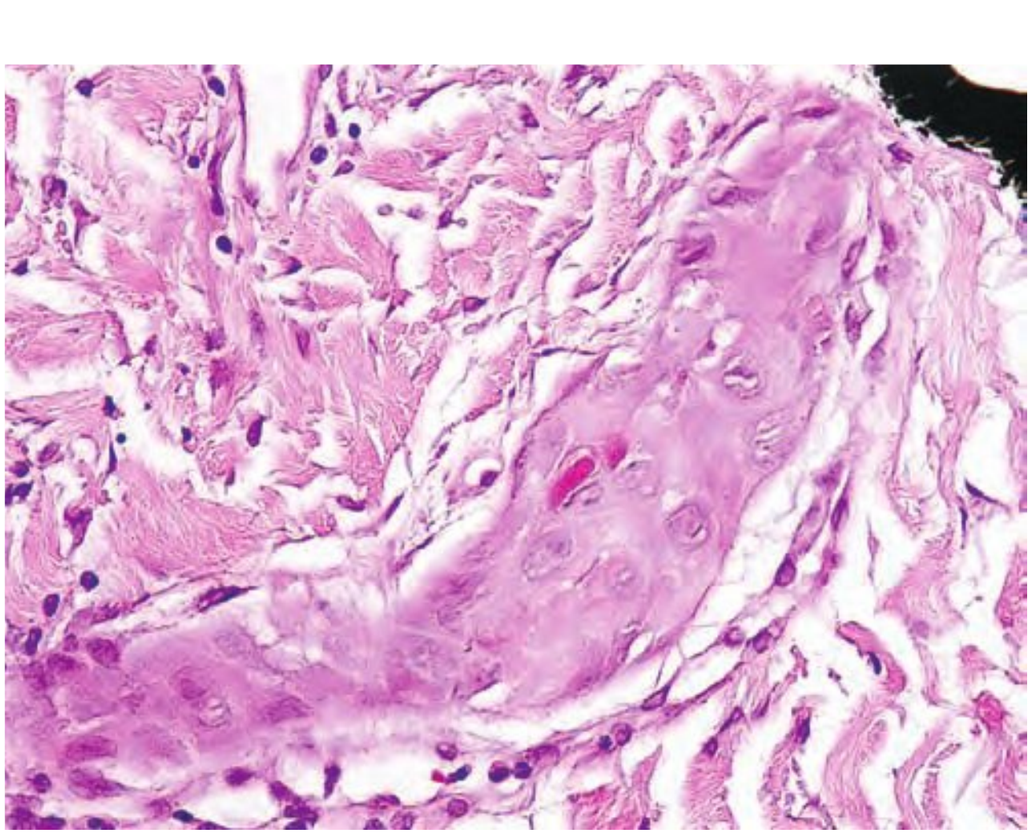


FIGURE 11-21. Syringosquamous metaplasia. This eccrine duct is lined by squamoid cells with ample eosinophilic cytoplasm and large nuclei rather that the normal cuboidal cells.

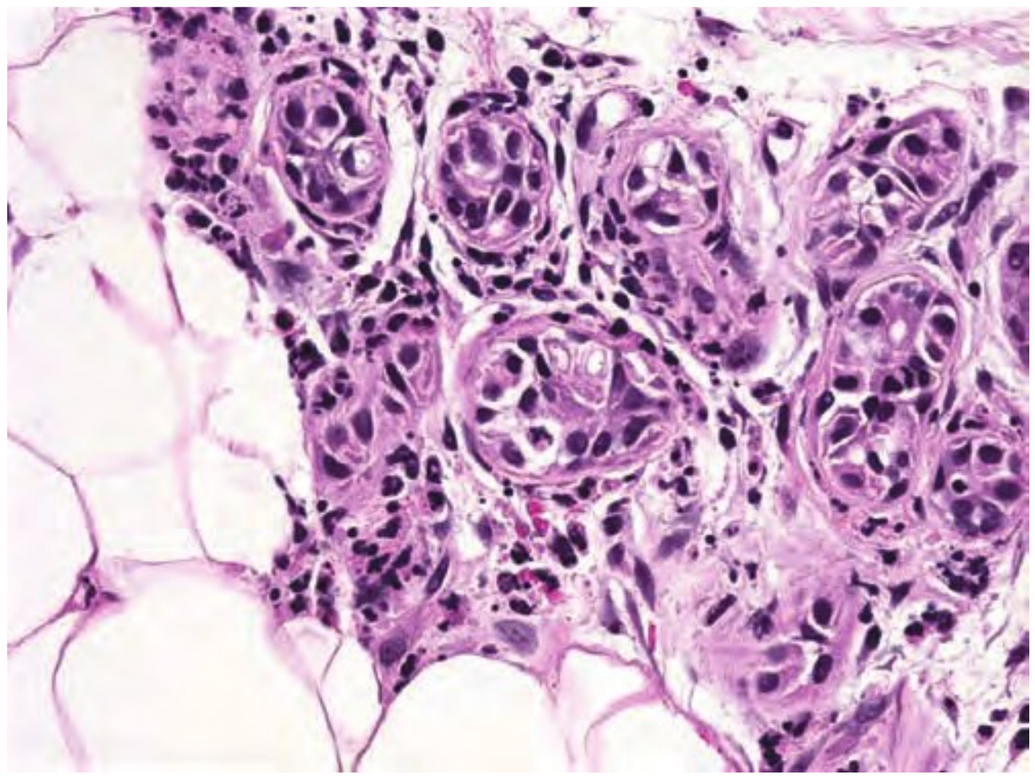


FIGURE 11-22. Neutrophilic eccrine hidradenitis. Neutrophils and lymphocytes are present in the perieccrine adventitia and eccrine coil. Increased cytoplasmic eosinophilia and pyknotic nuclei characterize eccrine necrosis.

CUTANEOUS ERUPTIONS RESULTING FROM ADMINISTRATION OF HUMAN RECOMBINANT PROTEINS

Technologic advances in recombinant DNA research have resulted in the availability of human recombinant cytokines (including colony-stimulating factors) for administration to patients to effect immunologic manipulation for therapeutic benefit. Based on the actions of human cytokines, specific agents are administered, generally to immunocompromised patients, to enhance the number and/or activity of leukocytes, platelets, or erythrocytes. This action is aimed at hematopoietic cells in the marrow and/or mature leukocytes in the peripheral circulation or tissues.

Mucocutaneous effects of systemic administration of at least 13 cytokines have been described (Table 11-2). The findings generally occur (a) at injection sites, (b) as variably distributed eruptions, or (c) as exacerbation or induction of other dermatologic disorders, such as psoriasis.

Etanecept, a recombinant tumor necrosis factor-α receptor fused to the Fc fragment of IgG_2, and recombinant interferon-β

TABLE 11-2 Mucocutaneous Effects of Systemic Administration of Cytokines

Cytokine	Reported association
Interleukin-1 α and β	Phlebitis, mucositis
Interleukin-2	Diffuse erythema, exacerbation of psoriasis, and autoimmune diseases
Interleukin-3	Flushing
Interleukin-4	Edema
Interleukin-6	Erythematosus eruption
Granulocyte-macrophage colony-stimulating factor	Diffuse eruption, Sweet's syndrome
Granulocyte colony-stimulating factor	Neutrophilic dermatoses, vasculitis
Tumor necrosis factor-α	Erythroderma, psoriasis
Tumor necrosis factor-α receptor/immunoglobulin G_2 Fc	Injection site reaction
Epidermal growth factor receptor inhibitor	Acneiforme eruption, psoriatic palmoplantaris pustulosis
Interferon-α	Alopecia, injection-site reaction, exacerbation of psoriasis, severe eczema
Interferon-β	Mostly injection-site reactions, including vasculitis
Interferon-γ	Exacerbated graft-versus-host reactions

1a and 1b have been associated with injection-site reactions, lichenoid dermatitis, and erythema multiforme (35,127).

Recombinant human/mouse monoclonal anti–epidermal growth factor receptor (EGFR) causes a variety of cutaneous eruptions, as might be anticipated based on the role of EGFR in cutaneous homeostasis; 85% of these eruptions are acneiform (120). This eruption of erythematous follicular papules and plaques may occur on the face, trunk, or extremities and is associated with intense pruritis and fever (120).

Granulocyte colony-stimulating factor is used to accelerate repopulation of the granulocytic lineage of hematopoietic cells after bone marrow depletion either from chemotherapy or bone marrow transplantation. Large dermal histiocytes intercalating collagen bundles are characteristically seen as a result of this neutrophil recovery process. In addition, injection-site reaction, pyoderma gangrenosum, Sweet's-like eruption, leukocytoclastic vasculitis, and folliculitis have been attributed to hematopoietic growth factors (128).

When asked to examine a skin biopsy specimen from an eruption suspected to be caused by a cytokine, the pathologist should know the temporal relation between administration of the cytokine and appearance of the eruption, white blood cell count, and actions of the cytokine. Ideally, the cutaneous eruption will have begun soon after initiation of cytokine therapy, and the histopathology of the eruption will relate in some way to recognized effects of the cytokine.

Histopathology. The morbilliform eruption induced by pharmacologic doses of human recombinant GM-CSF illustrates these criteria (128). The upper dermis contains a perivascular and interstitial infiltrate of neutrophils, eosinophils, and lymphocytes (129) (Fig. 11-23). The relative proportion of cell types varies. Macrophages are increased in number and size and may contain melanin when situated in the upper dermis (130). The epidermis may display intercellular edema with exocytosis of inflammatory cells. Vasculitis is absent.

Granulocyte colony-stimulating factor is associated with the development of erythematous plaques that contain numerous neutrophils and upper dermal edema, thus resembling the skin lesions of Sweet's syndrome (128) (Fig. 11-24).

Findings at the site of etanercept injection include a superficial perivascular inflammatory infiltrate composed primarily of lymphocytes, with eosinophils admixed with small numbers of neutrophils and macrophages. Mild dermal edema and vasodilation are also noted (83,127). Interferon injection sites have shown a mild perivascular lymphocytic infiltrate and thrombosis of deep vessels without fibrinoid necrosis (131).

The acneiform eruptions associated with anti-EGFR show florid suppurative superficial folliculitis (120).

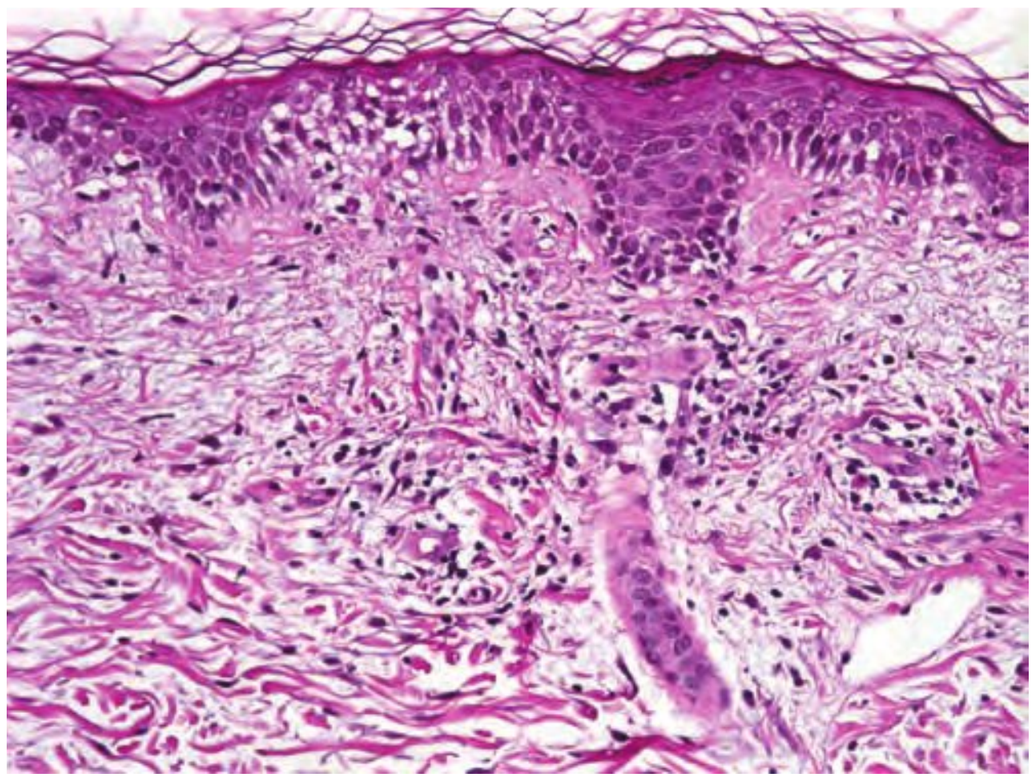


FIGURE 11-23. Granulocyte-macrophage colony-stimulating factor. A diffuse perivascular and interstitial inflammatory cell infiltrate is present with associated vascular dilation and spongiosis.

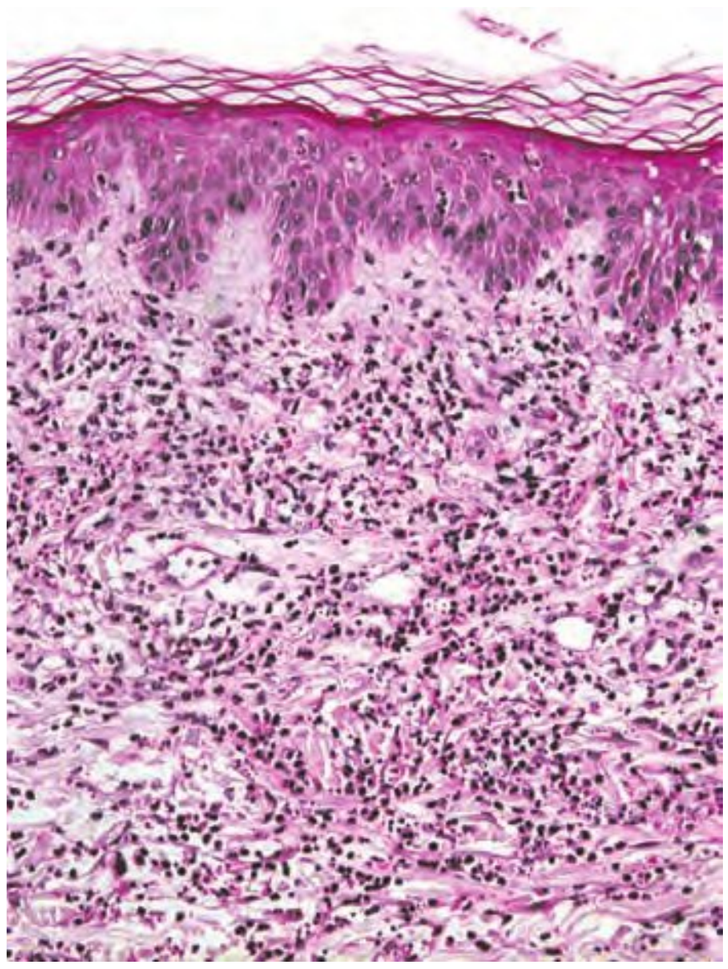


FIGURE 11-24. Granulocyte-macrophage colony-stimulating factor. The density of the inflammatory infiltrate may be florid, resembling Sweet's syndrome, as in this case.

Pathogenesis. In the case of eruptions associated with GM-CSF and G-CSF, the histologic findings relate to the administration and known actions of the cytokine. In a period of peripheral neutropenia, one finds numerous granulocytes in tissue from these eruptions. In addition, the effects of GM-CSF on macrophages are demonstrable in the skin by observing their expanded number and size. Immunostains to macrophage/monocyte markers may be useful to highlight this finding. Injection-site reactions with etanercept are suggestive of a delayed-type hypersensitivity reaction, whereas those of interferon-β suggest enhancement of preexisting disease-related platelet activation (132).

CUTANEOUS MANIFESTATIONS OF ANTIRETROVIRAL THERAPY

Antiretroviral therapy options include protease inhibitors, nonnucleoside reverse transcriptase inhibitors, and nucleoside reverse transcriptase inhibitors. Although exanthematous eruptions and urticaria have been described with the use of these agents, they have also been associated with several unique findings. The lipodystrophy syndrome, identified originally with the use of protease inhibitors and subsequently with the use of nucleoside analogs, is characterized by peripheral lipoatrophy and central adiposity. Protease inhibitors and nucleoside analogs are associated with paronychia with pyogenic granulomas of the lateral nail fold (133). Unique patterns of hyperpigmentation involving nails, skin, and mucous membranes are seen secondary to melanocyte stimulation by zidovudine (6). The patterns of nail pigmentation include entire nail pigmentation, transverse banding, and multiple longitudinal bands of any or all nails of fingers and toes. Leukocytoclastic vasculitis and DRESS are also associated with this group of agents (134).

Histopathology. Histologic features of the lipodystrophy syndrome secondary to protease inhibitors are the same as lipodystrophy from other causes (see Chapter 20).

MINOCYCLINE PIGMENTATION

The prolonged administration of minocycline, a semisynthetic tetracycline, may result in three distinct types of cutaneous pigmentation: (a) a blue-black pigmentation occurring within areas of inflammation or scarring, usually on the face, especially in active or healed acne lesions; (b) a blue-gray pigmentation of previously normal skin, most commonly seen on the legs but also occurring on the forearms; and (c) a diffuse, muddy brown discoloration, sometimes accentuated in sun-exposed areas (135). In addition to that of the skin, nail and scleral pigmentation also occur (136). A systemic minocycline-induced hypersensitivity syndrome presents 2 to 4 weeks after the start of therapy. Symptoms include fever, rash, peripheral eosinophilia, and internal organ involvement (137). Internal organ involvement includes hepatitis or abnormal liver function test results, pneumonitis, and renal abnormalities (137,138).

Histopathology. The histologic picture shows differences among the three types of pigmentation. The focal blue-black pigmentation of the face in the first type is associated with hemosiderin-laden macrophages (Fig. 11-25). In contrast, the blue-gray pigmentation in the second type, most commonly observed on the legs, shows staining for iron and also reacts with the Fontana-Masson stain. The muddy brown

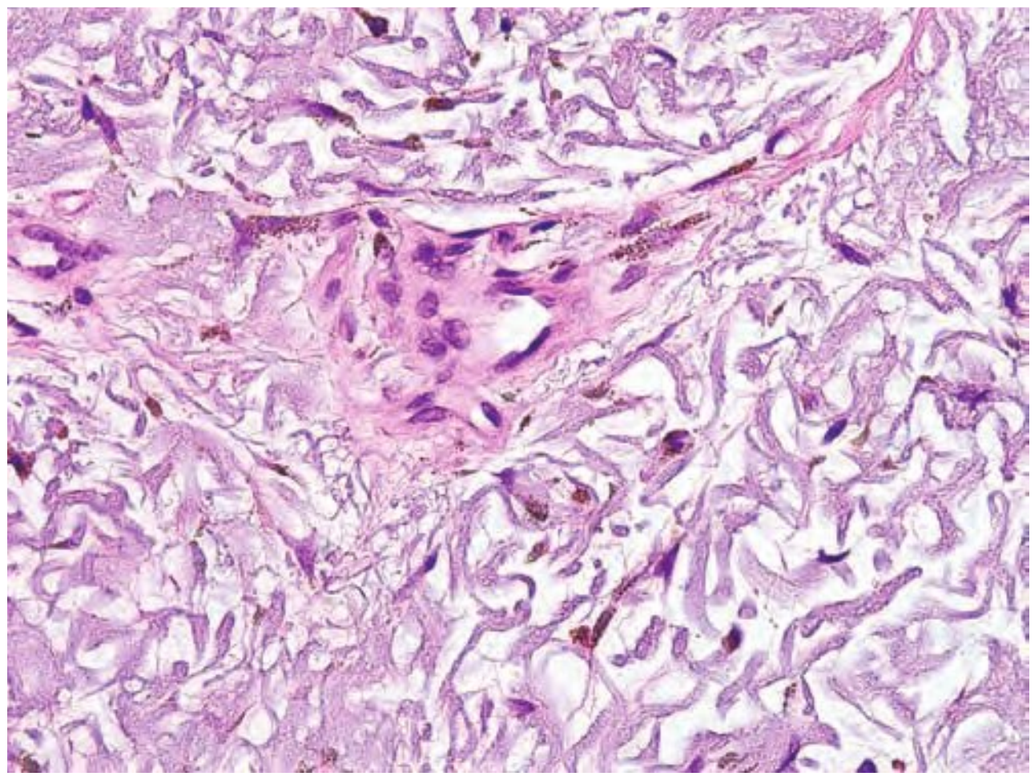


FIGURE 11-25. Minocycline hyperpigmentation. Pigment is present in dermal melanophages and dendritic cells, with a perivascular predominance.

pigmentation in the third type reveals increased melanization of the basal cell layer and melanin within macrophages in the upper dermis.

Histogenesis. It appears likely that the iron-containing pigment in the first two types of pigmentation represents a drug metabolite–protein complex (139). The pigment in the second type, which reacts with the Fontana-Masson stain, does not contain melanin because it does not bleach with hydrogen peroxide. The pigment in the third type reacts like melanin and may represent a phototoxic phenomenon. The pathogenesis of minocycline-induced hypersensitivity reaction has not been elucidated.

CLOFAZIMINE-INDUCED PIGMENTATION

Clofazimine is administered to patients with leprosy and may cause a pink to pink-brown dyspigmentation soon after initiation of therapy. The pigmentation resolves slowly after discontinuation of clofazimine. The most notably involved areas are the obvious leprosy lesions (140).

Histopathology. The upper dermis contains numerous foamy macrophages that possess cytoplasm with brown granular pigment. This pigment stains for lipofuscin but not for melanin or iron.

Pathogenesis. On electron microscopy, the macrophages are found to contain phagolysosomes with either lipid or electron-dense granules with a lamellar substructure consistent with lipofuscin or ceroid pigment (140). The mechanism by which clofazimine causes these changes is unclear.

PENICILLAMINE-INDUCED DERMATOSES

The prolonged administration of penicillamine can cause alterations in collagen and elastic tissue that may result in areas of atrophy of the skin. Anetoderma and serpiginosa elastosis perforans are observed. Alteration of epidermal desmosomal elements may induce pemphigus (see earlier discussion).

Penicillamine-Induced Atrophy of the Skin

Patients on prolonged penicillamine therapy may show atrophy of the skin of the face and neck; light blue, atrophic macules resembling anetoderma; easy bruising resulting in small hemorrhages into the skin followed by milia; or small, white papules at sites of venipuncture in the antecubital fossae (141).

Histopathology. The anetoderma shows diminution or absence of elastic tissue. The areas of easy bruising of the skin and the papules at sites of venipuncture show either diminution or degeneration and homogenization of collagen (142).

Histogenesis. The formation of elastic tissue and collagen involves the participation of aldehydes to produce stable cross-links. By reacting with aldehydes to form thiazolidine compounds, penicillamine impairs the formation of such stable cross-links (143).

Penicillamine-Induced Elastosis Perforans Serpiginosa

Elastosis perforans serpiginosa may occur in patients receiving prolonged treatment with penicillamine. Although the clinical picture does not differ from that of idiopathic elastosis perforans serpiginosa (see Chapter 15), the histologic and electron microscopic features of the altered elastic fibers are unique. Both penicillamine-induced atrophy of the skin and penicillamine-induced elastosis perforans serpiginosa may occur in the same patient.

Histopathology. In comparison with the idiopathic type of elastosis perforans serpiginosa, the penicillamine-induced type, on staining for elastic tissue, shows less hyperplasia of elastic fibers in the papillary dermis, except in areas of active transepidermal elimination (Fig. 11-26). However, in the middle and deep layers of the dermis, a greater number of hyperplastic elastic fibers are present than in idiopathic elastosis perforans serpiginosa. These fibers have an appearance that is specific for penicillamine-induced elastosis perforans serpiginosa. Lateral budding is noted, with the buds arranged perpendicular to the principal fibers. The coarse elastic fibers thus show a serrated, sawtooth-like border and have been aptly compared to the twigs of a bramble bush and have been referred to as "lumpy-bumpy" (141) (Fig. 11-27). Similar changes in individual elastic fibers are observed in nonlesional skin and have been seen in a skeletal artery (142).

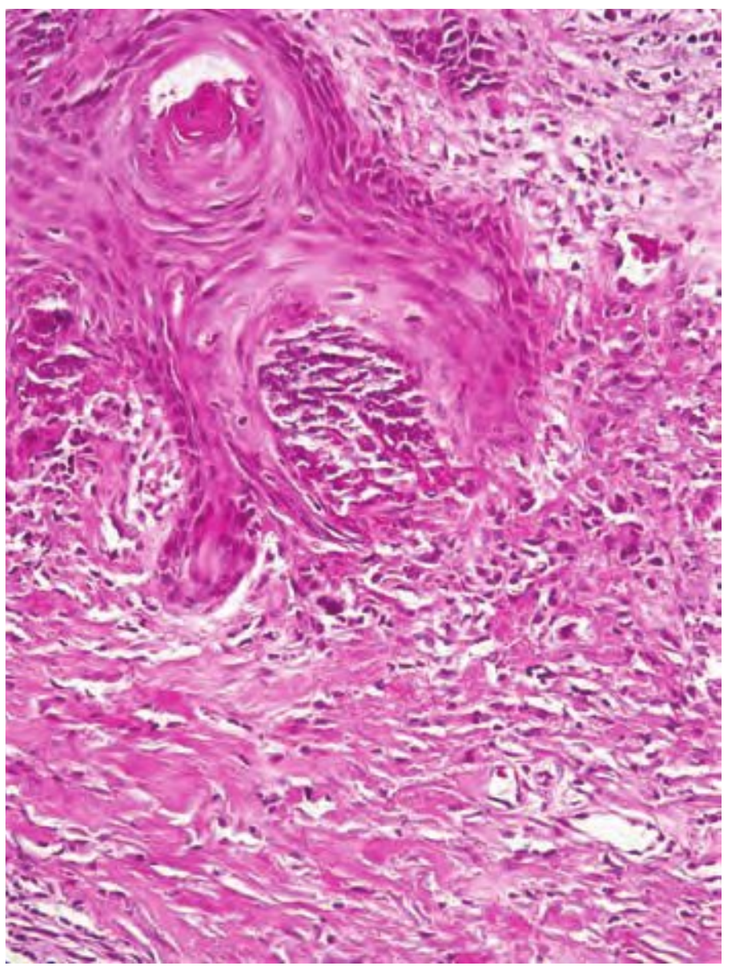


FIGURE 11-26. Penicillamine-induced elastosis perforans serpiginosa. This image shows thickened elastic fibers in the process of transepidermal elimination. The papillary dermal elastic fibers otherwise appear normal on routine stained sections.

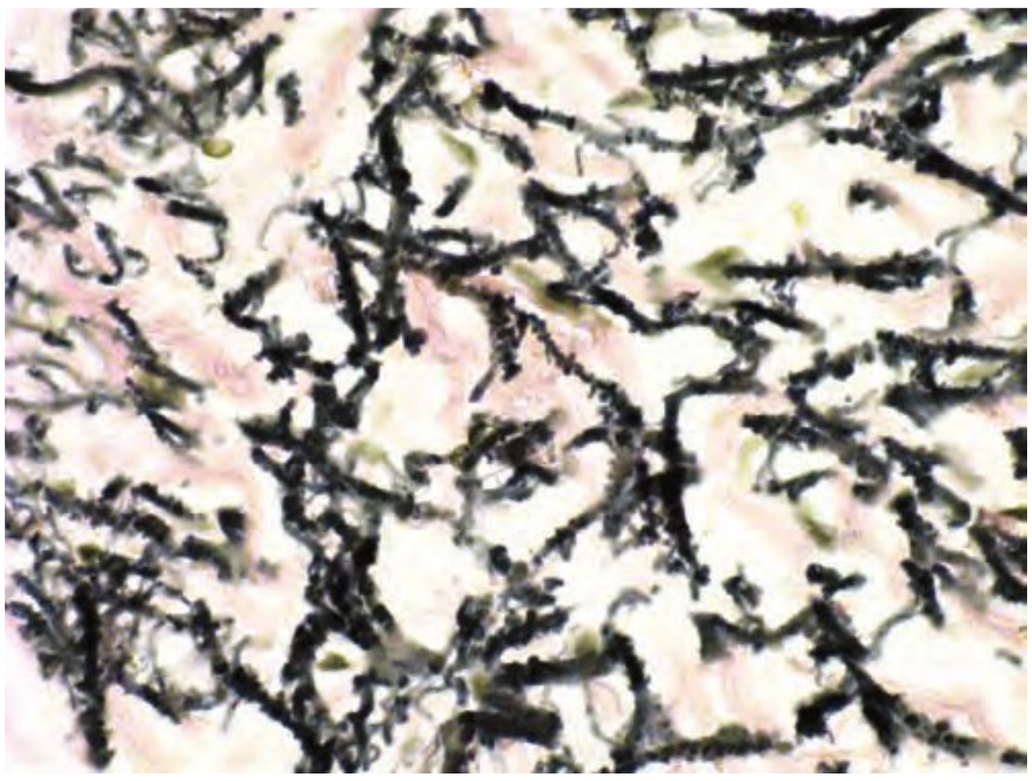


FIGURE 11-27. Elastosis perforans serpiginosa. The classic fibers in the mid dermis show lateral budding characteristic of penicillamine effect. Verhoeff-von Gieson elastic stain.

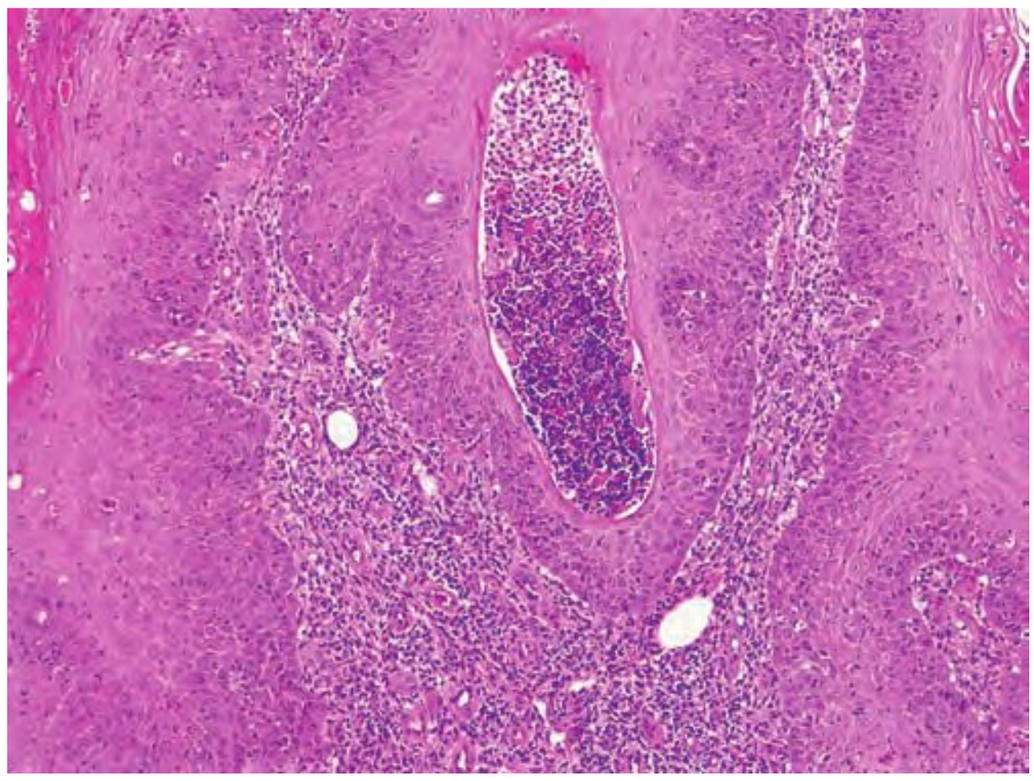


FIGURE 11-28. Bromoderma. There is downward proliferation of the epidermis with a large intraepidermal abscess. A dense inflammatory infiltrate is present in the dermis.

Pathogenesis. On electron microscopic examination, the affected elastic fibers show an inner core that closely resembles a normal elastic fiber with dark microfibrils embedded in electron-lucent elastin. Peripheral to this, a wide, homogeneous, electron-lucent coat is seen that has the appearance of elastin and shows numerous saclike protuberances bulging outward between the adjacent collagen fibers (144).

HALOGEN ERUPTIONS

Ingestion of bromides may cause, besides a pustular eruption, the formation of vegetating, papillomatous plaques called *bromoderma.* The plaques, which usually occur on the lower extremities, often show pustules at their peripheries. Although bromoderma often appears only after prolonged intake of bromides, it may arise soon after administration as well.

Iododerma, usually seen on the face, begins as a rule with multiple pustules that rapidly coalesce into vegetating plaques. Like bromoderma, the plaques of iododerma often show pustules at their peripheries, but they usually show less papillomatous proliferation and a softer consistency than bromoderma, and they often ulcerate. Iododerma is frequently associated with severe systemic signs and symptoms and may be fatal in rare instances (145). Although the eruption usually arises after prolonged ingestion of iodides, it may start within a few days, especially in patients with chronic renal disease. *Fluoroderma* has been described after the frequent application of a fluoride gel to the teeth for the purpose of preventing caries during ionizing radiation to the face (146). The lesions consist of scattered papules and nodules on the neck and in the preauricular regions.

Histopathology. The histologic picture in the halogen eruptions is suggestive rather than diagnostic. The difference between bromoderma and iododerma lies largely in the epidermal changes, which usually are much more pronounced in bromoderma, although there is some overlap. The dermal changes are essentially the same and vary with the age of the lesion.

In early lesions, the dermis in both bromoderma and iododerma shows a dense infiltrate of neutrophils, which, in areas of dermal necrosis, show nuclear dust. There may be intradermal abscesses. Eosinophils are present in most cases and may be numerous. Extensive extravasation of erythrocytes may also be seen. At a later stage, the proportion of mononuclear cells increases, and histiocytes may show abundant cytoplasm or large nuclei. The blood vessels are increased in number and dilated and may show proliferation of endothelium.

The epidermal changes in bromoderma are often pronounced. In addition to papillomatosis, one may observe considerable downward epidermal proliferation, occasionally to such a degree as to produce the picture of pseudocarcinomatous hyperplasia. The acanthosis may center around upper-level follicular epithelium. Frequently, intraepidermal abscesses are present (Fig. 11-28). The intraepidermal abscesses are filled with neutrophils, eosinophils, and some desquamated keratinocytes, most of which appear necrotic, although some resemble acantholytic cells. Some epithelial islands in the upper dermis, instead of enclosing an abscess, are filled with keratin.

In iododerma, the epidermis may be eroded or ulcerated. At the margin of the ulcers, one may find intraepidermal abscesses. In old lesions, pseudoepitheliomatous hyperplasia may be encountered, although usually less than in bromoderma. Fluoroderma has been described only as a mild eruption, but it shares with iododerma and bromoderma the presence of eosinophils, neutrophils, and erythrocytes in the dermis and of microabscesses in the epidermis (146).

Pathogenesis. Even though there is often a very long interval between the first ingestion of iodides or bromides and the appearance of the cutaneous lesion, halogen eruptions appear to be an allergic phenomenon; once a person has become sensitized, the eruption recurs within a few days on the readministration of iodides or bromides. Halogen eruptions probably arise on the basis of delayed hypersensitivity.

ARGYRIA

Argyria is caused by prolonged ingestion or mucosal application of silver salts. When ingested, there is a slate-blue discoloration on the skin, especially in the sun-exposed areas. The oral mucosa, conjunctivae, fingernail beds (but not toenail) (147), intestines, liver, spleen, and peritoneum may also be involved (148,149). Argyria (and chrysiasis) has been reported after acupuncture and in a silversmith following multiple cutaneous punctures by a silver filament (150,151).

Histopathology. In the dermis, there are extracellular fine, small, round, uniformly sized brown-black silver granules, both singly and clustered. The deposition is predominantly extracellular and found in both sun-exposed and unexposed skin. They are present in the greatest numbers in the basement membrane zone surrounding the sweat glands (Fig. 11-29) and in the connective tissue sheaths around the hair follicles and sebaceous glands, in the walls of capillaries, in the arrectores pilorum, and in the nerves (149). Silver granules are also found in the dermal papillae and scattered diffusely throughout the dermis. Elastic tissue stains reveal a predilection of the granules for elastic fibers, which explains the presence of finger-like chains of granules projecting into the dermal papillae (149). In contrast, silver is not seen in the epidermis or its appendages. Although visible in routine stains, dark-field microscopy reveals brilliantly refractile, white particles against a dark background.

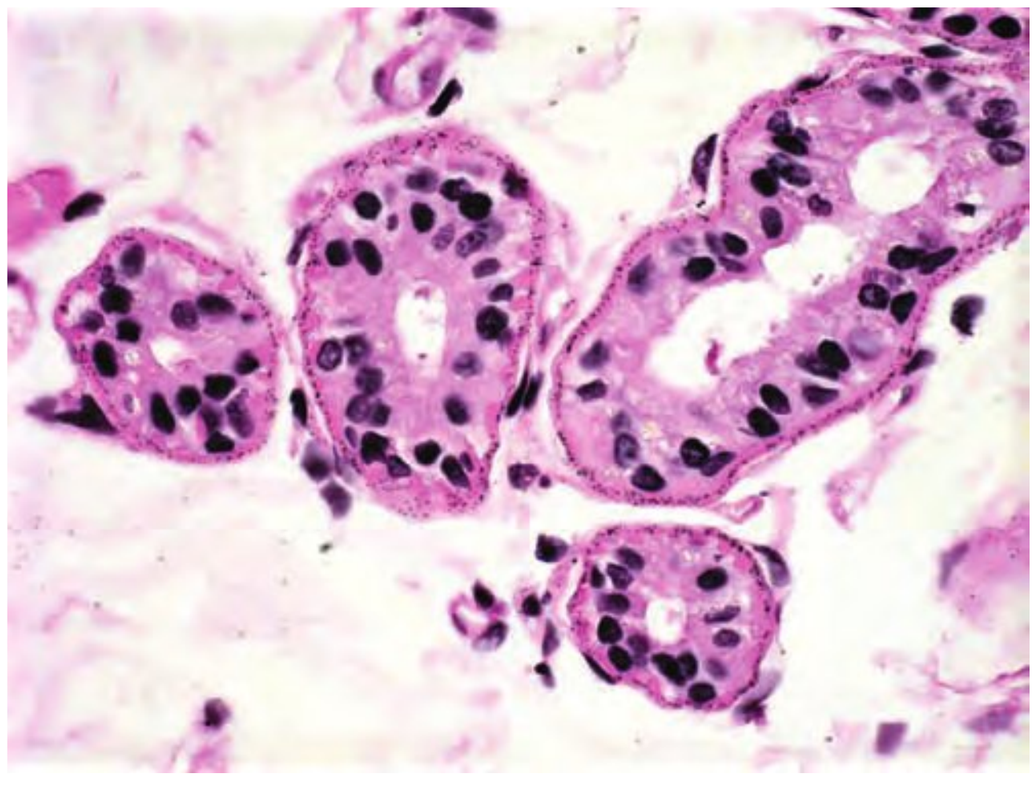


FIGURE 11-29. Argyria. Silver granules are present in the basement membrane surrounding the sweat glands.

In addition to silver, there is an increase in the amount of epidermal melanin, particularly in sun-exposed skin. Melanophages may also be scattered throughout the upper dermis. Deposits of silver are also found in internal organs. Incubation of sections in a solution consisting of 1% potassium ferricyanide in 20% sodium thiosulfate results in decolorization of silver.

Pathogenesis. Electron microscopy reveals extracellular aggregates of irregularly shaped granules varying in size from 200 to 400 nm in diameter but ranging up to 1,000 nm (152).

The increase in the amount of melanin in the basal cell layer and occasionally also in the upper dermis suggests that the presence of silver in the skin may stimulate melanocyte activity. Increased epidermal melanin is observed also with deposits of other heavy metals, such as iron in hemochromatosis (see Chapter 17) and mercury in mercury pigmentation (see later discussion). The pronounced slate-blue pigmentation in exposed skin is caused by increases in both melanin and silver (153).

CHRYSIASIS

Chrysiasis is slate blue discoloration on sun-exposed skin caused by the prolonged parenteral administration of gold salts, generally for the treatment of rheumatoid arthritis and recently secondary to Q-switched ruby laser treatment (154,155).

Histopathology. Gold granules are found predominantly within cells, particularly within endothelial cells and macrophages (156). However, extracellular granules may also be observed. They are larger and more irregularly shaped than silver granules. Although they are also light refractile with dark-field examination, the granules are orange-red birefringent on fluorescence microscopy (157).

Histogenesis. Electron microscopic examination shows the presence of electron-dense, angulated particles within phagolysosomes of endothelial cells and macrophages. X-ray spectroscopic analysis demonstrates a spectrum consistent with the presence of gold (157).

MERCURY PIGMENTATION

Regular application of a mercury-containing cream to the face and neck over many years may produce a slate-gray pigmentation of the skin in the areas to which the cream has been applied. Generally, the pigmentation is most pronounced on the eyelids, in the nasolabial folds, and in the folds of the neck (158). Most mercury-containing creams are no longer manufactured. Traumatic implantation of mercury may also occur.

Histopathology. Irregular, brown-black granules are found in the upper dermis, both extracellularly and within macrophages. In rare instances, granules are seen also in the basal cell layer of

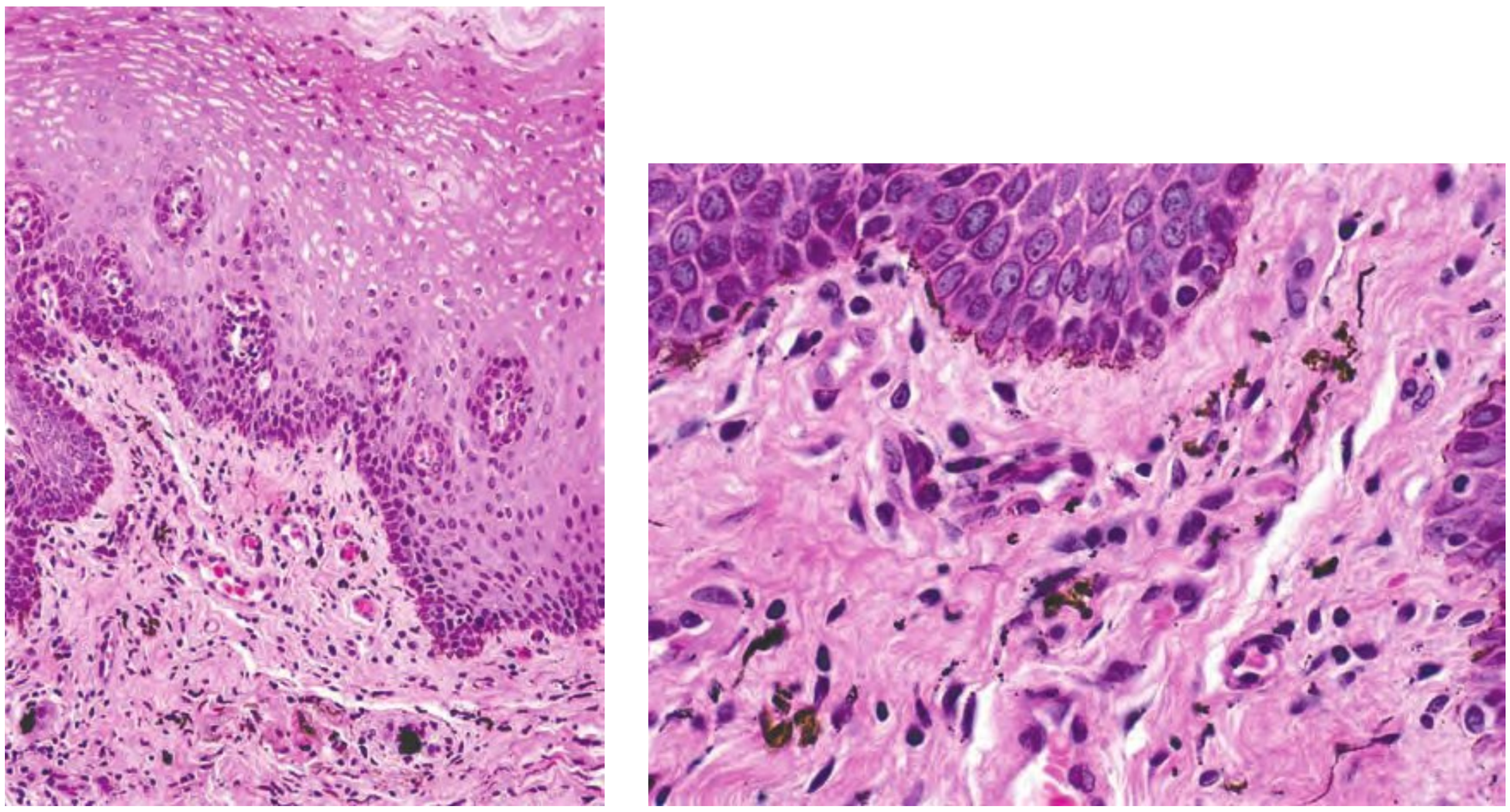


FIGURE 11-30. Mercury deposition. Large, black-brown mercury deposits along with multinucleate foreign body giant cells are seen in the papillary dermis (A) and along the basement membrane (B) in this case of traumatic mercury implantation in the buccal mucosa.

the epidermis. As in argyria and chrysiasis, dark-field microscopy reveals brilliantly refractile granules. Silver staining reveals normal or increased basalar melanin (159). Traumatic implantation of mercury results in variably sized, often large amorphous deposits of mercury in the dermis and subcutis. Chronic changes include dermal fibrosis and granulomatous inflammation (Fig. 11-30).

Pathogenesis. Electron microscopic examination shows the mercury particles, which are approximately 14 nm in diameter, to be aggregated into irregular granules with diameters of up to 340 nm. The granules are associated with elastic fibers as well as along the collagen fibers. In macrophages, they are present within lysosomes or free in the cytoplasm. When seen in the epidermis, the mercury granules lie in the intercellular spaces of the basal cell layer (159).

Because the pigmentation is most pronounced in skin folds that are protected from the sun and there may be no increase in the amount of melanin, it can be concluded that most of the pigmentation is caused by the mercury rather than the melanin.

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CHAPTER 12

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John L.M. Hawk

The Photosensitivity Disorders

Cutaneous disorders caused by exposure to ultraviolet radiation (UVR), the so-called photodermatoses, comprise drug and chemical photosensitivity, the DNA repair-deficient disorders, the UVR-exacerbated dermatoses, and the largest and most common group, the idiopathic, probably immunologically based photodermatoses (1). This last group is in turn made up of polymorphic (polymorphous) light eruption (PMLE), actinic prurigo (AP), hydroa vacciniforme (HV), chronic actinic dermatitis (CAD; formerly also sometimes known as *photosensitivity dermatitis and actinic reticuloid syndrome*, or *persistent light reaction*), and solar urticaria (SU) (1–3). Recent work has strongly suggested that these conditions are indeed immunologically mediated, the first four probably being delayed-type hypersensitivity (DTH) reactions against UVR-altered endogenous skin autoantigen, with the differing clinical features between the disorders conceivably being determined by differing cutaneous sites or levels of antigen formation, whereas the last is probably an immediate-type hypersensitivity response against similarly produced cutaneous or circulating substances. Final confirmation of this hypothesis for the putative DTH reactions now requires definitive identification of antigens for the conditions.

Drug and chemical photosensitivity, the DNA repair-deficient disorders, and the UVR-exacerbated dermatoses are considered elsewhere in this book, but the idiopathic, probably immunologically based photodermatoses are discussed in this chapter.

POLYMORPHIC (POLYMORPHOUS) LIGHT ERUPTION

PMLE is a commonly occurring, transient, intermittent, approximately symmetrical UVR-induced eruption of nonscarring, erythematous, itchy papules, plaques, or vesicles of usually only some exposed skin (Fig. 12-1) that is most severe during spring, summer, and sunny vacations and most common in young women (2,3). It is seen most frequently at temperate latitudes, affecting up to one in five subjects of any skin coloring, with attacks following around 15 minutes to a few hours of sun exposure, or occasionally a few days after a period with little exposure such as on vacation, and lasting for hours, days, or rarely weeks before often recurring, sometimes with gradual reduction in severity, from spring until fall. Some but usually not all exposed skin is affected, usually symmetrically, with normally uncovered sites most frequently being spared. Diagnosis is made from the history and clinical findings in the presence of normal circulating antinuclear factor and extractable nuclear antibody titers and of normal urinary, stool, and blood porphyrin concentrations. However, if there is diagnostic uncertainty, lesional histology is generally very helpful, while broad-spectrum or monochromatic skin irradiation may respectively induce the typical eruption or abnormal erythemal or papular responses. Treatment, either prophylactic or remedial, is for the most part effective. Often, the restriction of UVR exposure, use of appropriate clothing, and regular application of high-protection, broad-spectrum sunscreens during exposure are satisfactory for mild disease. In more severe instances, prior to the beginning of summer, four to six weekly courses of broadband or, more commonly, low-dose narrowband (311–312 nm) ultraviolet B (UVB) phototherapy, or slightly more reliably, low-dose psoralen photochemotherapy (PUVA), are usually effective. If an eruption should develop despite these measures, a short course of systemic steroid therapy usually abolishes it quickly. Azathioprine and cyclosporine have rarely been used effectively for very severe disease. The value of other previously advocated medications, such as antimalarials and beta-carotene, has not been confirmed in controlled trials.

Histopathology

The histologic findings vary according to the age of the lesion sampled. Very early lesions show either a normal epidermis or mild spongiosis with focal lymphocyte exocytosis and an underlying mild or occasionally moderate, superficial and deep, perivascular and periadnexal, lymphohistiocytic inflammatory cell infiltrate (2–5) (Fig. 12-2); the lymphocytes have a T-helper phenotype (CD3/CD4 positive). Interestingly, in experimentally induced PMLE lesions, the infiltrate in the first 72 hours postinduction also has a predominant T-helper phenotype but thereafter a mainly T-cytotoxic type (CD3/CD8 positive) (6). Occasional eosinophils and rare neutrophils may also be found. As lesions progress, there is marked edema of the papillary dermis and more prominent dermal inflammation (Fig. 12-3), along with focal interface change and mild hydropic basal cell degeneration in some biopsies (Fig. 12-4);



FIGURE 12-1. Polymorphic (polymorphous) light eruption. Erythematous confluent papules on sun-exposed skin.

in such cases, the histologic picture may resemble cutaneous lupus erythematosus (see next section). Exceptionally, a fairly prominent dermal infiltrate may raise the possibility of lymphoma. In a few cases, the histologic findings may be minimal despite the presence of prominent clinical changes (7).

Pathogenesis. The eruption of PMLE is induced by exposure to UVR, particularly from strong summer sunlight (2,3). Artificial

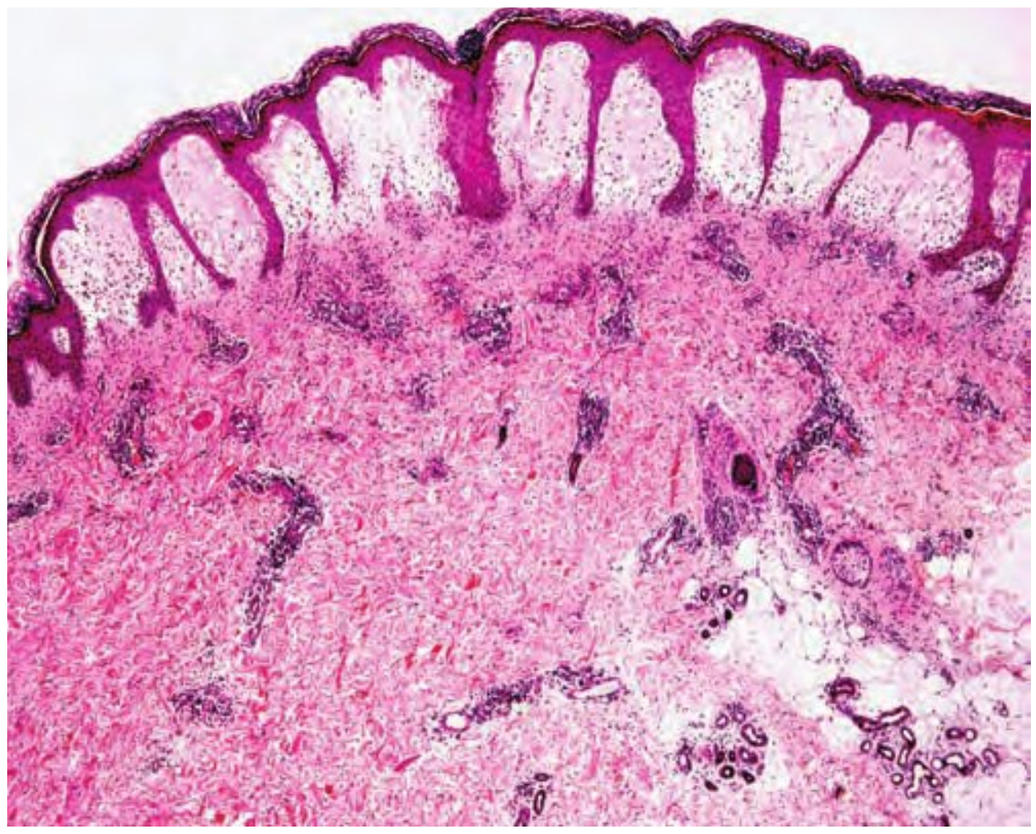


FIGURE 12-3. Polymorphic (polymorphous) light eruption. Established lesion showing prominent papillary dermal edema as well as moderately prominent, superficial and deep, perivascular and periadnexal, mononuclear inflammatory cell infiltrate.

reproduction is less easy, and exact action spectra have not been conclusively determined. Nevertheless, broadly speaking, the responsible wavelengths appear to be UVB in around half of patients and ultraviolet A (UVA) in three quarters, which includes both in one quarter, while visible light has also rarely been incriminated. The eruption itself appears very likely to be a DTH response in view of its pattern of dermal cellular infiltration, cytokine production, and adhesion molecule expression, arguably to UVR-induced, endogenous, cutaneous autoantigen. Further, it appears that a genetically determined impairment of the normal UVR-induced suppression of

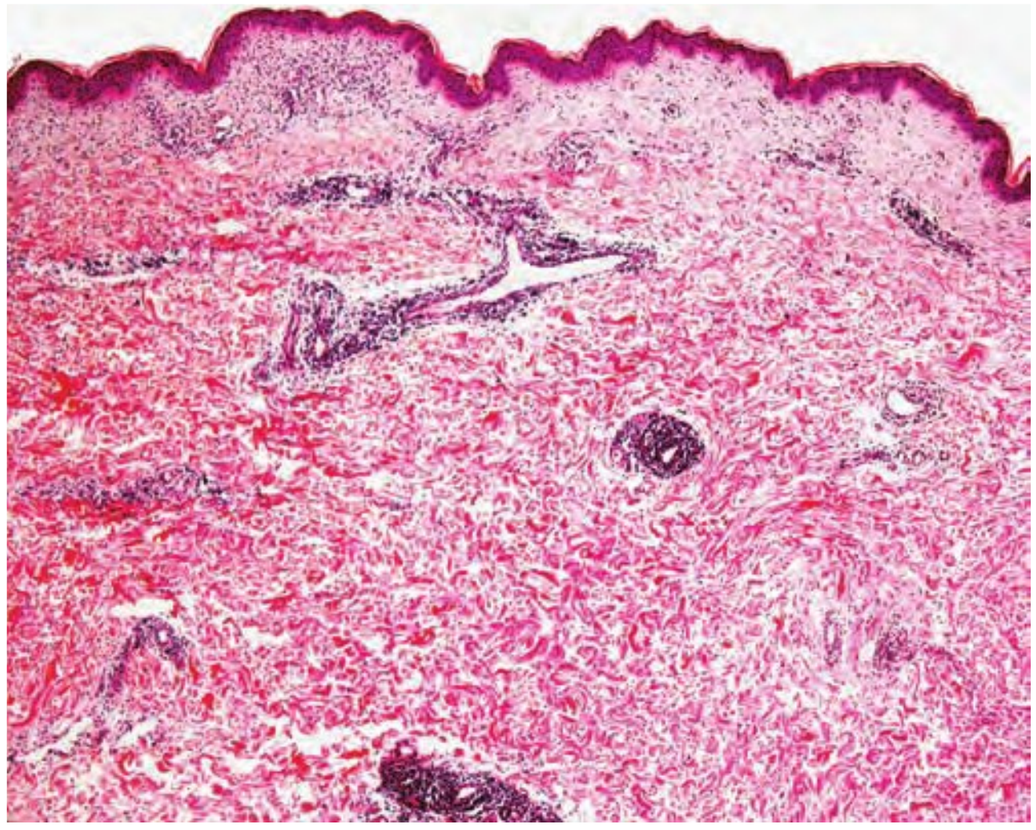


FIGURE 12-2. Polymorphic (polymorphous) light eruption. Early lesion showing superficial and deep, perivascular and periappendageal, inflammatory infiltrate.

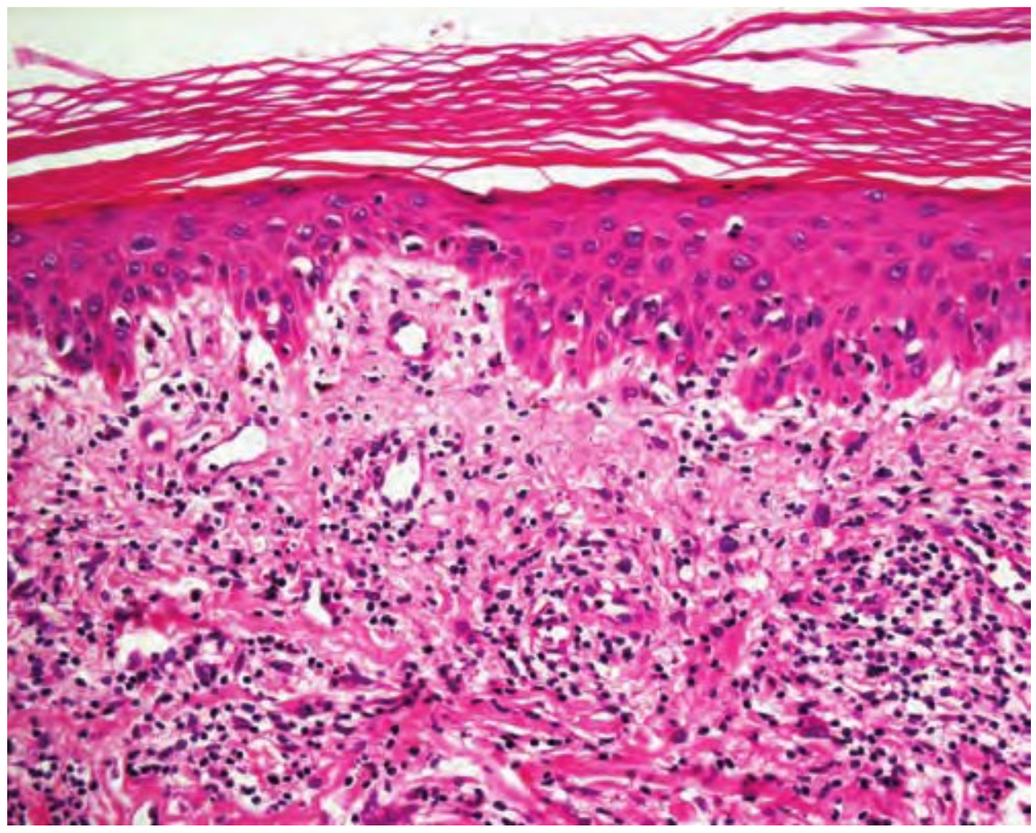


FIGURE 12-4. Polymorphic (polymorphous) light eruption. Mild spongiosis and focal interface change with hydropic degeneration of basal cells; the latter may suggest lupus.

induction, but interestingly not elicitation, of DTH reactions in the skin is responsible (8).

Differential Diagnosis. The diagnosis is generally apparent from the clinical history, in which sun exposure is nearly always clearly incriminated in causing the typical eruption, provided that the circulating antinuclear and extractable nuclear antibody titers and urinary, stool, and blood porphyrin concentrations are normal. Histologically, PMLE must be differentiated from lupus erythematosus, the porphyrias, AP, Jessner's lymphocytic infiltrate, cutaneous T-cell lymphoma, chilblains, and rosacea (2,3). In cutaneous lupus erythematosus, the interface change is more prominent not only in the epidermis but also in adnexal structures, apoptotic keratinocytes are often seen, and papillary dermal edema is not a feature. In addition, dermal mucin deposition may be seen in lupus and is absent in PMLE. AP usually displays changes secondary to excoriation, variable epidermal hyperplasia, and more prominent lymphocyte spongiosis and exocytosis; however, early lesions in both conditions may show very similar microscopic findings, except that dermal edema is usually absent in AP. In Jessner's lymphocytic infiltrate, epidermal changes are absent, there is no papillary dermal edema, and the dermal mononuclear cell infiltrate tends to be more prominent. Cutaneous T-cell lymphoma is only rarely included in the differential diagnosis of PMLE, mainly when the dermal infiltrate is prominent; however, the exocytosis of lymphocytes with irregular nuclear outlines is not a feature of the latter, which usually also shows variable spongiosis. The histology of chilblains is almost identical to that of PMLE, particularly when there is prominent papillary dermal edema, but fortunately the clinical setting of each disease usually allows distinction. Rosacea shows no epidermal change, dermal edema is absent, the dermal infiltrate is mild and surrounds superficial small blood vessels and adnexal structures, and focal lymphocytic exocytosis into hair follicles is often seen.

ACTINIC PRURIGO

AP is an itchy, papular or nodular, excoriated, chronic eruption, usually much worse in summer, of the light-exposed and, to a lesser extent, covered skin of children, usually girls, occurring relatively rarely worldwide, although it is comparatively common among native and mixed-race Americans (2,3). It may often but not always resolve by early adulthood and most often affects the face and distal limbs, while the proximal limbs and forehead beneath the hair fringe, which are less often exposed, are mostly spared. However, the buttocks are sometimes involved through apparent sympathetic immunologic spread. Superficial, pitted, or linear scars may affect the face at sites of previous lesions, whereas chronic cheilitis and conjunctivitis are also possible. In addition, some patients describe acute attacks of rash development following specific sunlight exposure as occurs in PMLE. Therapy is often helpful, consisting in mild cases of restricted sun exposure, the use of protective clothing, the application of high-protection, broad-spectrum sunscreens, and the use of emollients and topical steroids on affected sites, whereas in some cases, prophylactic, low-dose narrowband UVB phototherapy or PUVA, as for PMLE, may be useful, particularly in spring for patients who have cleared of their eruption in winter. Topical calcineurin inhibitors may also perhaps help in such patients, even if not confirmed by formal studies, whereas oral thalidomide clears around three quarters of affected subjects, although a marked risk of teratogenicity and moderate possibility of peripheral neuropathy necessitate great care in its use. Oral immunosuppressive therapy such as with azathioprine or cyclosporine also seems likely to help, if clinically appropriate.

Histopathology. The histology varies according to the clinical evolution (9). Thus, early intact lesions show variable, often mild, epidermal spongiosis and a superficial and deep dermal, perivascular, mononuclear cell infiltration similar to that of PMLE but in the absence of substantial papillary dermal edema (Fig. 12-5). However, this latter finding may be seen in occasional biopsies, and histologic distinction from PMLE may then be impossible, requiring close clinicopathologic correlation (10). Occasional eosinophils are often seen. The lesions of AP are frequently excoriated, such that careful attention should be paid when biopsy is performed to avoid lesions with such prominent secondary changes (Fig. 12-6). Evolving lesions may also occasionally display focal interface change with hydropic degeneration of basal cells, such that distinction from cutaneous lupus may then be difficult (Fig. 12-7). In rare cases, there may be a heavy, superficial and deep dermal, mononuclear cell infiltrate with difficulty in distinction from lymphoma, especially if associated interface changes are present. In older lesions, there is usually variable lichenification (Fig. 12-8),

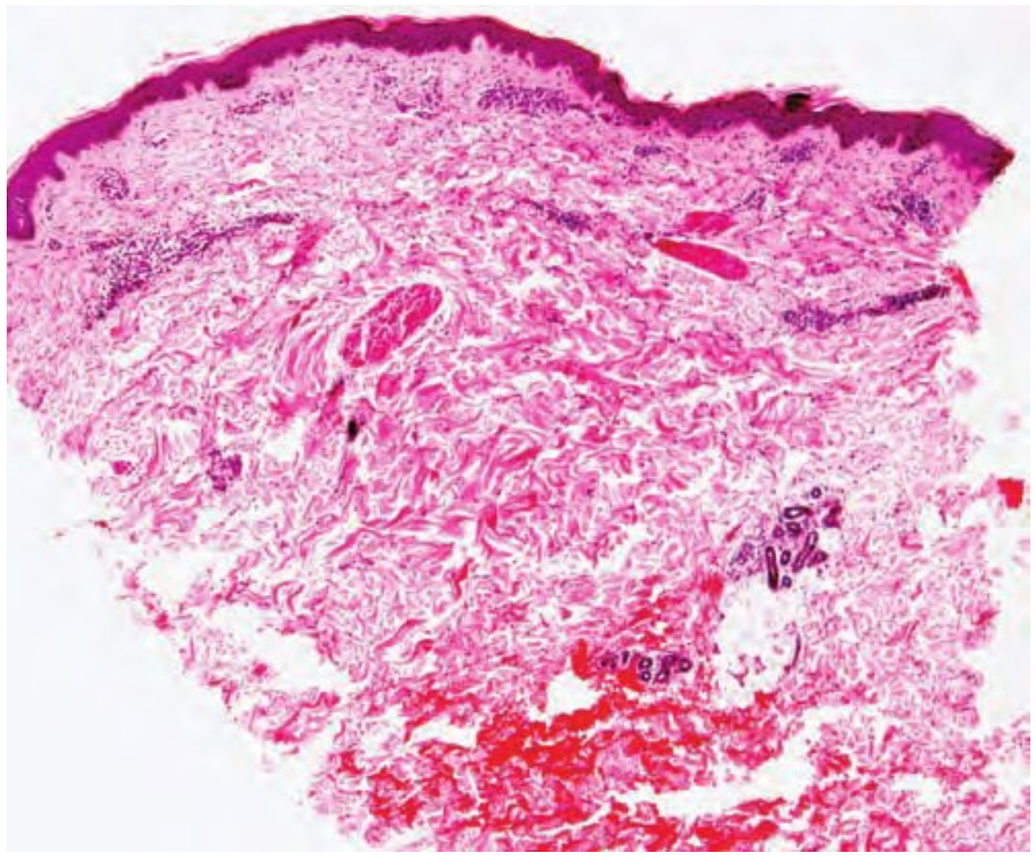


FIGURE 12-5. Actinic prurigo. Early lesion with absence of epidermal change, and mild to moderate, superficial and deep, perivascular and periadnexal, mononuclear inflammatory cell infiltrate.

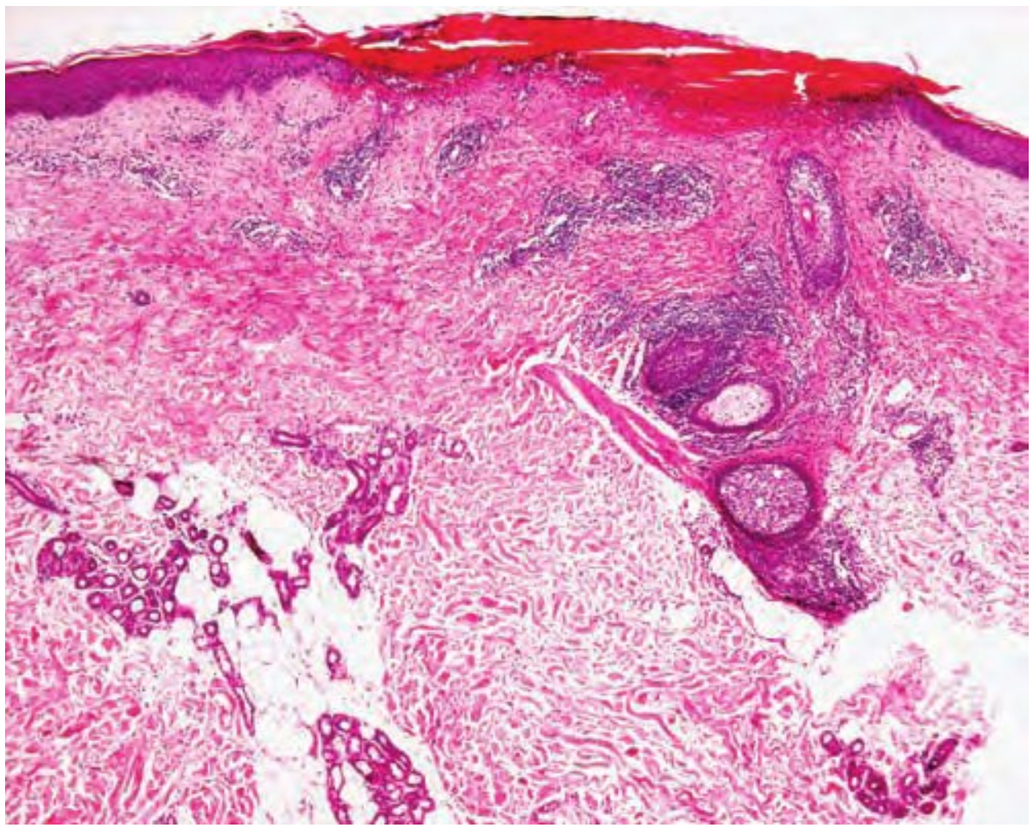


FIGURE 12-6. Actinic prurigo. Prominent superficial necrosis secondary to excoriation and fairly heavy perivascular and periadnexal inflammatory cell infiltrate.

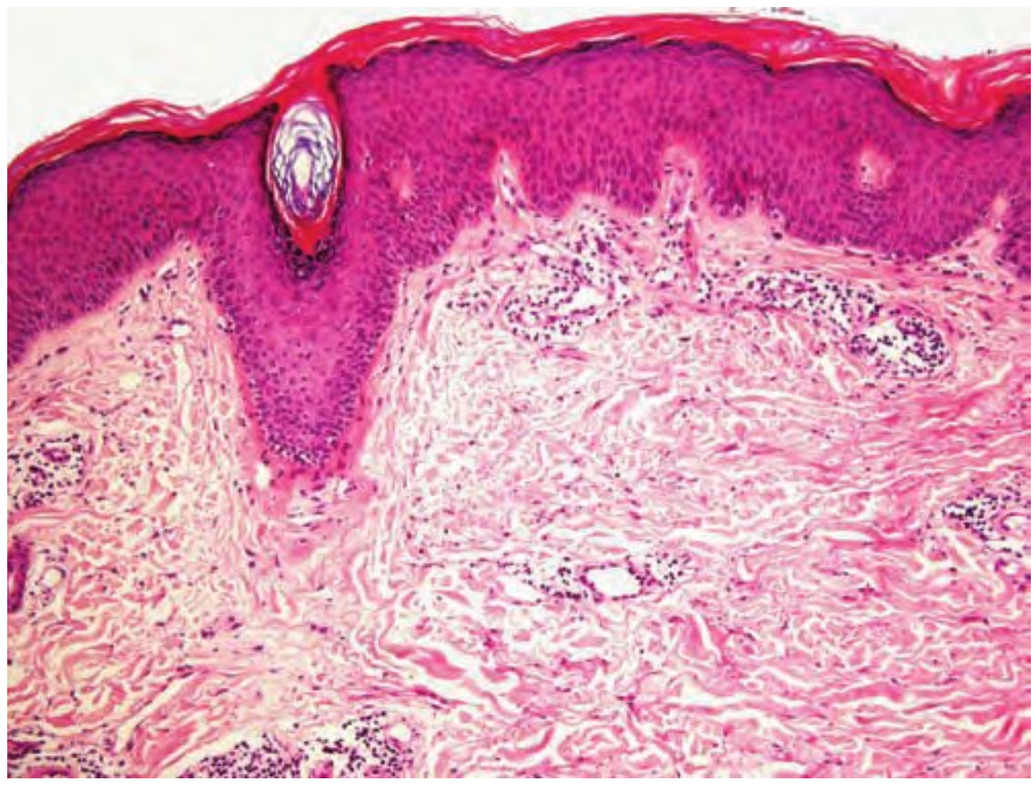


FIGURE 12-8. Actinic prurigo. Older lesion showing lichenification.

focal papillary dermal fibrosis, a moderately heavy mononuclear cell infiltrate, and irregular epithelial hyperplasia similar to the features of chronic eczema, or even prurigo nodularis (2,3). The AP inflammatory cell infiltrate has a T-helper phenotype (CD3/CD4 positive). AP must thus be differentiated from the same disorders as PMLE in its rarer acute form and from other causes of chronic eczema or prurigo in its chronic forms. Finally, although AP histology may often be fairly nonspecific, the lesions of AP cheilitis characteristically show a dense lymphocytic infiltrate with frequent well-formed lymphoid follicles (10,11), a finding regarded as potentially very helpful in cases of diagnostic doubt.

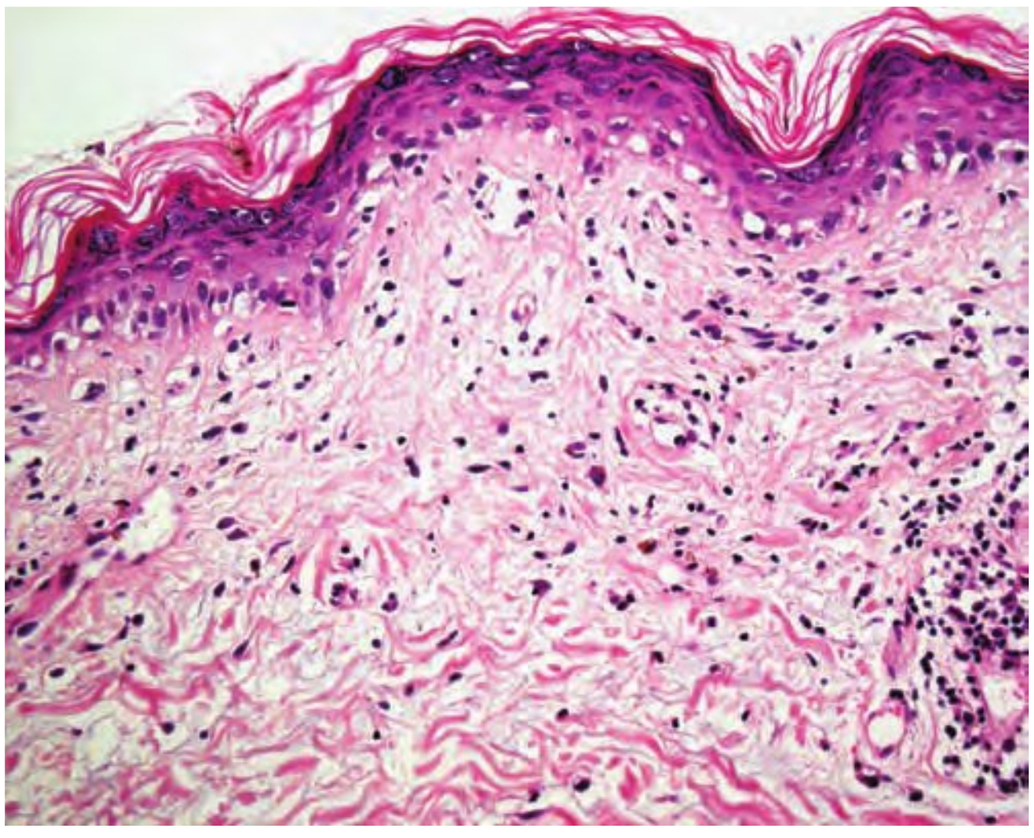


FIGURE 12-7. Actinic prurigo. Interface change may be more prominent than in PLME and histologic distinction from lupus more difficult.

Pathogenesis. UVR exposure appears to be of prime importance in the causation of AP, given the greater severity of the disorder in summer and after sun exposure as well as the relatively frequent abnormal erythemal or papular skin responses to monochromatic irradiation (2,3). Such reactions occur in one half to two thirds of patients, often to UVB wavelengths alone but sometimes also to UVA; responses to broad-spectrum irradiation have not been reported. Further, the clinical behavior of acute attacks of AP, its histologic appearances, its marked familial association with PMLE, and its differentiation from PMLE in large part by the HLA subtypes DRB1*04 (DR4) and more specifically DRB1*0407 (2,3,12), all strongly suggest that it is very likely a genetically prolonged form of PMLE and also a DTH reaction against UVR-induced, cutaneous autoantigen. However, without the isolation so far of proven causative antigen, this is still ultimately speculative.

Differential Diagnosis. AP must be differentiated from PMLE, lupus erythematosus, insect bites, scabies, lymphoma, nodular prurigo, and eczema; its seasonal variation, affected sites, and sometimes positive light tests may assist in this differentiation, as too may its histology, particularly if a lesion is fresh. However, close clinicopathologic correlation is essential for reliable diagnosis. In biopsies with interface change, distinction from lupus erythematosus may be difficult, but in AP, such change is usually very patchy, focal, and limited to the epidermis, while apoptotic keratinocytes are usually absent. If a prominent dermal infiltrate is seen, the diagnosis of T-cell lymphoma may well come into consideration, but cytologic atypia and epidermotropism are lacking in AP. Finally, in its usual chronic forms, the distinction of AP from chronic eczema is impossible on histologic grounds alone.



FIGURE 12-9. Hydroa vacciniforme. Scarring is seen in late stages.

HYDROA VACCINIFORME

HV is a very rare, intermittent, UVR-induced, blistering, scarring eruption of only some exposed skin, usually in children and only rarely in adults (1–3,13–15). The condition generally has onset by 10 years of age, with resolution by early adulthood. Usually sparse, occasionally coalescent, symmetrically scattered, sometimes hemorrhagic vesicles and bullae occurring within hairs of sun exposure are characteristic, particularly of the face, ears, and limbs. These umbilicate and crust over days, healing thereafter in weeks to leave persistent, disfiguring pock scars (Fig. 12-9). Treatment is usually difficult. The restriction of UVR exposure and use of clothing cover are helpful, whereas the careful, regular application of high-protection, specifically broad-spectrum, sunscreens also has efficacy. In resistant cases, courses of prophylactic low-dose UVB phototherapy or PUVA are also helpful on occasion. All other therapies have seemed at best marginally useful.

Histology. The main, very characteristic, histologic abnormality is that of progressive intra- and intercellular epidermal edema leading to prominent reticular degeneration, vesiculation, and finally confluent epidermal necrosis (Figs. 12-10 and 12-11). The vesicles contain fibrin and acute inflammatory cells and overlie a dermal cellular infiltrate of predominantly perivascular lymphocytes, histiocytes, and neutrophils (2,3,13). A vasculitis is not seen. In some cases, there is focal necrosis of the superficial dermis. Prominent secondary changes in late lesions may obscure the characteristic findings.

Pathogenesis. The eruption of HV is clearly inducible by sunlight exposure, whereas artificial induction is more difficult, requiring repeated broad-spectrum or, less reliably, UVB skin exposure, but exact action spectra have not been determined (2,3,13,14). Blood, urine, and stool porphyrin concentrations, lesional viral studies, and circulating viral, antinuclear factor, and extractable nuclear antibody titers are normal. Further, the very PMLE-like clinical features of HV apart from its scarring

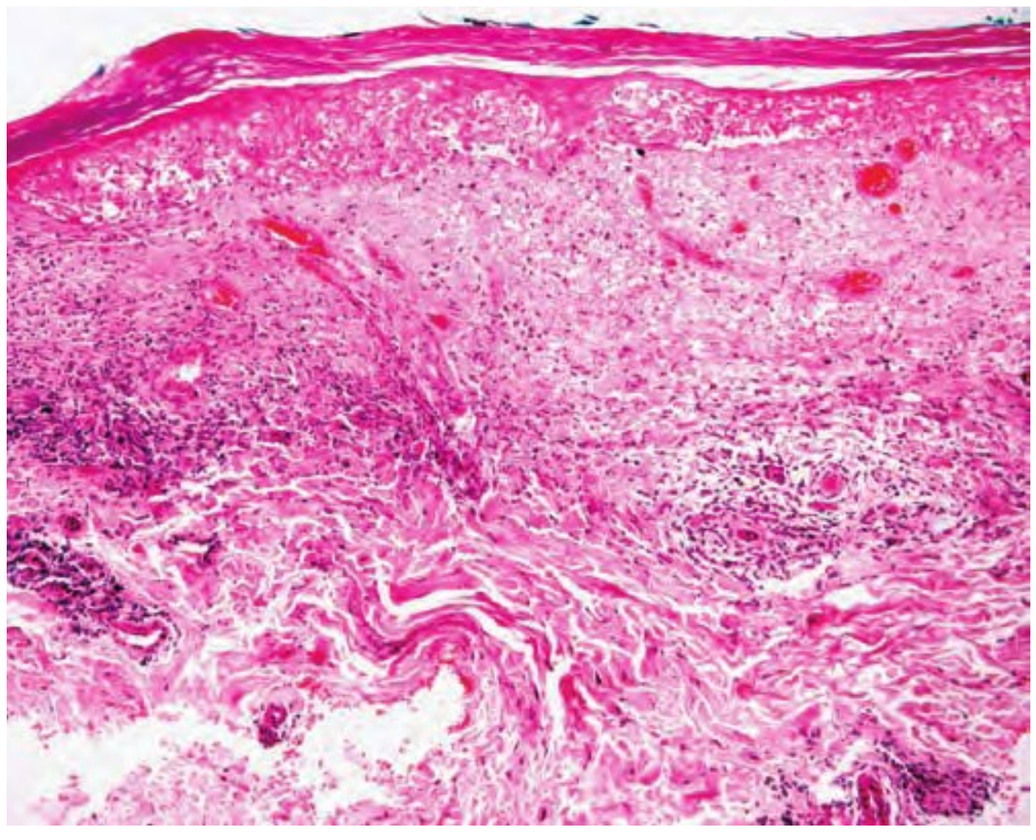


FIGURE 12-10. Hydroa vacciniforme. Prominent confluent epidermal necrosis associated with dermal perivascular inflammatory cell infiltrate.

and PMLE-like dermal perivascular mononuclear cell infiltration together strongly suggest similar pathogeneses for the two disorders; therefore, that HV may also be a DTH-type immunologic response to UVR-induced, endogenous, cutaneous autoantigen. In HV, however, the location of the putative antigen, the presence of a toxic photoproduct, or the intensity of the reaction may conceivably lead to the characteristic scarring.

Differential Diagnosis. HV must be differentiated from cutaneous viral disorders, the porphyrias, lupus erythematosus; and the other idiopathic, probably immunologically based

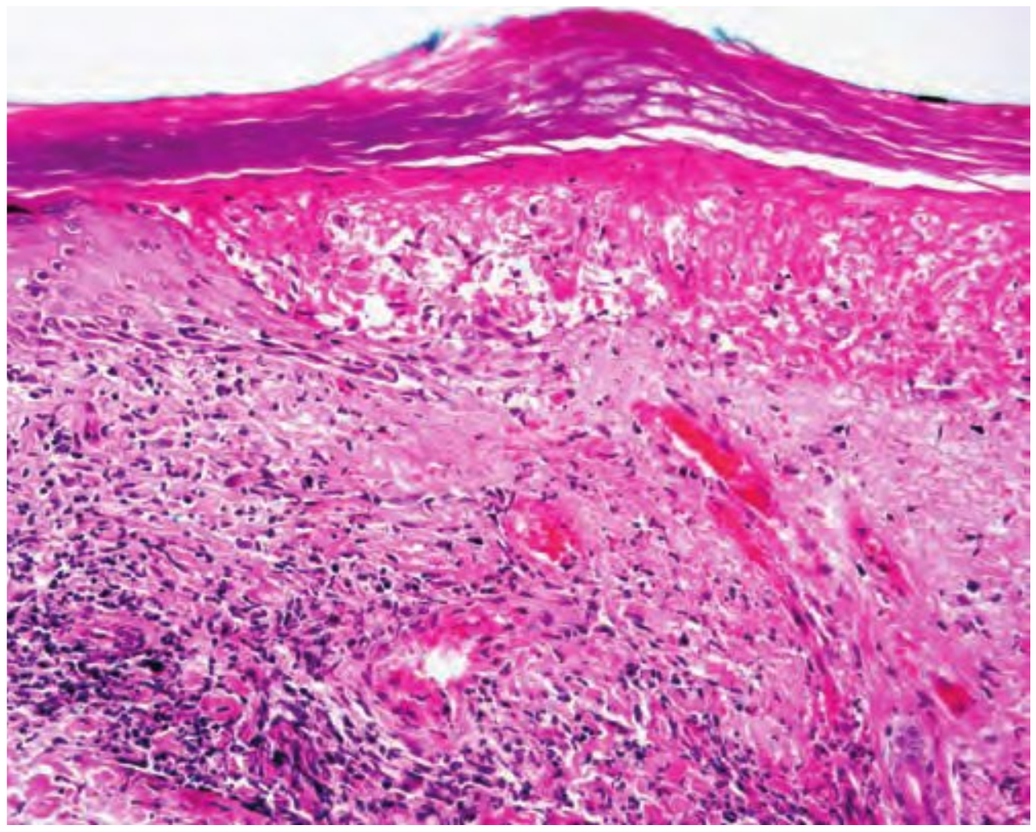


FIGURE 12-11. Hydroa vacciniforme. Marked reticular degeneration of the epidermis at the edge of the lesion and very superficial dermal necrosis with fibrin deposition.

photodermatoses by its clinical features and largely diagnostic histopathology, provided that appropriate viral studies, blood, urine, and stool porphyrin concentrations as well as circulating antinuclear factor and extractable nuclear antibody titers are also normal. The pattern of necrosis is remarkably similar to that seen in viral (including herpetic) infections and hand, foot, and mouth disease. Nevertheless, distinction from herpetic infection is easy, as HV lesional biopsies lack viral inclusions, multinucleated keratinocytes, and nuclei with ground glass appearance; also, hair follicle necrosis is lacking. However, distinction from hand, foot, and mouth disease is more difficult, but the clinical settings of the two diseases are totally different. Finally, a T-cell lymphoma variant with facial necrotic lesions simulating HV has been described in Asian and native Central American Indian children and rarely in adults (16,17), but histologic distinction is not difficult, as atypical lymphoid cells are readily apparent in the lymphomatous infiltrate.

CHRONIC ACTINIC DERMATITIS

CAD (photosensitivity dermatitis and actinic reticuloid syndrome, persistent light reaction) is a rare, persistent, often disabling, UVR- and occasionally visible light-induced eczema of exposed and sometimes also covered sites (2,3,18). It is most common in older men at temperate latitudes and most severe in summer. It may affect previously normal subjects or patients with prior endogenous eczema, photoallergic or allergic contact dermatitis, perhaps oral drug photosensitivity, or maybe rarely PMLE. Allergic contact sensitivity to ubiquitous airborne, occasionally photoactive agents often coexists. There is itchy, scattered or confluent, subacute or chronic eczema of the exposed skin, which may be lichenified (Fig. 12-12), excoriated, or more severely, erythematous, shiny, infiltrated, discrete or coalescent papules or plaques on a background of erythema, eczema, or just normal skin. Erythroderma is also rarely possible. Malignant transformation has been claimed on occasion but never convincingly substantiated, although a CAD response as part of cutaneous T-cell lymphoma itself may perhaps rarely occur (19). UVB- UVA-, and occasionally also visible light-induced pseudolymphomatous CAD, has previously been described as *actinic reticuloid*, UVB-induced eczematous CAD as *photosensitive eczema* or *photosensitivity dermatitis*, and UVB- and A-induced eczematous CAD as *photosensitivity dermatitis*, whereas CAD following photoallergic contact dermatitis has been called *persistent light reaction*. CAD treatment requires care, with the restriction of UVR exposure, wearing of appropriately protective clothing, application of high-protection broad-spectrum sunscreens, and avoidance of exacerbating contact allergens all being necessary but often of only moderate help. Topical calcineurin inhibitors may be useful in some cases, even those that are severe, whereas intermittent oral steroid therapy, low-dose narrowband UVB phototherapy, or probably more reliably PUVA, initially under high-dose oral steroid cover, may also be effective. Failing this, oral immunosuppressive therapy with azathioprine, cyclosporine, or occasionally mycophenolate generally clears the condition, if tolerated. Finally, CAD may often eventually remit (20).

Histology. In early CAD, the histology (2,3,18,21) may resemble that of any other spongiotic process, including eczema and contact dermatitis, with epidermal spongiosis, lymphocytic exocytosis, and a superficial and deep, perivascular, lymphohistiocytic, inflammatory infiltrate. In older lesions, however, there is variable, often marked, acanthosis of the epidermis and infundibular portions of hair follicles (Fig. 12-13), while spongiosis and lymphocytic exocytosis may be focally prominent



FIGURE 12-12. Chronic actinic dermatitis. Extensive lichenification and excoriation.

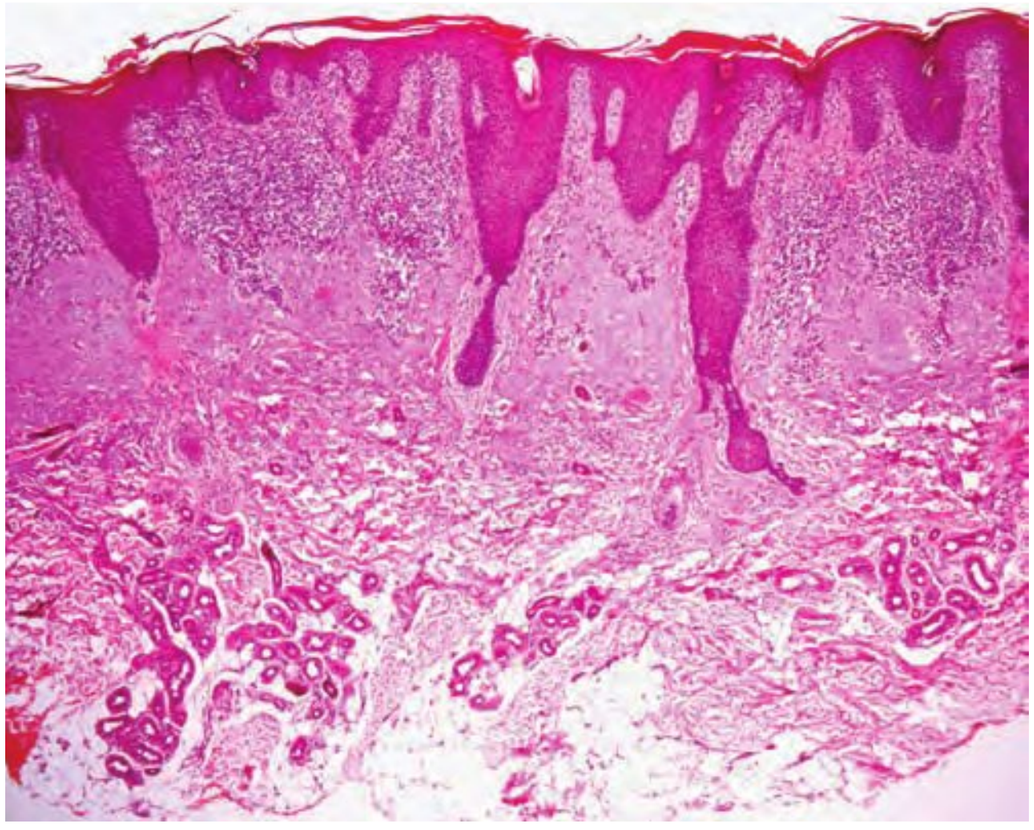


FIGURE 12-13. Chronic actinic dermatitis. Older lesion with prominent hyperplasia of epidermis and infundibular portion of hair follicles.

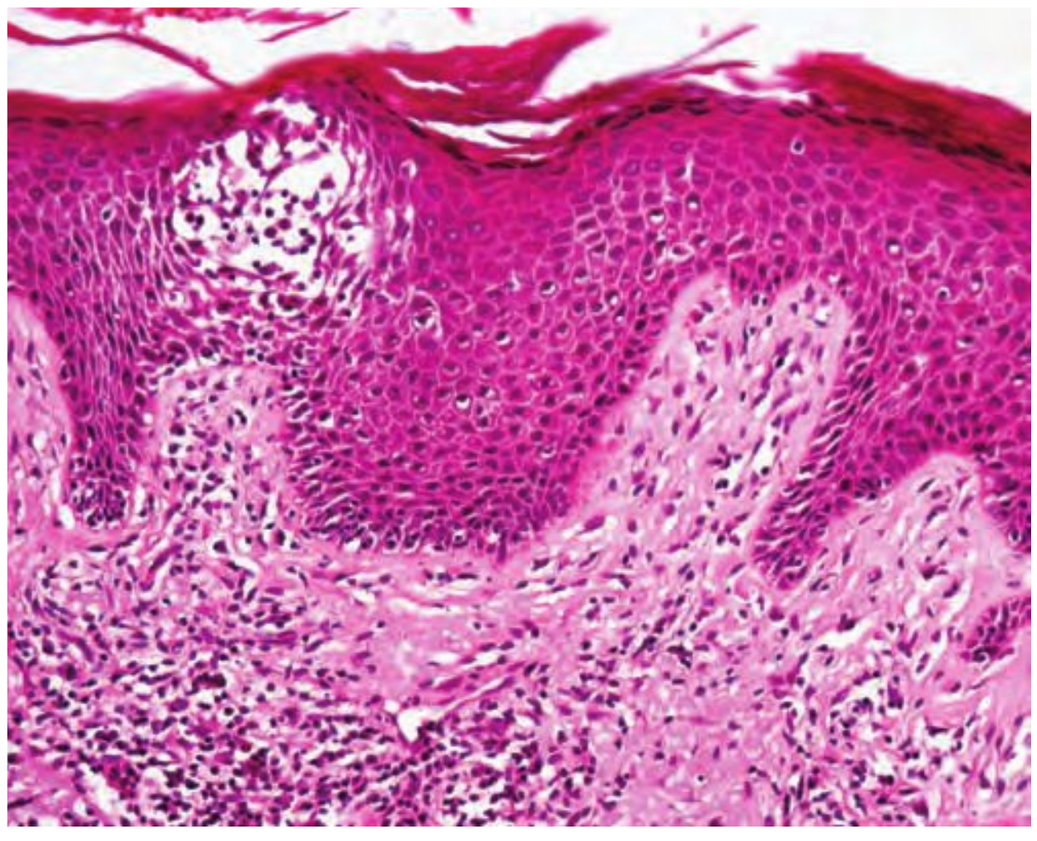


FIGURE 12-14. Chronic actinic dermatitis. Lichenification in association with prominent spongiotic changes and exocytosis of lymphocytes.

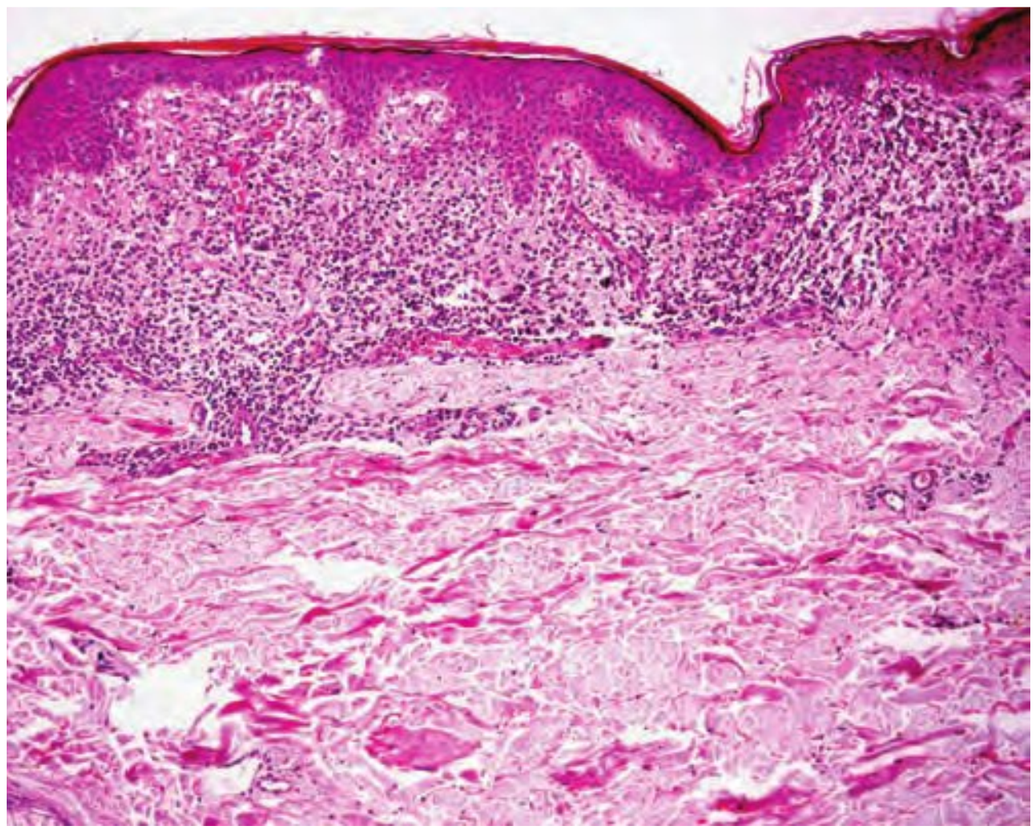


FIGURE 12-16. Chronic actinic dermatitis (actinic reticuloid variant). Prominent superficial dermal mononuclear cell infiltrate focally obscuring the dermal-epidermal junction.

(Fig. 12-14). Secondary changes from excoriation are also frequent in both early and late disease and consist of focal epidermal necrosis, scale-crust formation, dermal–epidermal junction fibrin deposition, and neutrophils with nuclear dust. In addition, there may be occasional Pautrier microabscess-like collections of cells, usually of the Langerhans type. In the papillary dermis, vertically streaked collagen, stellate fibroblasts, and small multinucleated cells, often described as Montgomery giant cells (Fig. 12-15), are frequently present; these latter, however, may commonly occur in any chronic inflammatory process. Deep in the dermis, there is often a predominantly perivascular, usually dense, mononuclear cell infiltrate of mainly T-lymphocytes, histiocytes, eosinophils, and plasma cells; in severe CAD, this may be even more prominent, along with marked focal epidermal lymphocyte exocytosis (Fig. 12-16), and a degree of irregularity of nuclear outline (Figs. 12-17 and 12-18). In such cases, formerly included within the term *actinic reticuloid*, distinction from cutaneous T-cell lymphoma may often be difficult. It has been suggested that the T-lymphocytes in such cases have a diagnostically helpful [predominantly CD8 (cytotoxic) positive] phenotype, and that most other reactive infiltrates and cutaneous T-cell lymphomas are instead mostly

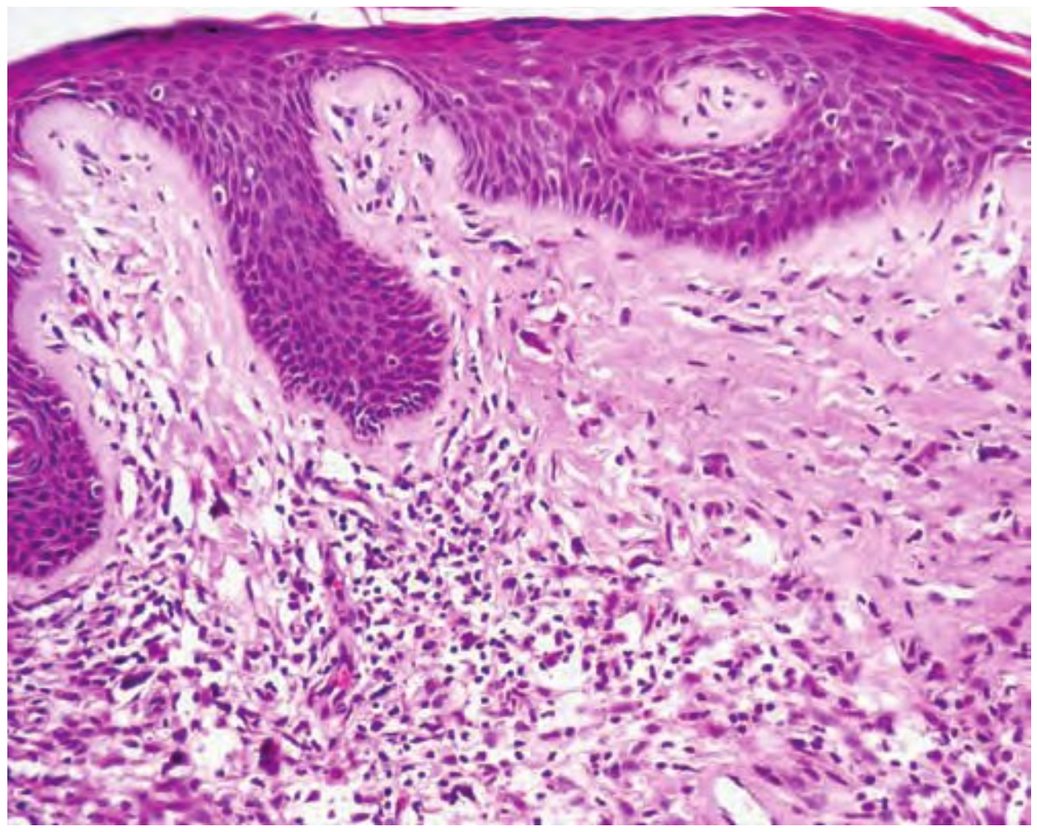


FIGURE 12-15. Chronic actinic dermatitis. Fibrosis of papillary dermis with mononuclear inflammatory cells and scattered small giant cells.

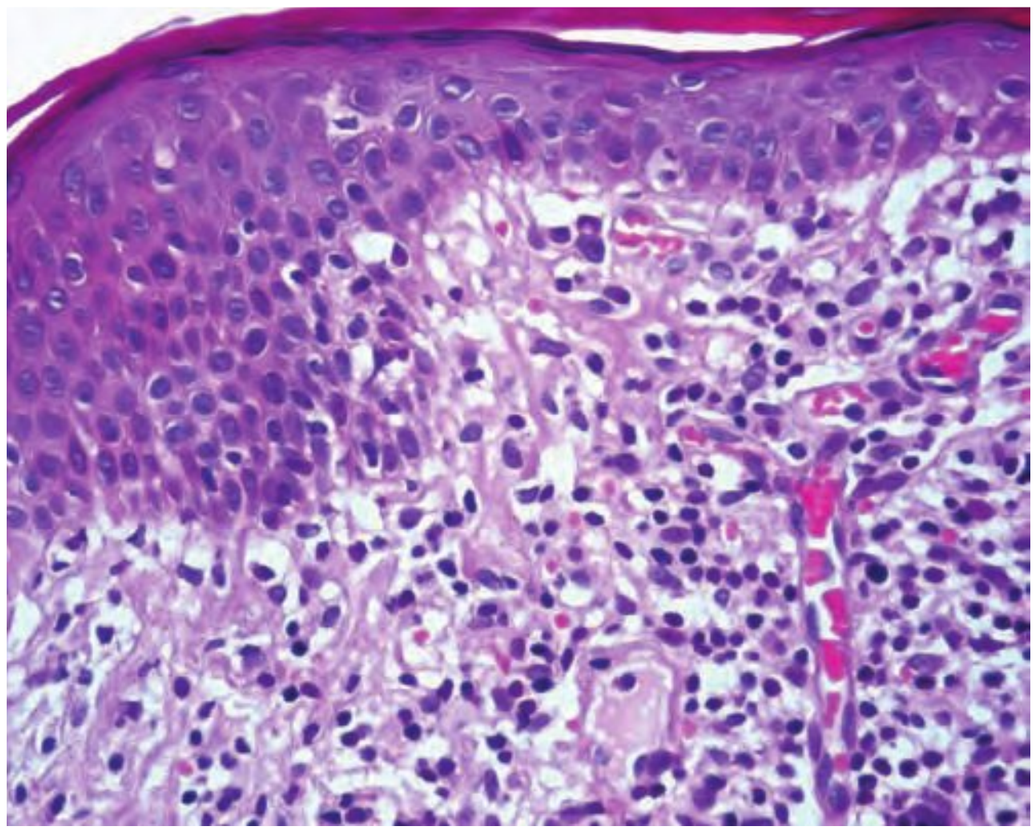


FIGURE 12-17. Chronic actinic dermatitis (actinic reticuloid variant). Focal epidermal exocytosis of lymphocytes, with some displaying irregular nuclear outlines.

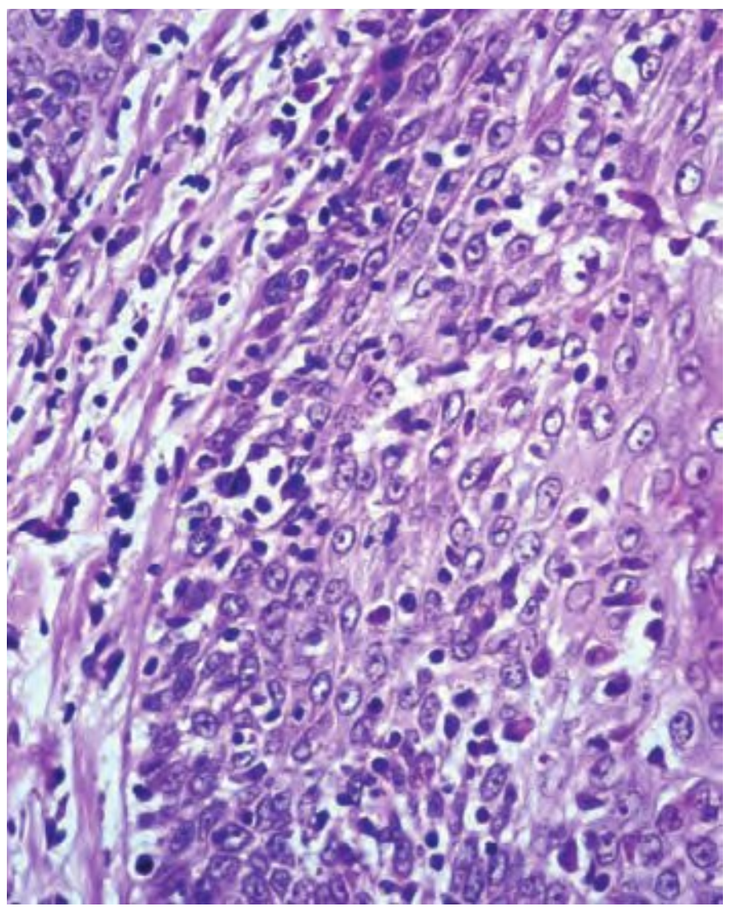


FIGURE 12-18. Chronic actinic dermatitis (actinic reticuloid variant). A Pautrier-like microabscess within the infundibulum of a hair follicle.

CD4 (helper) positive (22). However, personal experience suggests that this is not always so and that infiltrating helper T-lymphocytes often are prominent in CAD as well.

Pathogenesis. CAD is clinically and histologically reproducible at all skin sites in the absence of exogenous photosensitizer, in some patients with just UVB, in some both UVB and UVA, and in rare others all of UVB, UVA, and short visible radiation, whereas the clinical features and pattern of dermal cellular infiltration, cytokine production, and adhesion molecule activation are all essentially indistinguishable from those of allergic contact dermatitis (2,3,18). In that the latter is a known DTH response, it therefore seems highly likely that the same situation applies in the CAD reaction, presumably against photo-activated endogenous, cutaneous autoantigen. Furthermore, action spectrum studies have suggested that the UVR absorber initiating the process may conceivably sometimes be DNA or a similar or associated molecule (23). In addition, it is possible that the airborne allergic contact dermatitis common in CAD may increase cutaneous immune responsiveness and thus putative antigen recognition, or else that the frequently photoaged skin in the disease may lead to diminished normal UVR-induced cutaneous immunosuppression, as apparently occurs genetically in PMLE, and again greater antigen recognition. Finally, slower clearance of antigen may also occur in the aged skin of CAD, again arguably potentiating disease development.

Differential Diagnosis. CAD must be distinguished from other eczemas, in particular the seborrheic and atopic forms, from airborne and topical medicament contact dermatitis, and from cutaneous T-cell lymphoma. However, in that its histologic appearances are indistinguishable from those of other subacute or chronic spongiotic processes, or in its severe forms from cutaneous T-cell lymphoma, a clinical history is essential for firm diagnosis as well. Nevertheless, severe CAD is generally separable from lymphoma by its superficial dermal fibrosis, paucity of cytologically atypical lymphocytes, and at least focal prominent spongiosis.

SOLAR URTICARIA

SU is a rare UVR- or visible radiation-induced wealing of exposed skin. The more common primary SU occurs spontaneously, and the very rare secondary form follows photosensitization to drugs or chemicals (2,3,24). Primary SU is slightly more common in women, with onset at any age but mostly between 10 and 50 years. The eruption develops on exposed skin within 5 to 10 minutes and fades within an hour or two. Regularly uncovered sites such as the face and backs of hands are occasionally spared. A tingling sensation and patchy erythema generally precede separate or confluent wealing, the latter sometimes generalized and in severe instances occasionally associated with headache, nausea, bronchospasm, faintness, or systemic collapse. Secondary SU generally follows exposure to substances such as tar, pitch, dyes, drugs such as the discontinued benoxaprofen, or very rarely endogenous porphyrin in the porphyrias. Avoidance of the inducing radiation, the use of appropriate sunscreens, or in particular adequate doses of nonsedating antihistamines helps approximately half of patients. Resistant cases sometimes respond to low-dose narrowband UVB phototherapy, low-dose PUVA or particularly plasmapheresis, or failing that, very rarely to intravenous immunoglobulin or cyclosporine. However, a proportion of SU patients do poorly with all therapy.

Histopathology. The epidermis appears unremarkable. In the dermis, there is edema as evidenced by mild collagen bundle separation, along with slight, rarely moderate, perivascular and interstitial inflammatory cell infiltration with eosinophils and occasionally also neutrophils and lymphocytes (2,3,24,25) (Fig. 12-19).

Pathogenesis. Any UVR or visible radiation waveband, specific for a given patient, may induce primary SU (2,3,24). Wealing is probably mediated through allergic type I hypersensitivity to cutaneous or circulating, irradiation-induced allergen. Presumed circulating antibodies have also been identified, very likely of the IgE type. In secondary SU, the eruption apparently follows direct nonimmunologic injury after UVR absorption by the responsible chemical or drug and its secondary transfer to adjacent susceptible tissue. Histamine is probably the major chemical mediator in both forms.

Differential Diagnosis. Clinically, SU must be differentiated from other light-induced eruptions by its much shorter time course and characteristic wealing and from other forms of urticaria, particularly that which is heat induced. Histologic distinction, however, is not possible. The porphyrias, drug and chemical photosensitivity, and lupus erythematosus must also be excluded for final diagnosis.

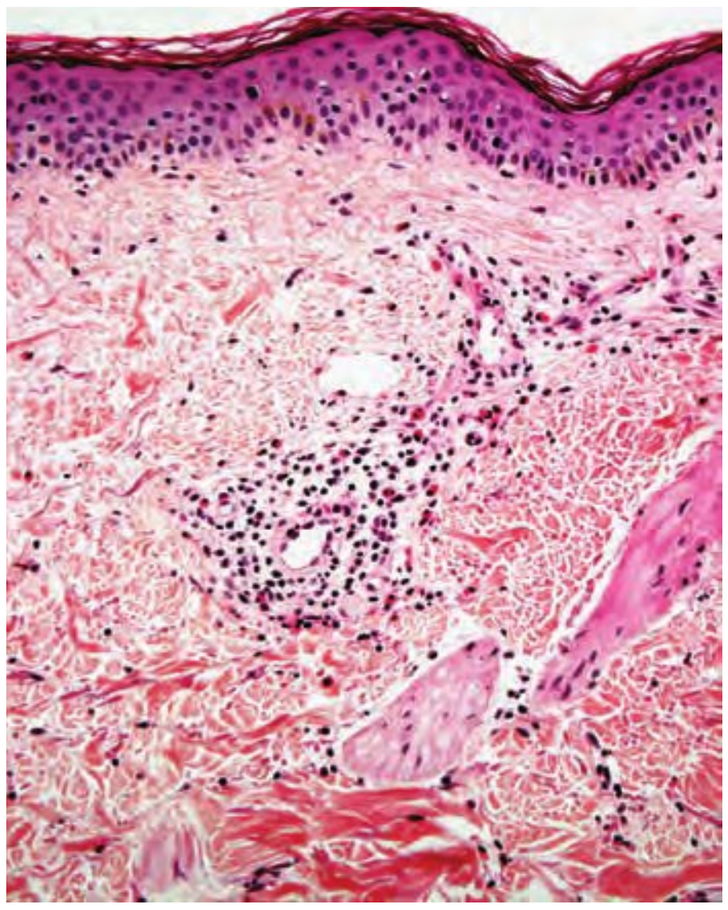


FIGURE 12-19. Solar urticaria. Dermal edema and a mild interstitial and perivascular inflammatory cell infiltrate of lymphocytes and eosinophils.

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CHAPTER 13

Jacqueline M. Junkins-Hopkins

Disorders Associated with Physical Agents: Heat, Cold, Radiation, and Trauma

Physical injury to the skin can result in a number of disorders of the epidermis, dermis, and/or subcutis, depending on the type of agent exposure. Direct injury to the skin by radiation and temperature-associated exposure results in distinct histopathologic skin alterations that will be discussed in this chapter. Disorders due to direct physical injury and surgical-related injury also are discussed; however, cutaneous alterations associated with cosmetic-associated procedures such as reactions to injectable material (e.g., silicone) are discussed elsewhere. Conditions that have other pathogenesis but may be related to temperature or physical exposure, such as Raynaud's phenomenon, physical urticaria, and cold panniculitis, are discussed in Chapters 10, 7, and 20, respectively.

HEAT-ASSOCIATED INJURIES

The effect of heat on the skin is determined by the skin thickness and degree, extent, and duration of the heat exposure. The source of the heat also influences the degree of tissue injury. For instance, dry heat results in charring and desiccation, whereas moist heat results in opaque coagulation. Immersion burns are more severe than flash and splatter burns, and electrical burns result in deep tissue necrosis (1). Exposure of the skin to extreme heat results in a first-, second- or third-degree burn, whereas prolonged or repetitive exposure to less intense heat results in changes of erythema ab igne. Surgery-related electrodesiccation-induced injury also has distinct histopathologic features and is discussed at the end of the chapter.

Burns

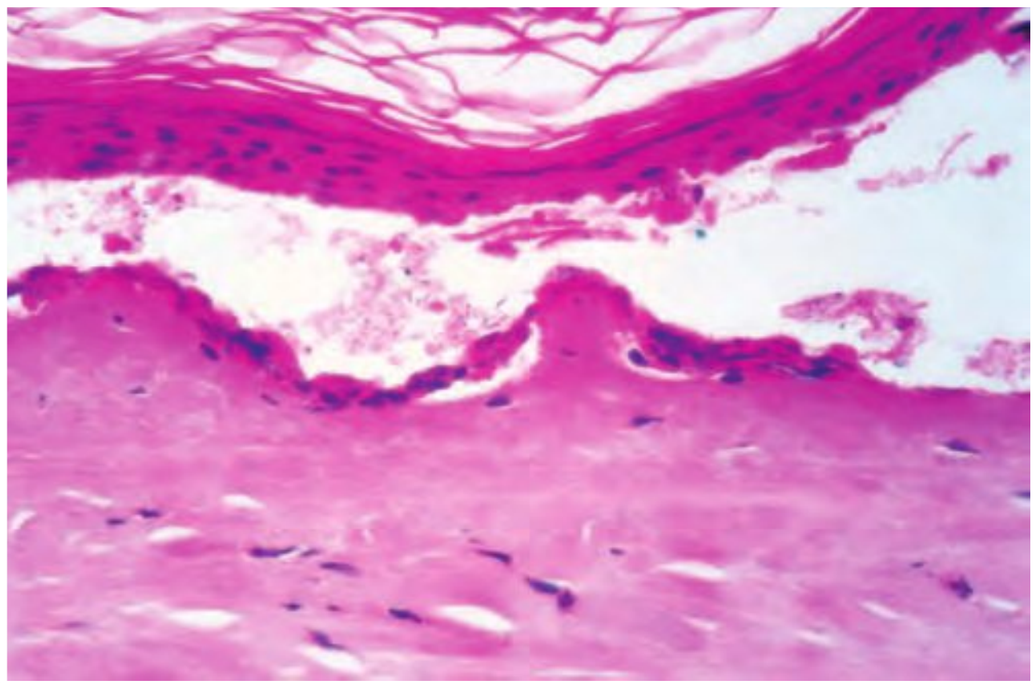
Burns to the skin may be due to *thermal injury* from flames or hot substances such as scalding water, contact, or flash burns from explosions; *chemical burns*, such as wet cement (2) or mustard gas (3); and *electrical injury*. The end result is similar in all burns, and these are classified according to the depth of injury (4).

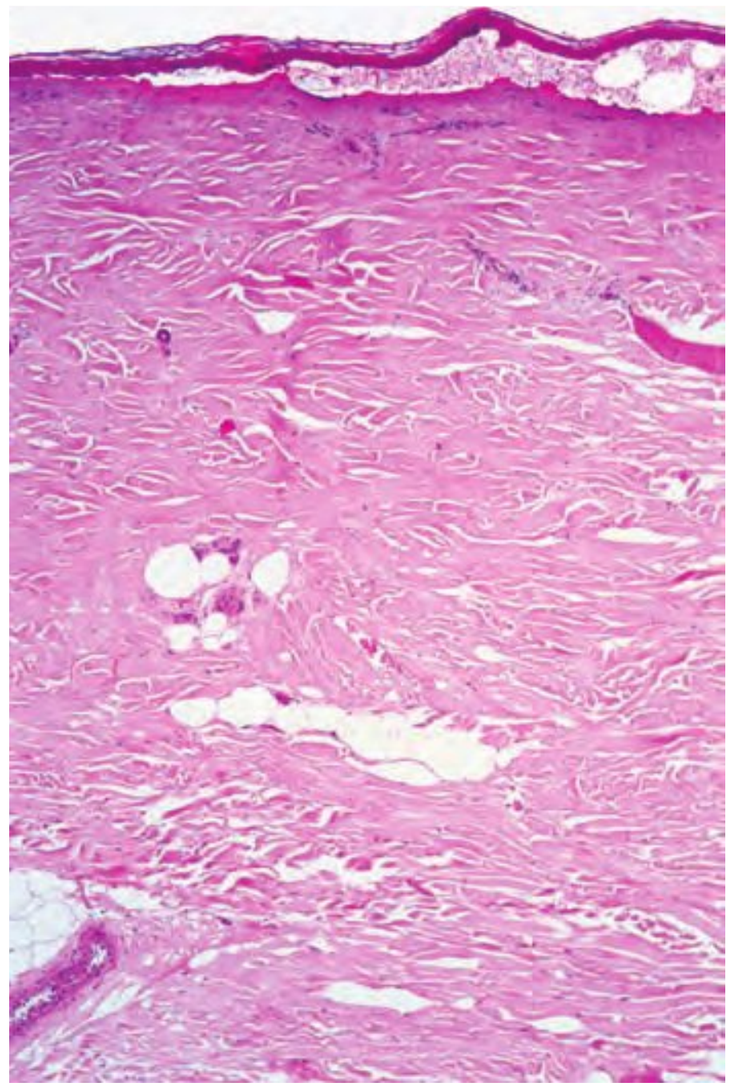
Tissue injury from direct exposure to heat is the most common, and is defined by the depth (partial or full thickness) or extent (first, second, or third degree) of tissue injury. The resultant tissue injury is a sequela of the release of inflammatory and vasoactive mediators released due to denaturation and coagulation of proteins and to edema from increased capillary permeability (5). Painful erythema and edema without vesiculation is seen in first-degree burns; vesiculation and blisters characterize superficial second-degree burns, which progress to pallor and anesthesia if both the epidermis and dermis are injured; and third-degree burns show massive necrosis with charring, denuded superficial tissue, granulation tissue, and scar formation (1). Deep second-degree burns and third-degree burns show overlapping features. Secondary bacterial infections may cause the injury of a superficial second-degree burn to extend deeper, with changes similar to a third-degree burn.

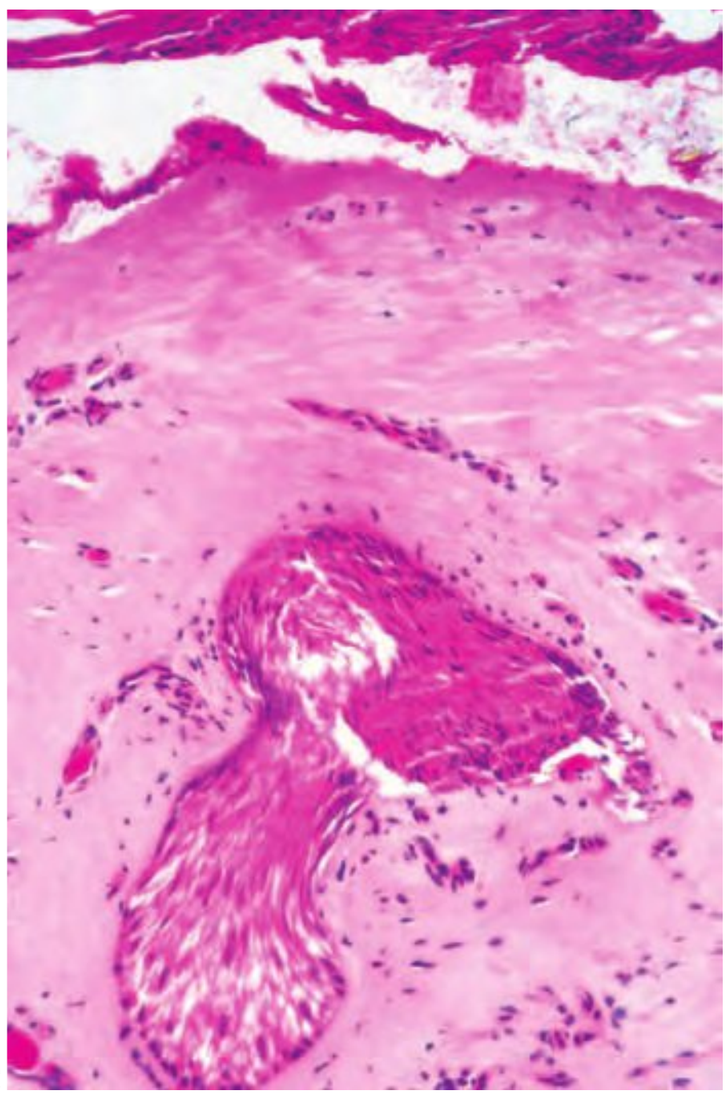
Chemical burns may be due to acid or alkalis, the latter of which penetrate more deeply, with delayed pain. Cement burns are an example and tend to occur on the lower extremities, associated with accidental seepage of cement onto clothing or boots (2). Occasionally, there may be burns from marking lines on playing fields. There is burning, pain, erythema, and vesiculation within about 6 to 48 hours of exposure (mean 38 hours). Erosions and necrosis similar to heat burns ensues. Mustard gas (yperite) burns in chemical warfare may be seen even with less than 1 hour of exposure, with a latent period of less than 6 hours. Patients present with pruritus, burning, pain, erosions, erythema, vesicles, bulla, ulceration, edema, and dyschromia, especially hyperpigmentation (3). Involvement of groin and axilla is more common, due to moisture. There may be a toxic epidermal necrolysis (TEN)–like picture.

Secondary inflammatory events or malignant conditions may arise at burn sites (see later discussion), and, rarely, neutrophilic dermatosis may be induced by thermal burn injury (6). Eccrine poroma (7), sarcoidosis, neurothekeoma, and schwannoma (8) may also be seen.

Histopathology. The histopathology depends on the degree of tissue damage. There is variable necrosis of the epidermis, dermis, and adnexal structures, with necrosis and eventual sclerotic changes of the dermis. The inflammatory infiltrate is variable and includes neutrophils, lymphocytes, and macrophages. Attempts have been made to estimate the age of the burn


A


B


C

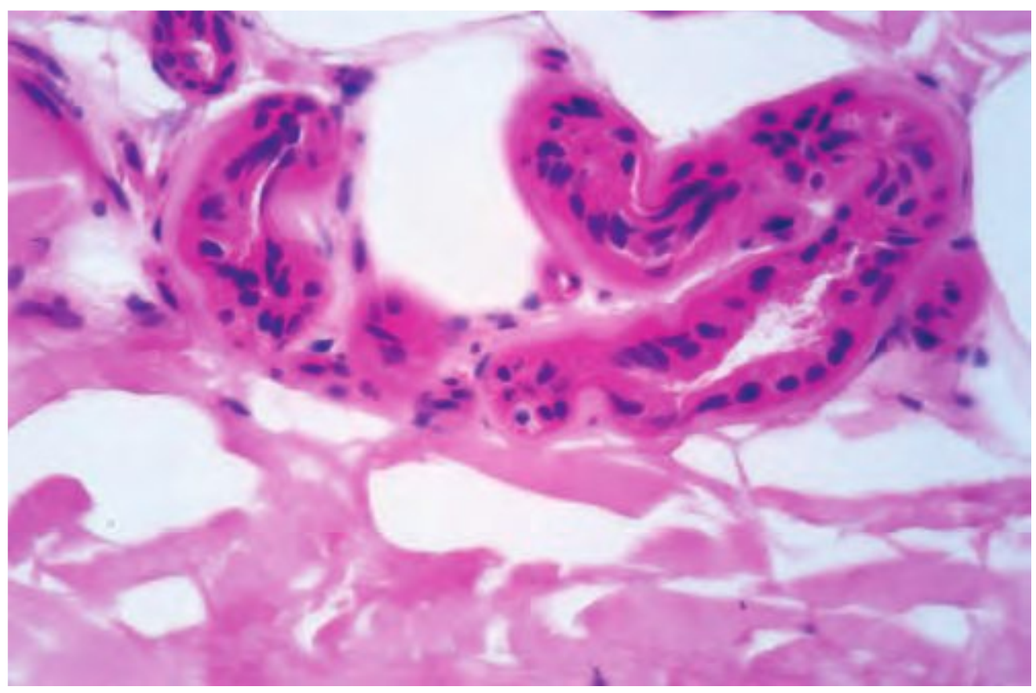

D

FIGURE 13-1. Third-degree burn. A: The epidermis shows full-thickness eosinophilic necrosis resulting in bullous disassociation from the dermis and incipient denution. This bulla formation can be seen in second- and third-degree burns. The collagen shows homogenized necrosis, with loss of distinction between collagen bundles. The fibroblasts are nonatypical, differentiating this from chronic radiation injury. B: There is pandermal eosinophilic homogenized alteration collagen, with necrosis of an eccrine gland. The epidermis shows bulla formation. C: Extension of the injury involving the pilosebaceous units differentiates a third-degree from a superficial second-degree burn. Burn injury to the pilosebaceous unit results in eosinophilic necrosis of the epithelium and elongation of the nuclei. The surrounding stroma shows coagulation of the collagen and vascular thrombosis. D: Eosinophilic alteration of an injured eccrine gland differentiates third- from second- and first-degree burns.

wound based on the degree of neutrophilic and macrophage infiltration (9). Acute inflammation tends to predominate in the first 6 hours to 2 days after injury; however, neutrophils can also be seen in later lesions. The latter may possibly be related to infection, which can often occur. Macrophages tend to be encountered from days 2 to 20, but many cases show a minimal or absent macrophage response. Lymphocytes tend to occur later.

The degree of burn is defined more specifically by the following features:

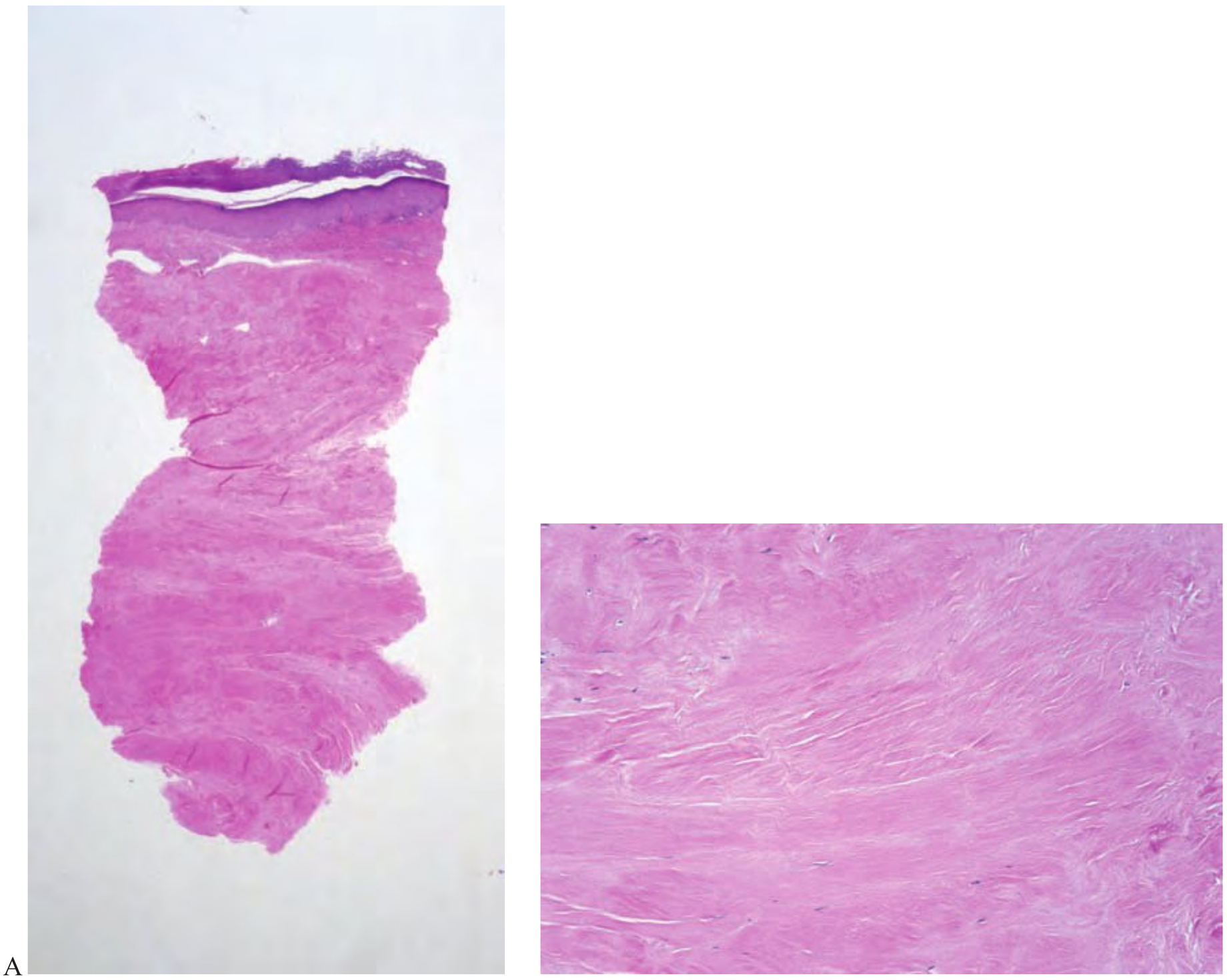
First-degree burns: Vasodilation is the predominant feature. Epidermal and subepidermal edema may progress to partial-thickness superficial epidermal necrosis. Full-thickness epidermal necrosis differentiates second- from first-degree burns.

Second-degree burns: In superficial second-degree burns, partial- to full-thickness necrosis and edema of the epidermis and subepidermal stroma result in blister formation. Typically, epidermal necrosis and separation from the dermis at the dermal–epidermal junction or within necrotic basilar keratinocytes are seen (Fig. 13-1). Although initially vasoconstriction occurs, the biopsies show prominent vasodilation and edema in the dermis. Necrotic changes may extend into the lower reticular dermis in deep second-degree burns, but the appendages tend to be spared, differentiating a second-degree from a third-degree burn. Apoptosis can be seen in the adnexal structures and dermal fibroblasts of deep partial burns (10).

Third-degree burns: Full-thickness coagulation necrosis of the epidermis and dermis, including the appendages, is seen (Fig. 13-1). The resultant scar is characterized by hyalinized collagen and an absence of adnexal structures (Fig. 13-2).

Chemical burns: Chemical burns may vary, depending on the substance. Dermal and adnexal necrosis similar to thermal burns may be seen. Histopathology of sulfur mustard shows four patterns:

1. Interface dermatitis, with or without necrosis, similar to TEN or erythema multiforme, with hyperpigmentation of the epidermal roof.



A B

FIGURE 13-2. Chronic burn scar. A: The dermis and subcutis are diffusely sclerotic and homogenized, with compete absence of adnexal structures, including arrector pili muscles, differentiating this from radiation injury and scleroderma/morphea. The absence of vascular proliferation and presence of homogenized thickening of the collagen differentiates a chronic burn from a scar from other reparative causes. B: The sclerotic collagen is nearly devoid of fibroblasts, in particular atypical ones, differentiating this from chronic radiation injury.

2. Spongiotic dermatitis, similar to acute contact dermatitis. Bulla formation is often at the dermal–epidermal junction, with or without acantholytic cells. The epidermal roof shows dysmaturation with cellular atypia.
3. Hyperpigmentation of the basal layer of the epidermis with dermal melanophages.
4. Dermal alteration, including coagulation necrosis, low-grade fibrosis with sclerodermoid changes, telangiectases, and perivascular inflammation, without vasculitis (3).

Differential Diagnosis. Radiation dermatitis is differentiated from burn scars by the presence of atypical radiation fibroblasts in the former. Complete absence of the adnexal structures favors a burn scar because the eccrine glands may be spared with radiation. In morphea/scleroderma, there is preservation of eccrine coils, and a lymphoplasmacellular infiltrate may be seen.

Burn Scar–Associated Malignancy

Chronic burn scars are subject to the development of dystrophic calcinosis cutis (11), and carcinomas, especially basal cell carcinomas, may arise acutely within 2 to 3 months after the injury (1). Delayed carcinomas arise after a latency that ranges from 10 to 70 years, with an average of approximately 30 years. There may be a shorter lag time (19 years) if there is poor wound care (12). The tumors most often arise on the extremities but may also arise on the head and trunk. Burn scar–associated cancers include squamous more often than basal cell carcinomas, but malignant melanoma (13), angiosarcoma (14), and anaplastic large cell lymphoma (15,16) may be seen. Squamous cell carcinomas are more often seen with scalding burns, whereas basal cell carcinomas are associated with burns from flames. Welders are also at risk for getting both basal and squamous cell carcinomas due to chronic exposure to both high temperatures and nonsolar ultraviolet radiation (17,18). The occurrence of cancer developing in burn scars was noted in 1860 by Heurteux, and trauma-induced carcinomas were described by Marjolin in 1828; these cancers are more aggressive than their sun-induced counterparts. Metastases may occur in up to approximately one third of the cases. Recurrence is also higher in cancers due to these chronic ulcers. The carcinomas arise from the edges of wounds or from epithelial remnants entrapped in the scar; thus, they may not occur as frequently if there has been grafting (1).

Acute Ultraviolet Burn

Mild ultraviolet-induced burns or sunburns resulting in erythema are characterized by the presence of scattered apoptotic keratinocytes, "sunburn cells," and variable subepidermal edema. Clinical blistering may result from severe burns due to full-thickness epidermal necrosis and/or dermal edema (Fig. 13-3). The preservation of appendages allows epidermal regeneration.

Ultraviolet Recall

This is also known by other names, including sunburn reactivation, sunburn recall, photo recall, and photodermatitis reactivation, and refers to the phenomenon in which a medication induces an acute cutaneous eruption restricted to the area of previous sunburn or ultraviolet (UV) light therapy (18). This is seen especially with methotrexate, but it can also be associated with other chemotherapeutic agents and antibiotics, such as ampicillin and trimethoprim-sulfamethoxazole. Two clinicopathologic presentations may be seen, depending on whether the UV recall reaction occurs days after UV exposure, as is seen with methotrexate, or weeks to months later, as is typically seen with antibiotics. Methotrexate-induced recall phenomenon generally occurs if methotrexate is given 1 to 5 days after sunburn occurs but not if the burn is concomitant or much earlier. This UV recall tends to be associated with pain and burning, with an erythematous to violaceous vesiculobullous eruption (18), and in most cases it is more severe than the initial sunburn. Ultraviolet recall reactions associated with antibiotics (19,20) differ from the methotrexate reaction. These tend to occur at a later interval—weeks to months from the sunburn—with a less severe, pruritic macular, papular; or morbilliform-like drug reaction (19). Changes of toxic epidermal necrolysis have rarely been reported with trimethoprim sulfa (21). The UV reaction with either presentation presents within a few days or within hours of the medication intake. Rechallenge may occur at a shorter interval than the initial reaction and with a more severe blistering reaction (21). It has been proposed that the methotrexate-induced reaction be considered a UV enhancement reaction and those associated with a delayed interval of UV exposure be considered UV reactivation (18).

Histologic features of UV recall are not well documented because the diagnosis is usually made clinically. A review of the literature described several histologic features, most of which indicate an element of interface or cytotoxic dermatitis, characterized by hydropic degeneration, dyskeratotic or apoptotic keratinocytes, dysmaturation, dyskeratosis, or acanthosis. There is also a variable perivascular lymphocytic infiltrate in the papillary dermis, sometimes with erythrocyte extravasation. Neutrophils

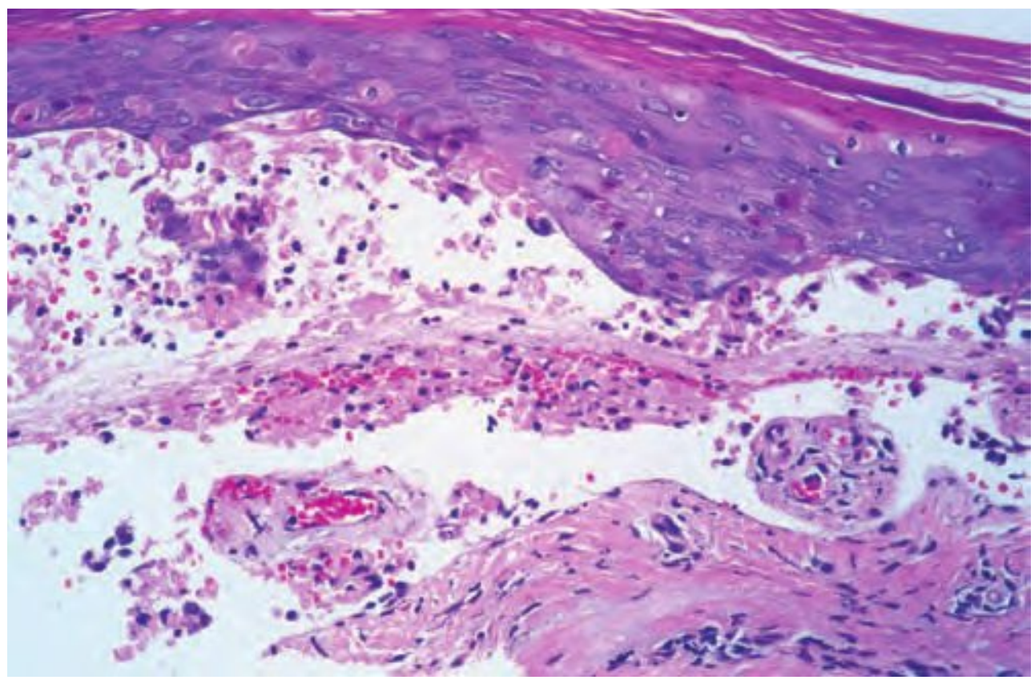


FIGURE 13-3. Acute ultraviolet (UV) radiation burn. This is an example of a UVA-induced burn showing full-thickness dyskeratotic keratinocytes throughout all layers of the epidermis, with subepidermal blister formation.

have been described. Clinical blisters have been associated with extensive epidermal necrosis with intraepidermal bullae formation (18).

ERYTHEMA AB IGNE

Erythema ab igne presents as localized, reticulated, dusky reddish brown patches with variable telangiectasia (Fig. 13-4) associated with repetitive infrared radiation exposure insufficient to produce a burn. Thermal keratoses, squamous cell carcinoma, and rarely bullae may arise in lesions of erythema ab igne (22). Historically, this was typically on the shins, buttock, or lower back associated with repetitive exposure to open hearths or stoves, hot water bottles, or steam heaters. More recently, prolonged repeated contact with heating pads, car seat heaters, laptop computers (23), and hot popcorn kernels

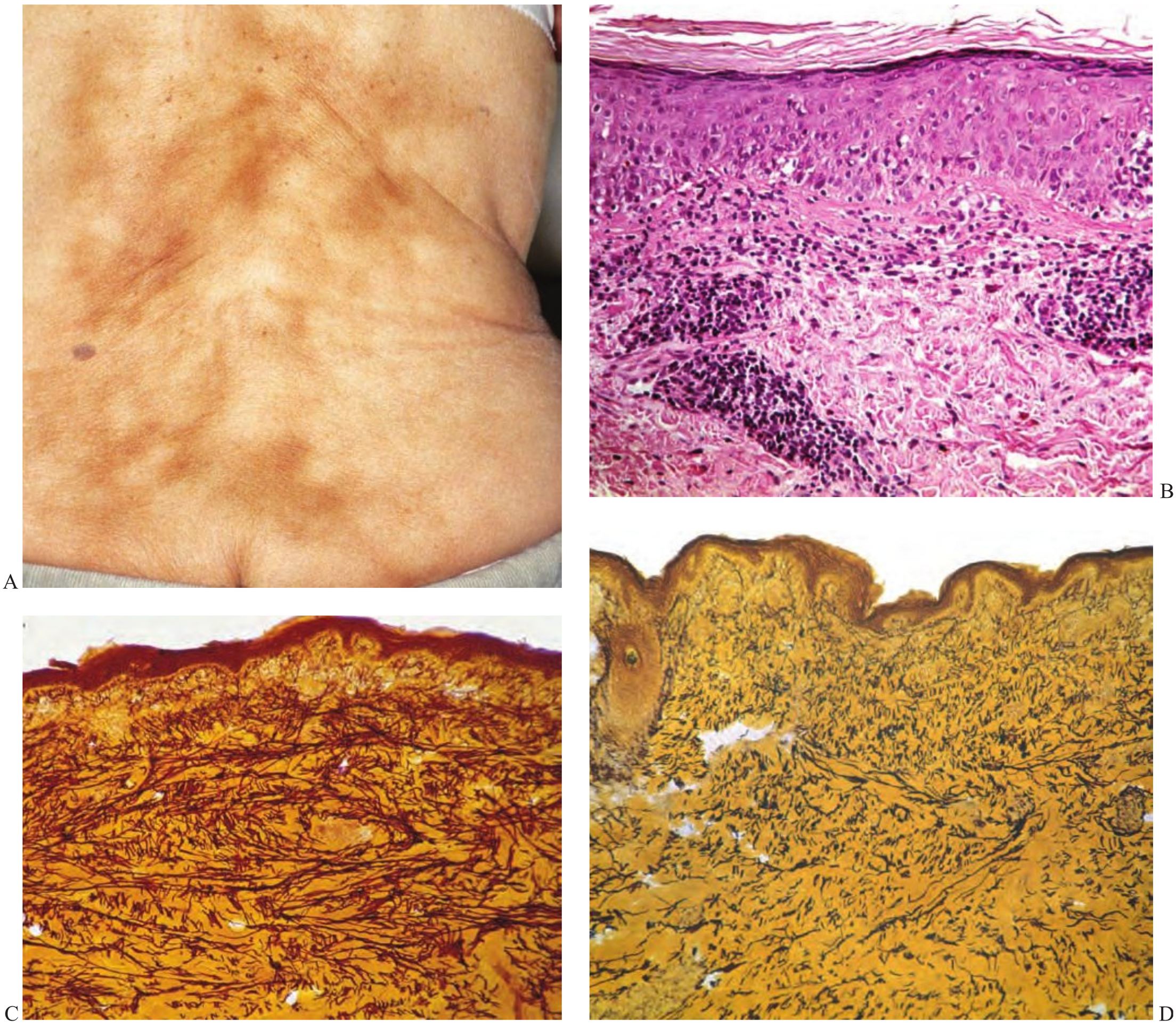


FIGURE 13-4. Erythema ab igne. A: Clinically, reticulated brown patches are seen in erythema ab igne. This may present on the lower back where there has been frequent use of a heating pad. B: Erythema ab igne has variable histologic features. This hematoxylin and eosin–stained biopsy shows a perivascular lymphocytic infiltrate in the superficial dermis that focally disrupts the dermal–epidermal interface. There is no discernible elastic fiber abnormality noted on routine staining. The absence of clumped basophilic elastic tissue differentiates erythema ab igne from solar elastosis. C: Staining for elastic tissue highlights the increased amount of elastic tissue in comparison to uninvolved skin (see panel D), characteristic of erythema ab igne. D: Elastic staining of uninvolved skin, showing a normal distribution of elastic fibers, as compared with panel C. (Photographs courtesy of Waine Johnson, MD.)

used for arthritic pain have been reported to cause erythema ab igne. This may rarely occur in children (24), and it may have a high tendency of recurrence in patients with mental retardation. Rare cases of truncal erythema ab igne due to heat application for pain as a manifestation of abdominal cancer have been reported. (25). The time of onset of erythema ab igne is usually months, but laptop-induced erythema ab igne has been shown to occur within 2 weeks of exposure (26).

Histopathology. Biopsies of erythema ab igne show variable histopathologic features, which are nonspecific in the absence of clinical-pathologic correlation. The biopsy may appear normal on hematoxylin and eosin staining, with the exception of mild acanthosis and hyperpigmentation of the basal keratinocytes. Epidermal atrophy, rete effacement, and pigment incontinence, with additional features of interface dermatitis, characterized by mild basal vacuolization, necrotic keratinocytes, and subtle squamatization, have been described in the early stages (27). The dermis shows dilation and congestion of postcapillary venules and a variable perivascular infiltrate of mild to moderate intensity consisting of lymphocytes, plasma cells, histiocytes, melanophages, mast cells, and neutrophils (27–30) (Fig. 13-4). Elastic stains demonstrate an increased amount of elastic tissue in the upper and mid-dermis. These fibers may be fragmented (22). Alcian blue stains may reveal an increase in hyaluronic acid. Deposition of iron has been described (28,30), but this may reflect the anatomic site of the lower legs (8). Basal keratinocytic atypia and frank squamous cell carcinoma *in situ* have been reported in erythema ab igne of the lower leg (31). Bullous lesions have been described as showing a subepidermal plane of separation associated with epidermal atrophy, rete effacement, and hydropic degeneration of basal cells with melanophages, consistent with a lichenoid tissue reaction (22). Similar cases of bullous erythema ab igne have been attributed to coexisting lichen planus, but this is felt by some to be a manifestation of intrinsic blistering. Direct immunofluorescence on these cases are either negative or show a pattern of immunoglobulin M staining in the papillary dermis consistent with colloid bodies. Ultrastructural investigations of erythema ab igne have been reported (30) and show changes consistent with apoptotic regressive changes of the basal keratinocytes, functional activation of melanocytes, and elastic fiber alterations indistinguishable from actinic elastosis due to chronic ultraviolet radiation. The keratinocyte damage appeared to represent heat-related damage and not a preneoplastic alteration. The vessels are dilated and increased in number. This may rarely present as cutaneous reactive angiomatosis, mimicking a malignant vascular neoplasm or diffuse dermal angiomatosis (32).

Differential Diagnosis. The elastic tissue alteration induced by ultraviolet radiation in solar elastosis is apparent on hematoxylin and eosin stains as solid and homogenized material, as opposed to erythema ab igne, which shows no perceptible elastic changes on routine staining. Erythema chronicum perstans may also show subtle interface dermatitis with pigment dropout but is distinguished from erythema ab igne by the clinical presentation and the absence of increased elastic fibers. A hypersensitivity reaction with interface changes may show some overlapping features, but the clinical history should prompt elastic tissue staining, differentiating the two entities.

RADIATION-INDUCED SKIN ALTERATIONS

Cutaneous alterations due to irradiation include acute and chronic radiation dermatitis, radiation recall dermatitis, and secondary cutaneous neoplasms. The inflammatory changes that occur in the skin after irradiation, or radiation dermatitis, occur as a result of biochemical changes on X-ray–penetrated cells without a detectable rise in temperature. The resultant injury is determined by the threshold radiation dose. This may occur at the portal of entry or exit. In addition to the dose of irradiation, host factors play a role in the development of radiation dermatitis, such as in ataxia telangiectasia homozygotes, which have up to threefold normal radiation sensitivity (33). Patients with underlying conditions such as connective tissue disease, diabetes mellitus, and hyperthyroid disease have been reported to have an exaggerated reaction to radiotherapy (34). Concomitant use of radiation sensitizers, such as doxorubicin and taxane antineoplastic agents, may predispose an individual to increased acute toxicity reactions to radiation (35). Cetuximab, an epidermal growth factor inhibitor that is often given concurrently with radiation therapy for advanced head and neck squamous cell carcinoma, may be associated with severe (grade 4) radiation dermatitis (36). In contrast, radiation-induced cancer is a stochastic effect, and thus the risk of developing a neoplasm is independent of the dose. Fluoroscopically guided procedures may cause radiation dermatitis in areas of skin not directly in the radiation port, usually the back (34). Radiation recall dermatitis refers to precipitation of an inflammatory reaction limited to a site of a quiescent radiation field induced by administration of medication. Other cutaneous consequences of irradiation include vitiligo (35), lichen planus (36), and bullous pemphigoid (37).

Acute, Subacute, and Chronic Radiation Dermatitis

Changes of acute radiation dermatitis may become apparent between 2 weeks and 3 months post procedure.

Erythema, desquamation, alopecia, xerosis, dyschromia, vascular compromise, and proliferation with telangiectasia, blistering, epidermal and dermal atrophy and necrosis, and ulceration may be seen in the acute phases. Phases of skin injury response have been outlined in detail, and criteria have been put forth by the National Cancer Institute (38). Grade 1 radiation dermatitis includes generalized erythema with dry desquamation. This may be accompanied by pruritus and dyspigmentation. This may be concentrated in the follicles, resulting in alopecia due to injury to the pilosebaceous glands. Grade 2 radiation dermatitis typically occurs in the skin folds after 4 to 5 weeks post treatment of doses 40 Gy or greater and

peaks at 1 to 2 weeks after the last treatment. There is persistent tender edematous erythema, which may progress to bullae or focal epidermal necrosis, with fibrinous exudates, termed moist desquamation. Superinfection may occur. In grade 3 there is more-extensive moist desquamation, extending beyond the folds. Grade 4 is characterized by ulceration, necrosis, and hemorrhage. Unresolved acute radiation results in chronic ulceration, fibrosis, and/or necrosis of the deeper structures, termed "consequential late" radiation dermatitis.

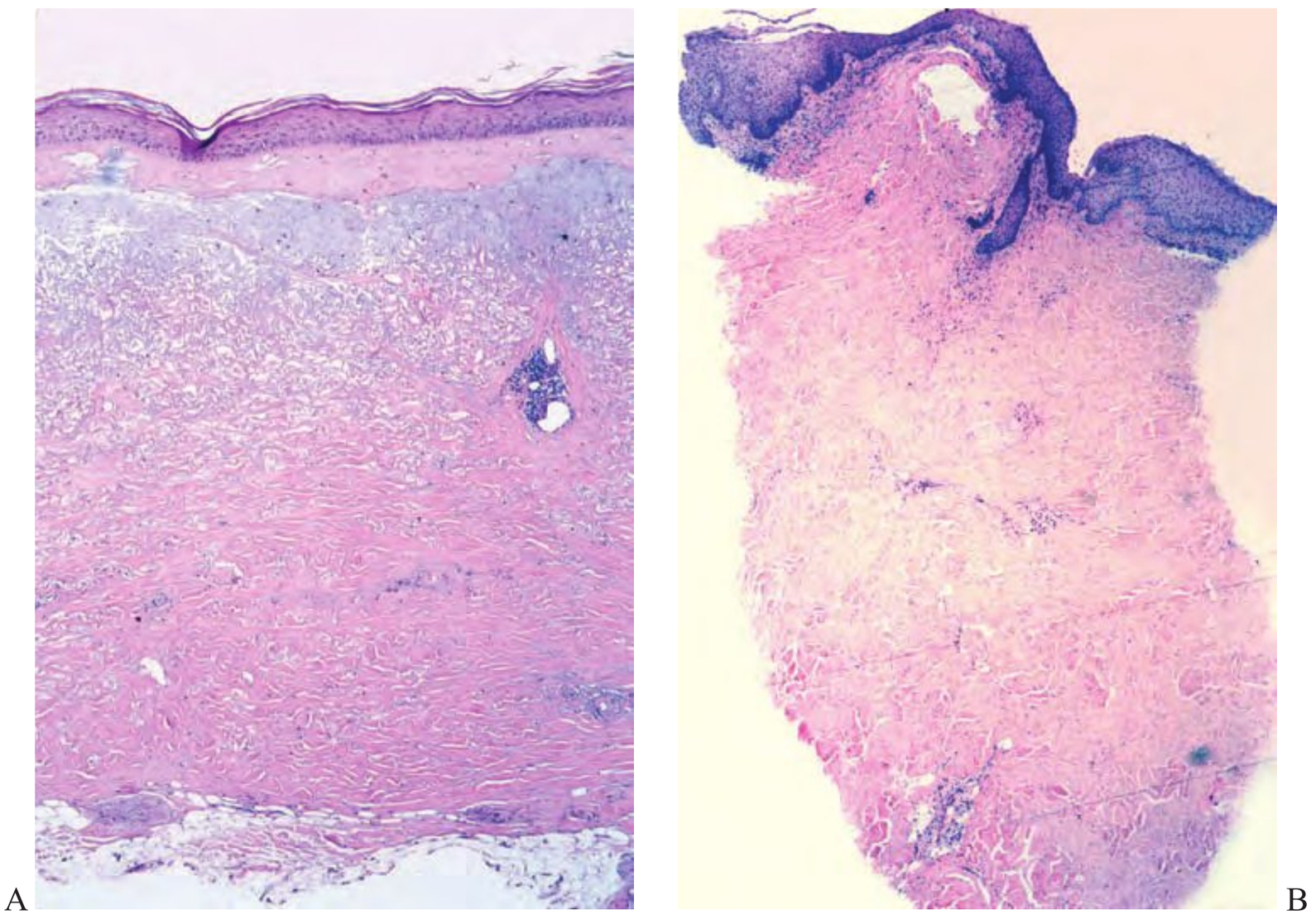
Changes of chronic radiation dermatitis are noted at 1 year post radiation but often represent progression of acute radiation dermatitis and thus may be evident earlier. Epidermal atrophy, xerosis, alopecia, anhidrosis, poikiloderma, hyperkeratosis, telangiectases, and fibrotic thickening of the dermis and subcutaneous tissue are seen. Late-onset dermal necrosis and changes of chronic radiation dermatitis with or without prior acute radiation may be seen years after the initial radiation. Nonhealing ulcers may be seen. Deep megavoltage radiation for noncutaneous malignancies may result in subcutaneous sclerosis that may extend into the underlying skeletal muscle (39).

Histopathology. Histopathologic changes of radiation dermatitis vary with the morphologic lesion biopsied (34).

Acute radiation dermatitis is characterized by scattered pyknotic keratinocytes and epidermal edema. Depending on the dose of radiation, epidermal necrosis with blister formation and sloughing of the epidermis (clinically referred to as "moist desquamation") may be seen. Hyperkeratosis is seen with dry desquamation. Dermal changes include dermal and endothelial cell edema, vasodilation, erythrocyte extravasation, and fibrin thrombi of vessels. Variable inflammation is noted throughout the dermis, with involvement of the epidermis. Acute necrotic changes similar to that seen in the epidermis also may occur in the adnexal epithelium, eventuating in absence of pilosebaceous structures. Complete destruction of eccrine glands is not common. In severe radiation injury, necrosis of the epidermis and dermis results in chronic ulceration.

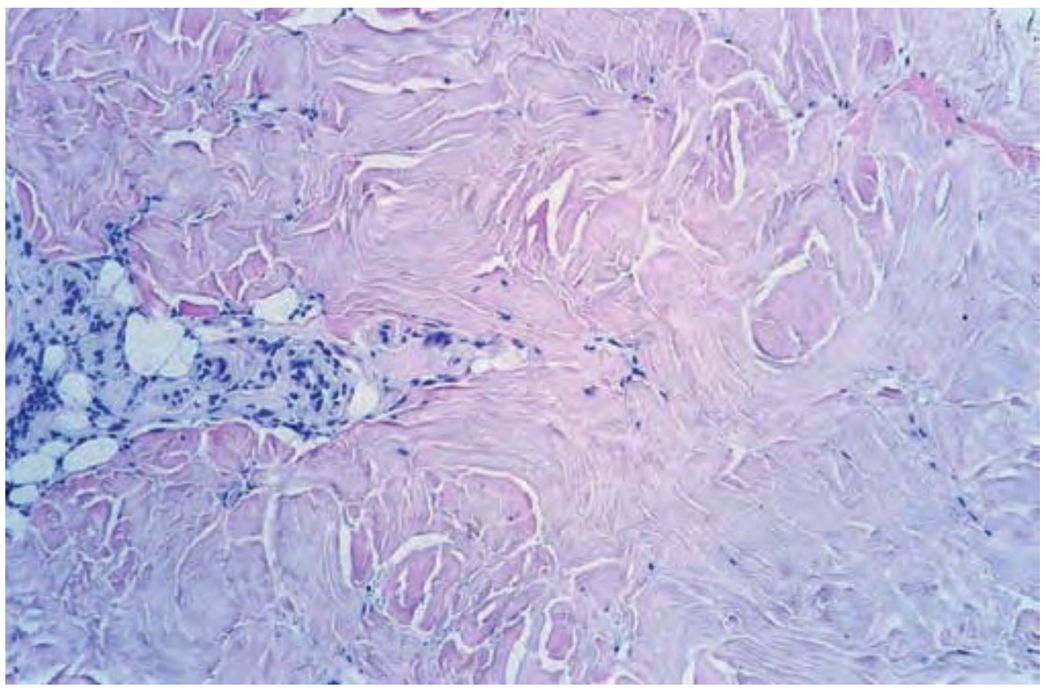
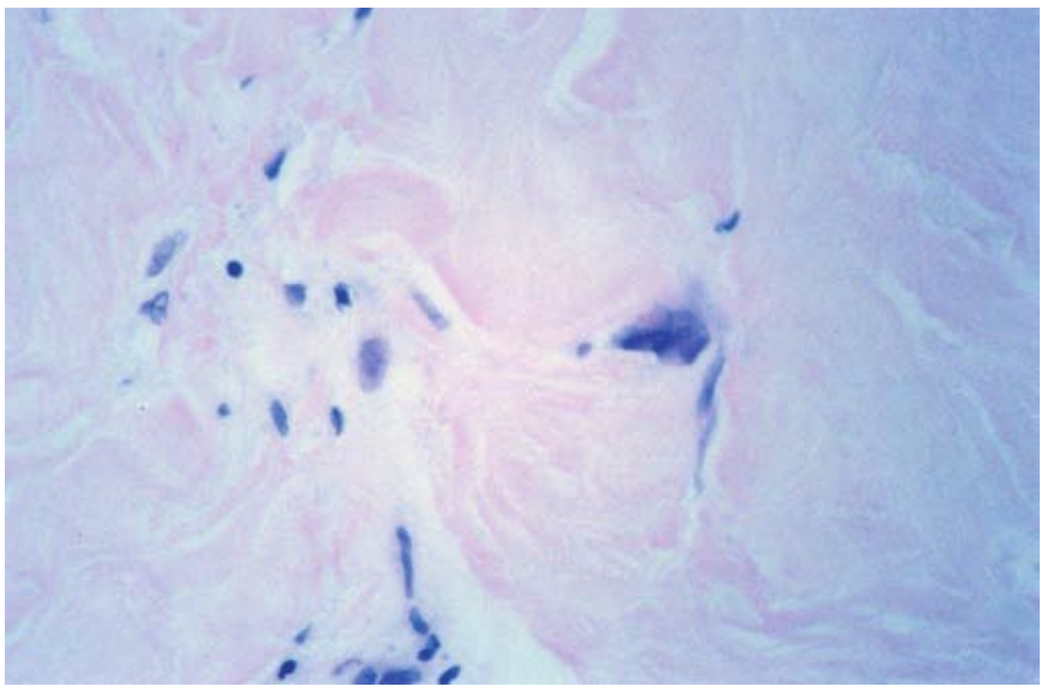
Late-stage or chronic radiation dermatitis is characterized by eosinophilic homogenized sclerosis of the dermal collagen, scattered large, bizarre, atypical "radiation fibroblasts," absence of pilosebaceous units, and vascular changes (Fig. 13-5) (40). The deep vessels show fibrous thickening, sometimes with luminal obliteration and recanalization, whereas superficially, telangiectases are prominent. The epidermal changes include atrophy, hyperkeratosis, and features of an interface reaction (Fig. 13-5). A maturation disorder with nuclear atypia and individual cell keratinization may be seen. Juxtaposed to atrophic areas may be epidermal hyperplasia that may extend downward and encase the telangiectatic vessels.

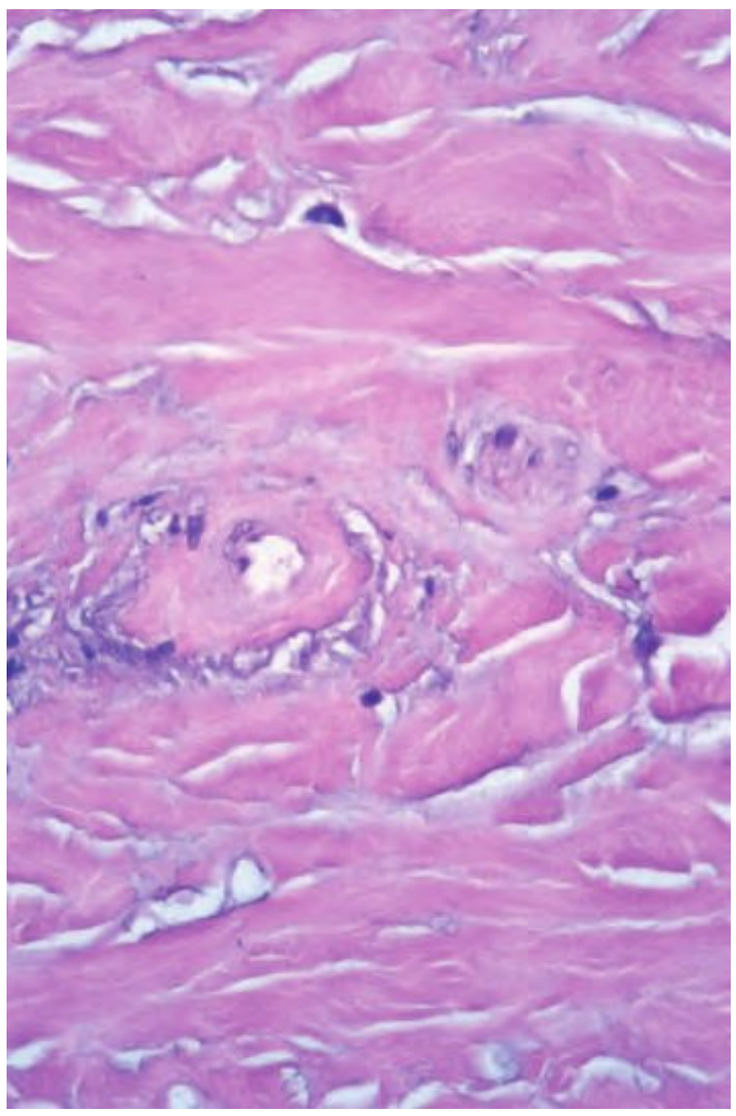
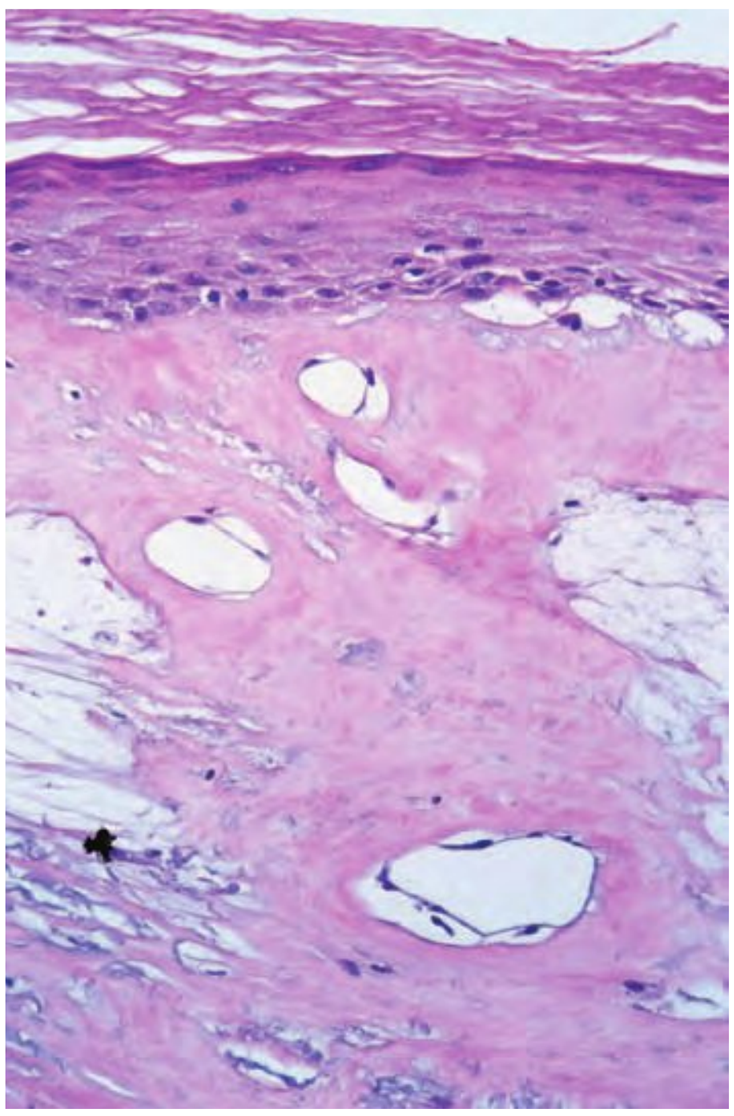
The origin of the radiation fibroblast is not known. Immunohistochemical studies have shown diffuse positive



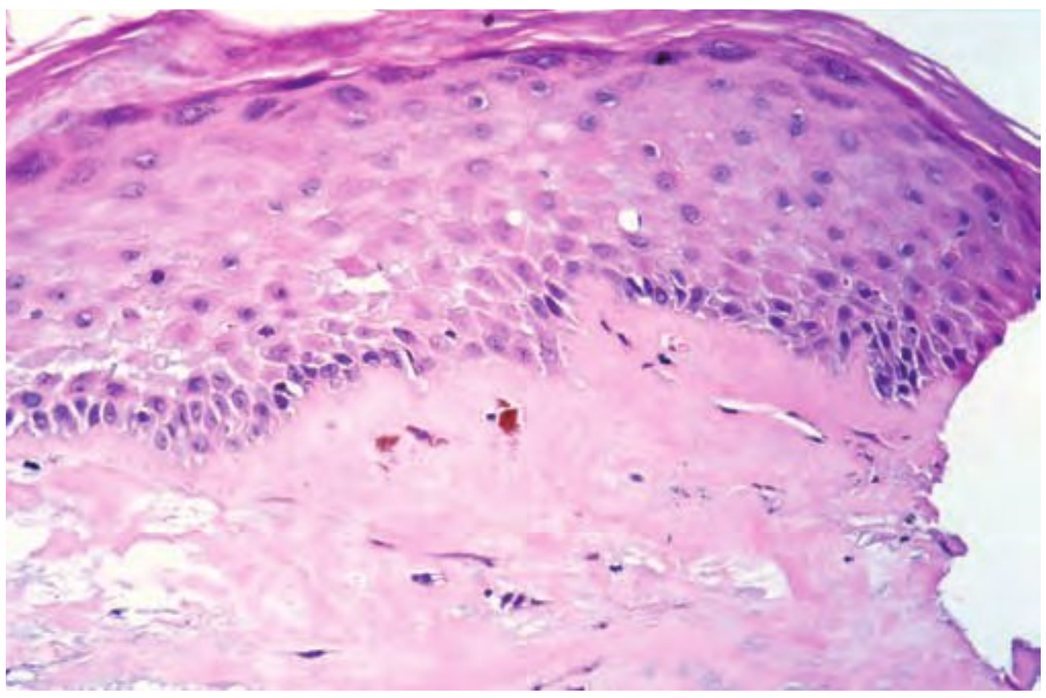
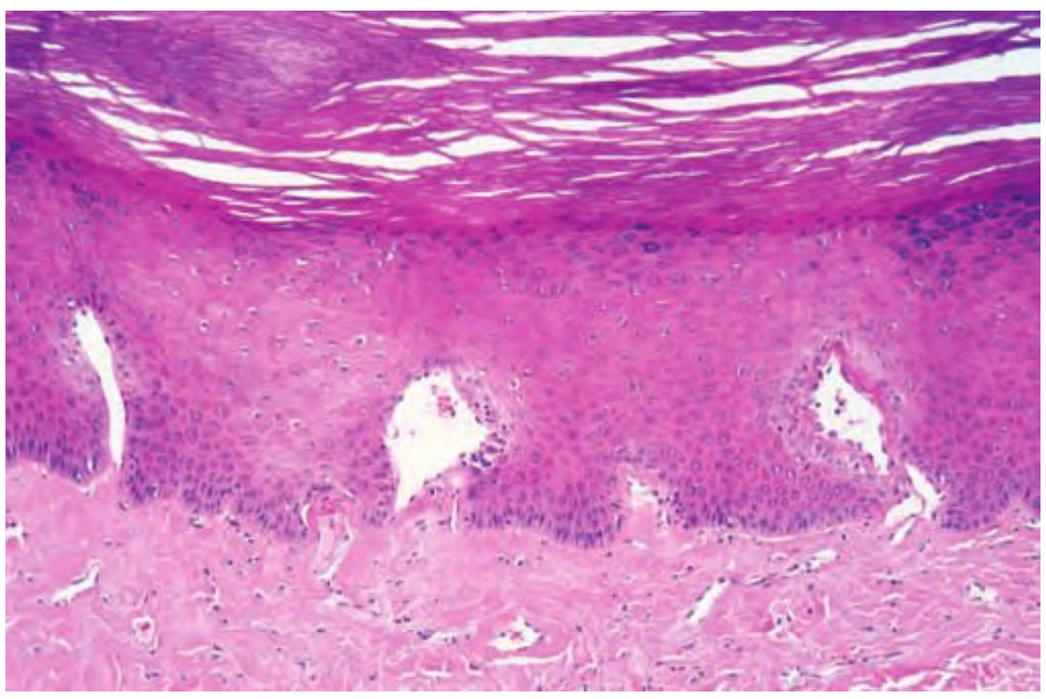
A B

FIGURE 13-5. Late-stage radiation injury. A: This biopsy shows features of chronic radiation dermatitis, including epidermal atrophy, pandermal collagen sclerosis with mild lymphocytic inflammation, and absence of hair follicles. B: A rectangular, "squared-off" silhouette due to the sclerotic collagen alteration. This biopsy also demonstrates the variation of epidermal atrophy and hyperplasia that can be seen in radiation dermatitis. (continued)

C   D

E F

G H

FIGURE 13-5. Continued. C: There is sclerotic collagen bundle thickening, with compression of eccrine glands. Preservation of eccrine glands differentiates this from a burn scar. D: Large, bizarre and atypical radiation fibroblasts amid the thickened collagen bundles differentiate radiation dermatitis from morphea and third-degree burn scars. These are sparsely scattered, in contrast to atypical cells of a sarcoma. E: Sclerosis of endothelial cells is seen amid thickened sclerotic collagen bundles. F: There is telangiectasia of the upper dermal vessels, with epidermal atrophy and sclerosis of papillary dermal collagen. G: The epidermis shows features of interface dermatitis, with liquefaction of the basal layer, rete effacement, and pigment dropout. H: The epidermis may show hyperplasia, incorporating the underlying telangiectatic vessels between the rete.

cytoplasmic staining of the radiation fibroblasts with antibody to factor XIIIa, with only focal staining with antibody to CD34 in some cells (41). However, others have not demonstrated as consistent factor XIIIa staining. The cells are negative for HHF-35 (muscle-specific actin), and Ki-67, and P53 (42).

Subacute radiodermatitis applies to the phase of radiation injury in which there are overlapping features of acute and chronic radiation dermatitis. The histology is that of interface dermatitis, with basal vacuolization and keratinocyte necrosis (Fig. 13-6) (43). The presence of satellite cell necrosis, characterized by close apposition of necrotic keratinocytes and $CD8^+$ TIA-1 positive T lymphocytes, suggests that cytotoxic lymphocyte-mediated apoptosis is involved in the pathogenesis of subacute radiation dermatitis. (44).

Radiation-induced malignancies include squamous cell carcinomas and basal cell carcinomas predominantly (45), and these often occur in the background of chronic radiation dermatitis. The squamous cell carcinomas display aggressive, metastasizing behavior and include spindled variants. True radiation-induced sarcoma malignancies are less common and usually arise in heavily irradiated tissue with a latent period of 3 to 24 years. These include malignant fibrous histiocytoma, fibrosarcoma, osteosarcoma, liposarcoma, chondrosarcoma, and sarcomas of pluripotential mesenchymal cell derivation (46). Desmoplastic cutaneous leiomyosarcoma has also been reported (47). Mesenchymal sarcomas frequently occur on the chest wall after irradiation for breast carcinoma or Hodgkin's disease (48). Angiosarcomas, including spindled cell variants, may be seen at

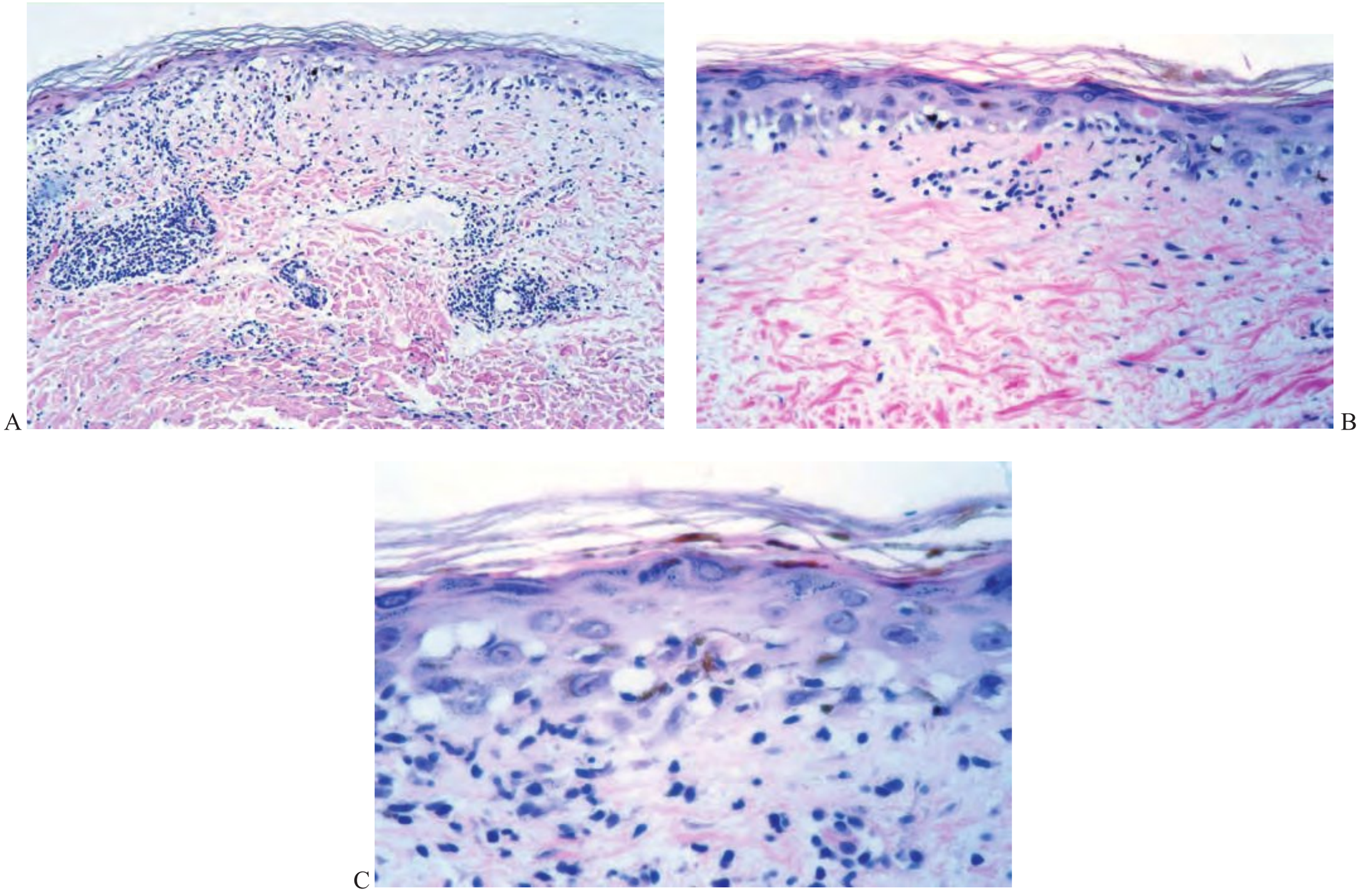


FIGURE 13-6. Subacute radiation dermatitis. A: In subacute radiation dermatitis, there is an inflammatory infiltrate involving the epidermis, papillary dermis, and vessels, without sclerotic collagen alteration. The epidermis is atrophic due to interface dermatitis. B: The interface dermatitis of subacute radiation dermatitis is indistinguishable from those of some other causes of interface dermatitis, such as fixed drug eruption and graft-versus-host disease, requiring clinical information to differentiate these entities. Lymphocytes disrupt the basal cell layer and are associated with vacuolization of the basal keratinocytes, dyskeratotic keratinocytes, and pigment dropout. Note that the collagen is nonsclerotic and the fibroblasts are nonatypical, in contrast to that in Fig. 13-4 B, C, which represent a later stage of this process. C: Satellite cell necrosis, or close approximation of lymphocytes with apoptotic keratinocytes, is seen in subacute radiation dermatitis, as well as in graft-versus-host disease and other cytotoxic dermatoses.

sites of prior irradiation, usually in conjunction with lymphedematous changes (49). Adjacent changes of chronic radiation dermatitis may be seen but are not always present.

Differential Diagnosis. Subacute radiation dermatitis may be indistinguishable from graft-versus-host disease and fixed drug eruption (50, 51). The latter is particularly difficult to differentiate from subacute radiation dermatitis in fluoroscopy-induced cases because the changes often do not occur at the irradiation portal site, and thus the clinician may be unaware of the association with radiation injury. Various hypersensitivity reactions may initially localize at a previous radiation port, simulating acute radiation dermatitis. This includes conditions with overlapping histology, such as erythema multiforme and toxic epidermolysis necrosis, which should be differentiated by the clinical progression of the condition. Morphea/scleroderma is favored over chronic radiation dermatitis by the absence of radiation fibroblasts. Lichen sclerosis may show similar telangiectasia and interface alteration, and there can be similarity in the papillary dermal pallor and homogenization, but the presence of deeper, thickened eosinophilic collagen bundles with radiation fibroblasts favor radiation changes. Clinical correlation may be confirmatory. Deep burn scars show complete absence of all adnexal structures without abnormal fibroblasts, in contrast to radiation sclerosis, in which the eccrine glands are often preserved. Radiation sarcomas should be differentiated from spindled squamous cell carcinoma by immunohistochemical staining (see Chapter 32).

Radiation Recall Dermatitis

Radiation recall dermatitis refers to the development of an acute inflammatory reaction occurring at the sight of a previously quiescent radiation field after infusion or intake of certain medications. This phenomenon has been extensively reviewed (52,53). Typical medications implicated include chemotherapeutic agents, especially the taxane family, methotrexate, and high-dose interferon-α 2b (54), but it has also been reported with antituberculous medication, antibiotics, simvastatin, codeine, and lanreotide, a somatostatin analog (55). It may occur from days to weeks, and sometimes years, after radiation therapy, with an interval ranging from 18 hours to 15 years (median of 40 days) (56). Acute toxicity need not have occurred with the initial radiation. Clinically, there is typically a pruritic macular papular erythematous eruption, which may blister or desquamate. A more severe reaction may occur, especially if the offending drug is given a short interval after the radiation, and may be associated with pain and necrosis. The dermatitis may simulate cellulitis, and rarely fever may be seen. (56). Extracutaneous recall reactions may involve the lung, esophagus, small intestine, musculoskeletal system, mucosa, and central nervous system. There may not be a reaction at all of the previously treated radiation sites. The exact pathophysiology of the reaction is unknown. Radiation recall reactions should be differentiated from radiosensitivity and radiation enhancement, which represents a reaction induced by drugs given less than 7 to 10 days after radiotherapy (52).

Histopathology. The histopathologic features of radiation recall are not well documented, are nonspecific, and depend on the clinical severity. The histology shows overlap with acute radiation dermatitis. Other features described include psoriasiform epidermal hyperplasia, follicular hyperkeratosis, pustules, basal cell vacuolization, and apoptotic or necrotic keratinocytes (57). Bulla formation due to prominent interface dermatitis may also be observed (58). Dermal changes include vascular dilation, endothelial cell atypia, and a perivascular and interstitial mononuclear or mixed inflammatory infiltrate. There are also features that may reflect an element of prior chronic radiation dermatitis, including fibrosis and radiation fibroblasts.

COLD INJURY TO THE SKIN

Direct injury to the skin due to extremes in cold temperatures can be seen in frostbite and nonfreezing cold injury. In the latter, there is injury above the freezing point associated with wet, immobile, venous stagnation conditions, such as trench foot. Both types of cold injury have a similar pathogenesis, which includes cyclic massive vasoconstriction and excessive vasodilation, endothelial cell leakage, erythestasis, arteriovenous shunting, segmental vascular necrosis—possibly due to decreased clearance of toxic substances—and massive thrombosis (59).

Frostbite

Frostbite is typically seen on acral sites and results from tissue freezing. An increased susceptibility is seen in patients with alcohol consumption, those who wear constrictive clothing, or those with peripheral vascular disease, in smokers, and in individuals exposed to windy conditions. Frostbite can be categorized based on the depth of injury. First-degree frostbite is characterized by erythema and edema after thawing that does not blister and subsides within several days. In second-degree frostbite, there is blister formation within the first 1 to 2 days after rewarming. This is followed by necrotic eschar formation and eventual autoamputation of the affected area. In third-degree frostbite, the entire dermis is edematous and may remain so for 1 month or more (1).

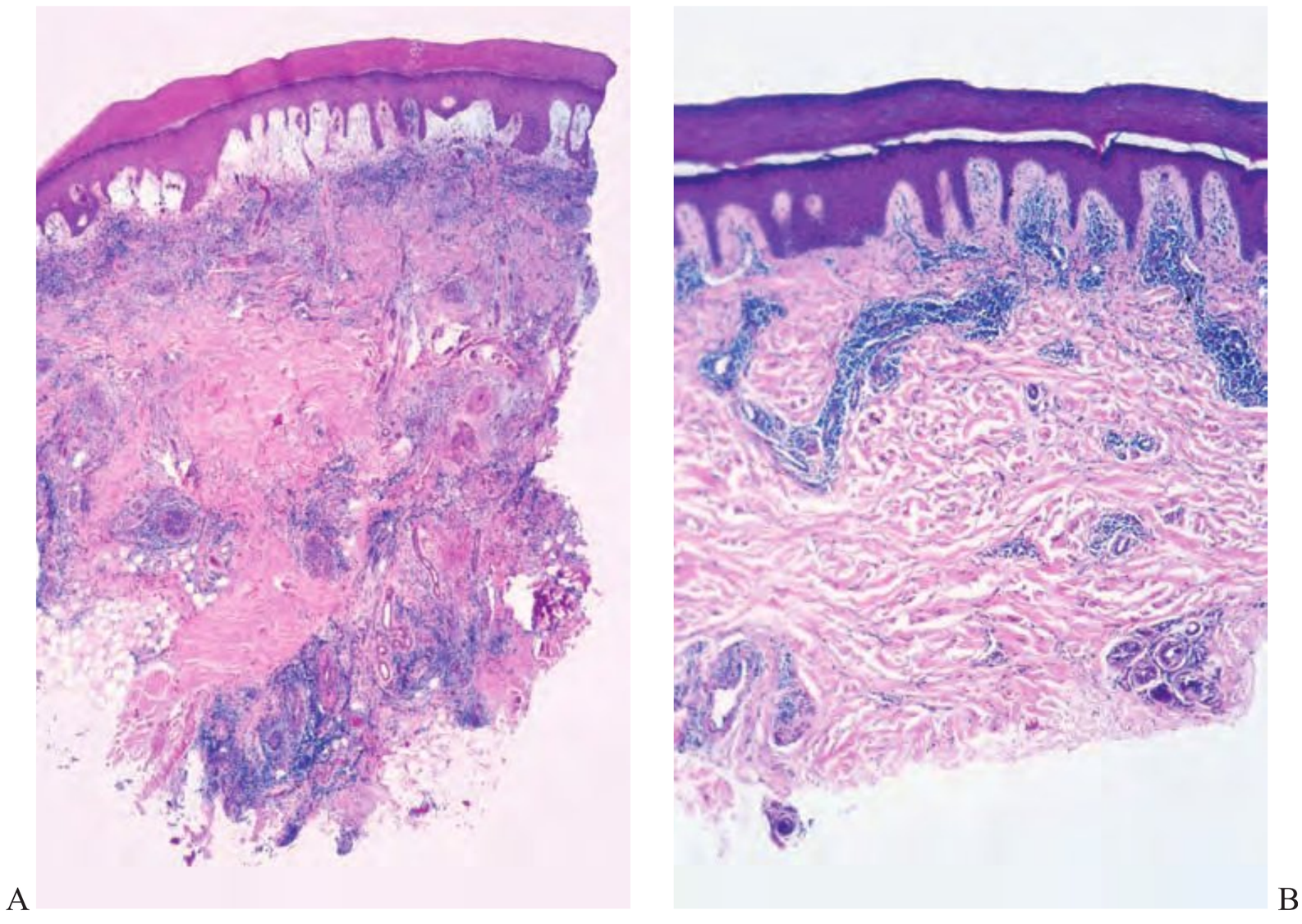
Pernio (Chilblain)

Pernio (chilblain) is a distinct form of cold-induced injury in which humidity, in addition to cold, plays a role in inducing the condition (60). There are acute and chronic presentations. Chilblains classically presents in young to middle-aged women as painful, burning, and/or pruritic erythematous to violaceous or cyanotic macules, papules, deep nodules, and plaques on the fingers, toes, distal extremities, and rarely face. Involvement of the thighs has been described in association with river crossings (60). The acute form is more common in young women. Lesions are noted within 12 to 14 hours of exposure in the acute form and persist for 10 to 14 days. The lesions may become hemorrhagic, bullous, or ulcerated, but they tend to be self-limited. The

chronic form has overlapping features with acute pernio but occurs in middle-age women and, with repeated winter recurrences, may result in slow-to-heal ulcers and scarring. A genetic predisposition has been implied, as well as a history of peripheral vascular disease (60). A childhood variant has been described and is associated with cryoproteins (62).

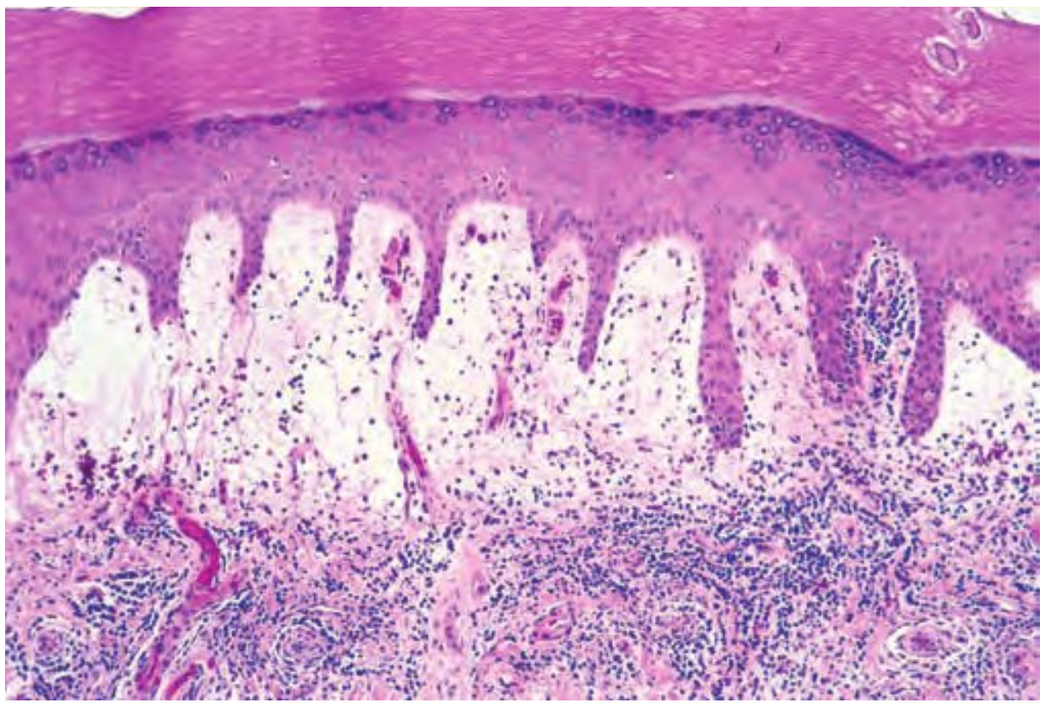
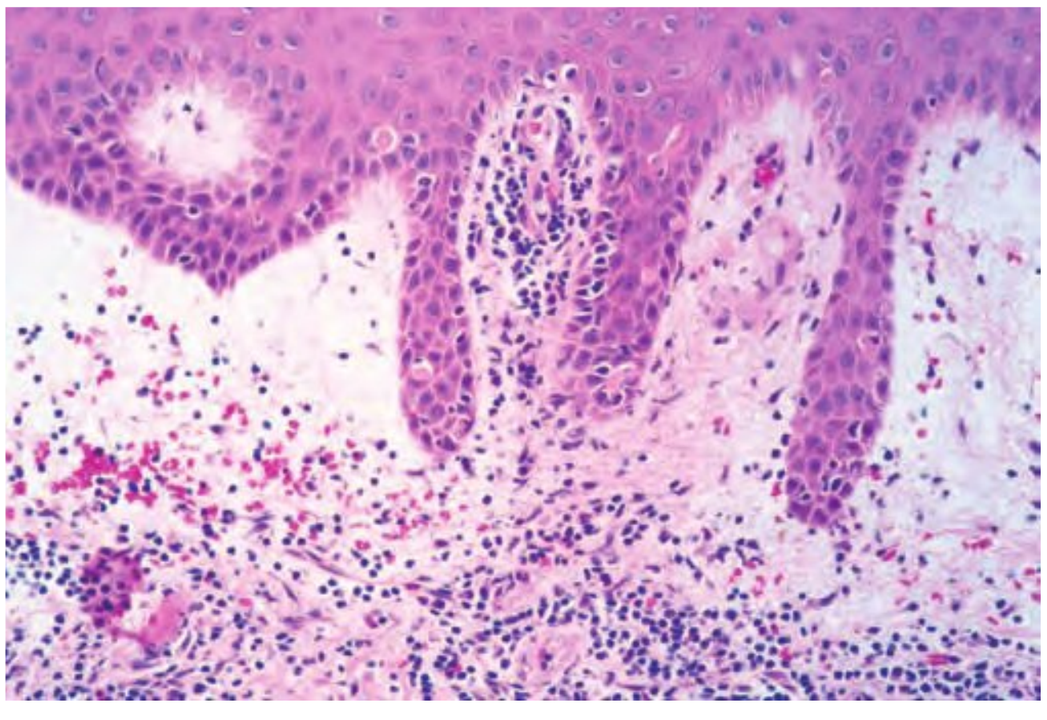
Pernio may arise in conjunction with histopathologic, clinical, and serologic features of lupus and is referred to as chilblain lupus erythematosus or lupus pernio (63–68). This may also arise in patients with chronic cutaneous or discoid lupus. Clinically, with the exception of rare verrucous lesions (69), these lesions look similar to idiopathic pernio. The main difference from idiopathic chilblains is that the lesions last for more than 1 month and persist into the hot season, and there is a very strong female predominance (68). These lesions may also arise on nondistal acral sites, such as the knees and elbows. Many of these patients have full-blown systemic lupus erythematosus (SLE), including renal disease and cerebritis; however, other patients with similar persistent chilblains lesions develop SLE in the future. Chilblains lupus may also be associated with Behçet's disease, hypergammaglobulinemia, and type III cryoglobulinemia. Many patients with chilblains lupus have antibodies to SSA/Ro, with associated Raynaud's phenomenon and photosensitivity (66,68); however, others have not found this tight association (70). Patients with chilblain lupus erythematosus may present without overt lupus but are at risk of progressing to systemic lupus erythematosus from 1 to 10 years or so later (66). Rarely, chilblain-like lesions may be seen with leukemia cutis (71) and chronic cocaine use (72).

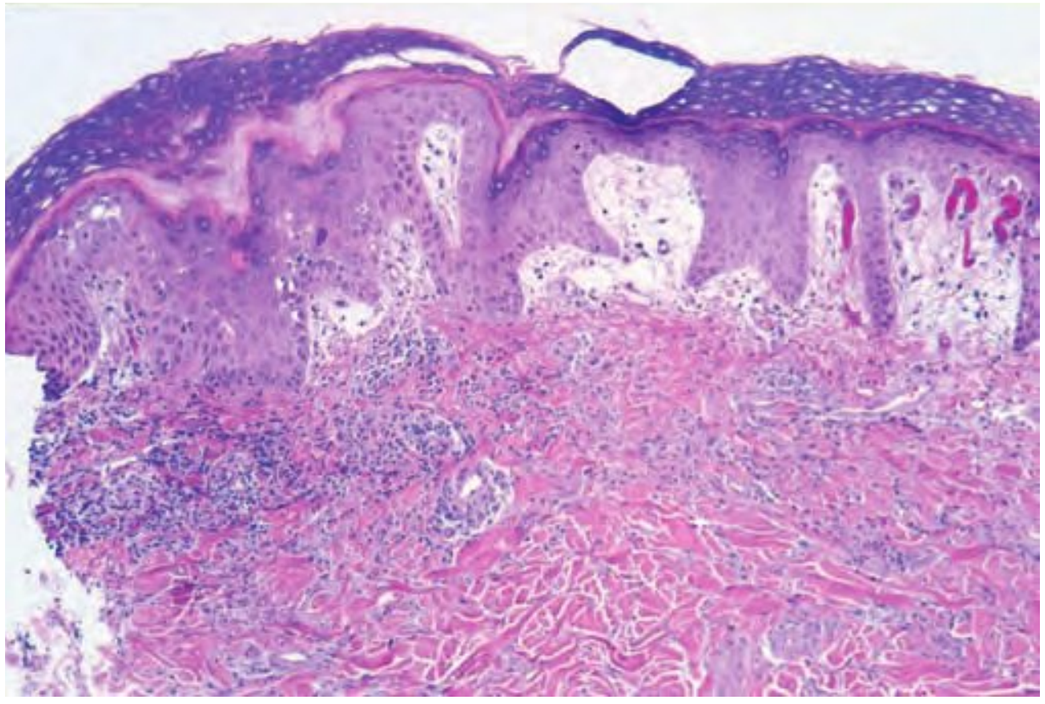
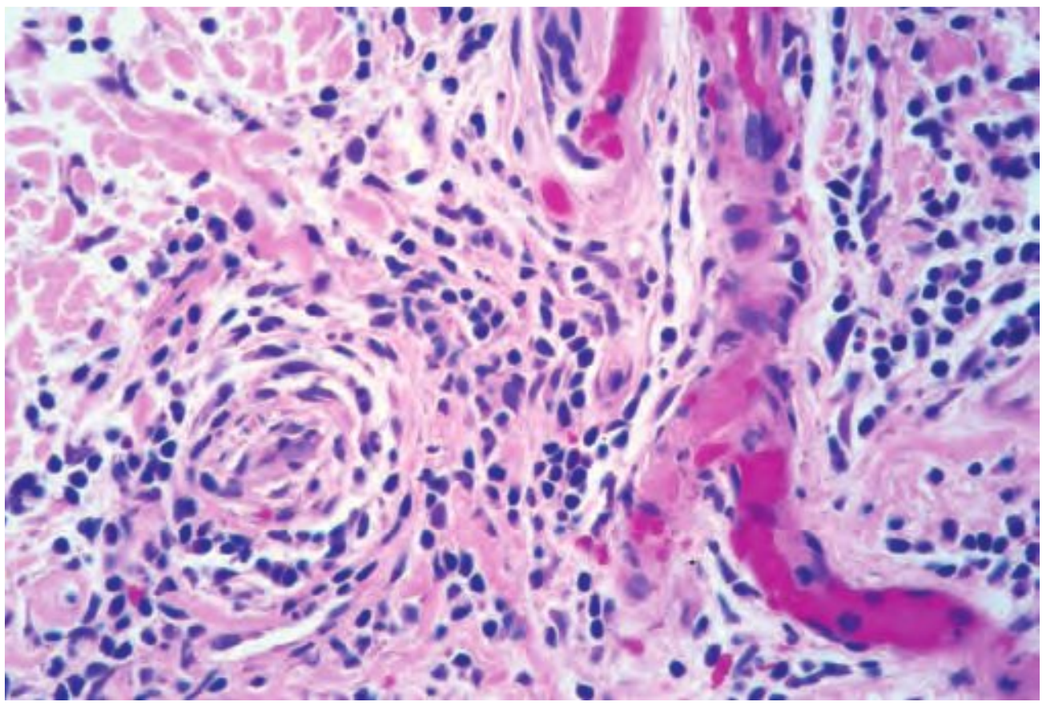
Histopathology. There is a superficial and deep T-lymphocytic infiltrate around the small venules and arterioles in the dermis and subcutis, with accentuation around the deep eccrine coils (Fig. 13-7). The interstitium may also be prominently involved in the superficial dermis. The infiltrate tends to be of moderate intensity but may be dense. The most superficial vessels of the papillary dermis are less involved by the infiltrate but may show congestion. Papillary dermal edema is characteristic, and although it may be quite striking, its presence is variable. A superficial variant exists, lacking involvement of the deeper portions of the tissue but showing papillary dermal edema. Lymphocytic vasculitis, characterized by endothelial cell swelling and edema and infiltration of the vessel walls by lymphocytes, without consistent presence of fibrinoid necrosis is seen (Fig. 13-7) (60). The epidermal changes range from scattered necrotic keratinocytes to epidermal pallor or necrosis. An effacing interface dermatitis is not typically seen in idiopathic pernio. In chilblain lupus erythematosus (lupus pernio), there are dermal changes similar to pernio, but in addition there is an interface dermatitis of lupus, and a positive lupus band test may be seen. Although it may not be possible reliably to distinguish chilblains lupus from idiopathic lupus, one study showed a more prominent perisudoral infiltrate in the latter. An interface dermatitis typical of lupus is not always present (68).



A B

FIGURE 13-7. Pernio (chilblain). A: A superficial and deep perivascular and perieccrine lymphocytic infiltrate involving acral skin with striking papillary dermal edema typifies perniosis. B: Although papillary dermal edema is characteristic, some cases of pernio may lack this feature. The deep perieccrine infiltrate helps to differentiate this from conditions such as erythema multiforme, which may show some similar features. (continued)

C  D 

E  F 

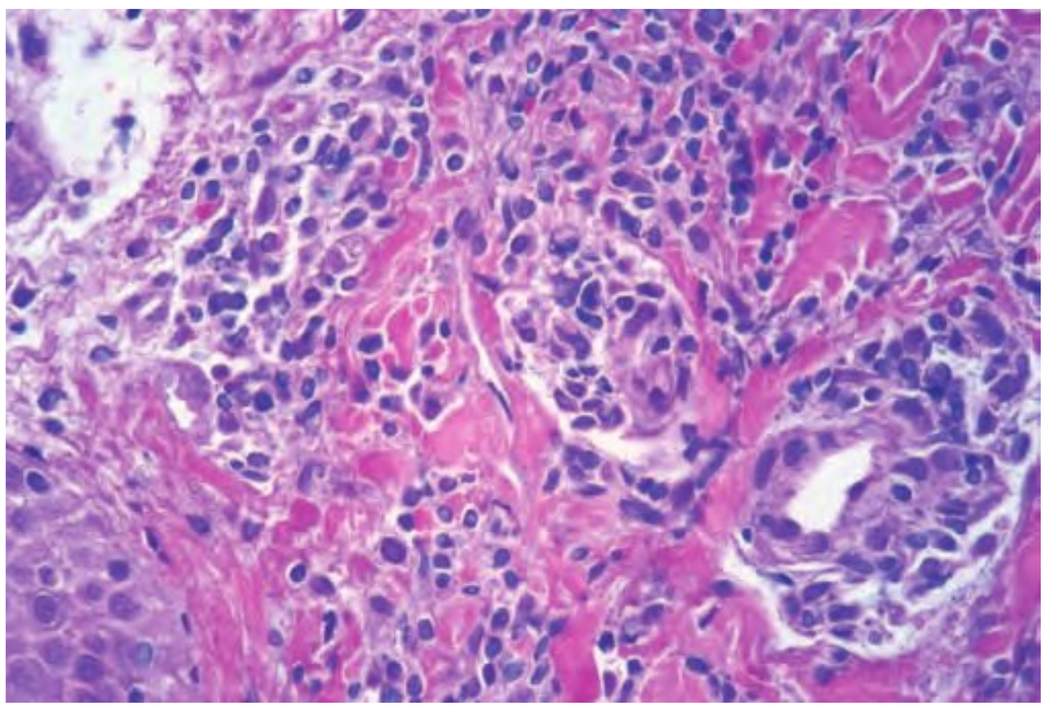
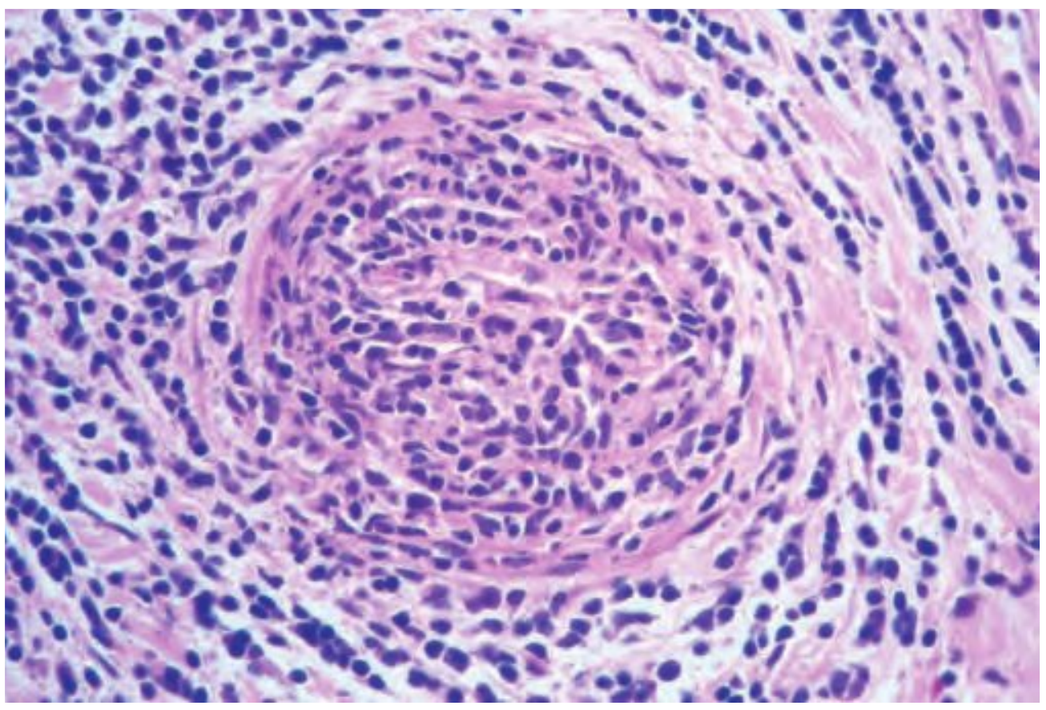
G  H 

FIGURE 13-7. Continued. C: Striking dermal edema may result in incipient dermolytic bulla formation. D: Involvement of the dermal papillary vessels may be minimal. Dyskeratosis may be present, but a frank interface reaction is not seen. If present, lupus or chilblain lupus should be considered. E: The degree of papillary dermal edema may vary. Lymphocytes may be interstitial to bandlike, in addition to perivascular. Prominent vascular congestion is seen in the dermal papilla. F: Various degrees of vascular damage may be seen. Here there is congestion and vasoocclusion with early necrosis of one small venule. In a nearby vessel, there is infiltration of the vessel wall, consistent with the lymphocytic vasculitis of pernio. G: In pernio, the endothelial cells are often swollen and show infiltration by lymphocytes, without evidence of necrotizing vasculitis. H: Medium-sized vessels may occasionally be infiltrated by lymphocytes. A granulomatous, neutrophilic, or eosinophilic component is not seen, differentiating pernio from other known causes of medium-size–vessel vasculitis.

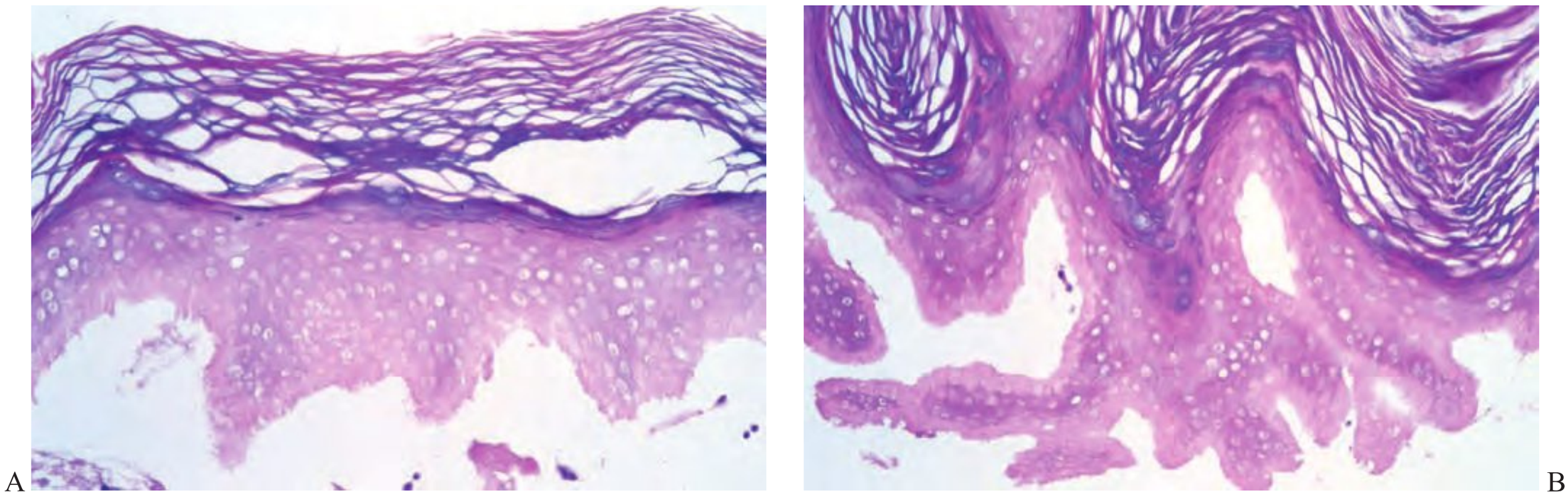


FIGURE 13-8. Cryotherapy-induced cold injury. A: There is pallor of the epidermal keratinocytes, with loss of the cellular outline. B: The cold injury has resulted in a subepidermal bulla. In cryotherapy of this seborrheic keratosis, there has been preservation of the stratum corneum architecture, probably due to the devitalized nature of this portion of the epidermis, whereas the remaining tissue shows homogenization of the epithelium, with dissociation of the epithelium from the dermis in a subepidermal fashion.

Differential Diagnosis. Pernio may be difficult to differentiate from lupus erythematosus. The presence of prominent dermal edema, eccrine coil accentuation of the infiltrate, and spongiosis favor pernio over lupus (65). Diagnostic criteria have been proposed to differentiate chilblain lupus erythematosus from idiopathic chilblains (67). The papular form of chilblains may be difficult to differentiate from erythema multiforme, and it may require clinical history to differentiate the two (73). The deep inflammatory component of pernio differentiates it from acral lesions of erythema multiforme. Polymorphous light eruption, dermal hypersensitivity, erythema annulare centrifugum, and lymphocytic infiltrate of Jessner can show a similar pattern of perivascular lymphocytic infiltrate. The presence of lymphocytic vasculitis and the clinical history of cold-induced acral lesions favor pernio. Other clinical and histologic mimickers of pernio including lesions of rheumatoid arthritis, cryofibrinogenemia, and antiphospholipid syndrome, and others lack the papillary dermal edema of pernio (74). Occasionally, the lymphocytic infiltrate may be so intense as to simulate cutaneous lymphoma, but the absence of atypia and presence of superficial dermal edema favor pernio. If there is cellular atypia, immunohistochemical investigations to exclude leukemia or lymphoma should be pursued.

Cryotherapy-Induced Injury

Cryotherapy is a commonly used tool to destroy benign and premalignant or, on occasion, malignant cutaneous lesions. This procedure may also be employed prior to curettage of keratoses. The dermatopathologist may encounter freeze-related changes in this latter circumstance. Rapid freezing with liquid nitrogen results in the production of highly destructive intracellular ice crystals (5). The extent of injury is determined, in part, by the thickness of the stratum corneum, the length of exposure to the liquid nitrogen, and the degree of pressure applied (75). Cell types differ in their susceptibility to cold injury. The hypopigmentation seen with cryotherapy reflects the susceptibility of melanocytes to this form of injury.

Histopathology. The microscopic features may differ, depending on the interval between cryotherapy and biopsy. Typically in rapid-freeze injury, the keratinocytes show a loss of cell outline, with ghostlike changes or homogenization of the epidermis (Fig. 13-8). This is associated with subepidermal–dermal bulla formation and subepidermal edema. The stratum corneum, being a devitalized structure, is not affected, and thus there is preservation of parakeratosis (75). There may be loss of melanocytes or pigment at the site of a prior cryotherapy site, with melanocytic hyperplasia or pigment dropout in the adjacent skin (5). With more intense cryotherapy, coagulation rather than edema is seen in the dermis. This may result in coagulation necrosis of hair follicles and possibly eccrine glands, and scar formation of the surrounding collagen. A polymorphous infiltrate, which includes eosinophils, has been described (76). Hemorrhage and thrombosis may be seen in the dermal papilla.

CUTANEOUS INJURY DUE TO PHYSICAL TRAUMA

Friction-Induced Blister

Prominent or repetitive shear-induced injury, especially on acral skin, such as the hands and feet, results in bulla formation. This may or may not be accompanied by hemorrhage.

Histopathology. A friction blister has an intraepidermal plane of separation, often beneath the stratum granulosum, in the upper portions of the epidermis (Fig. 13-9). The surrounding

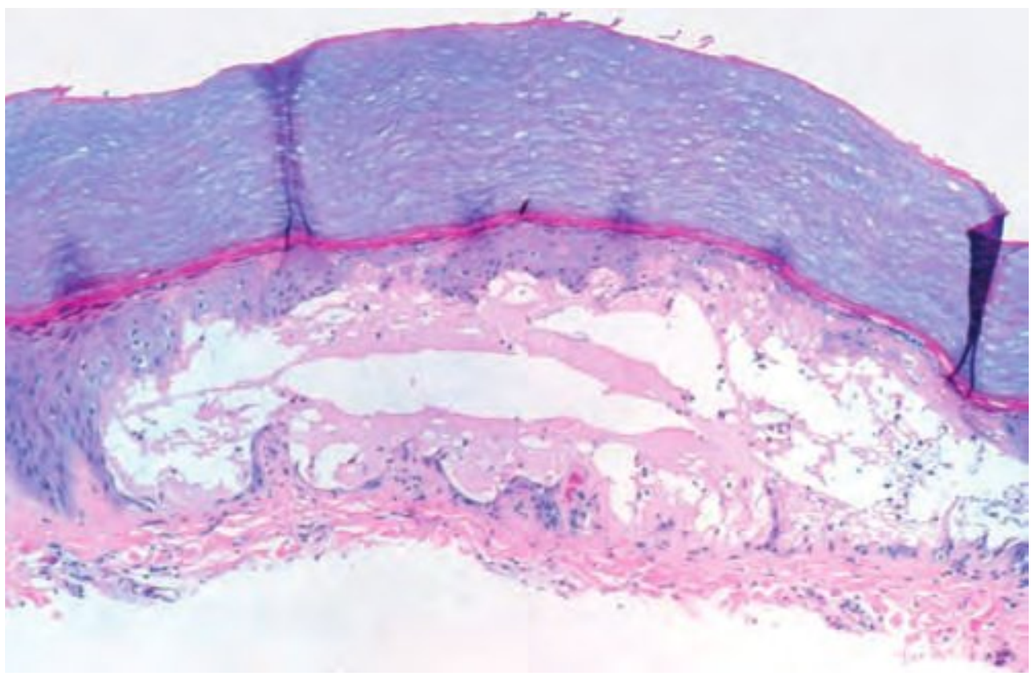


FIGURE 13-9. Friction blister. In friction blisters, one sees a noninflammatory intraepidermal blister, with pallor of the surrounding epidermis. The keratinocytes may show reticular degeneration or other sequelae of cytolysis or shearing.

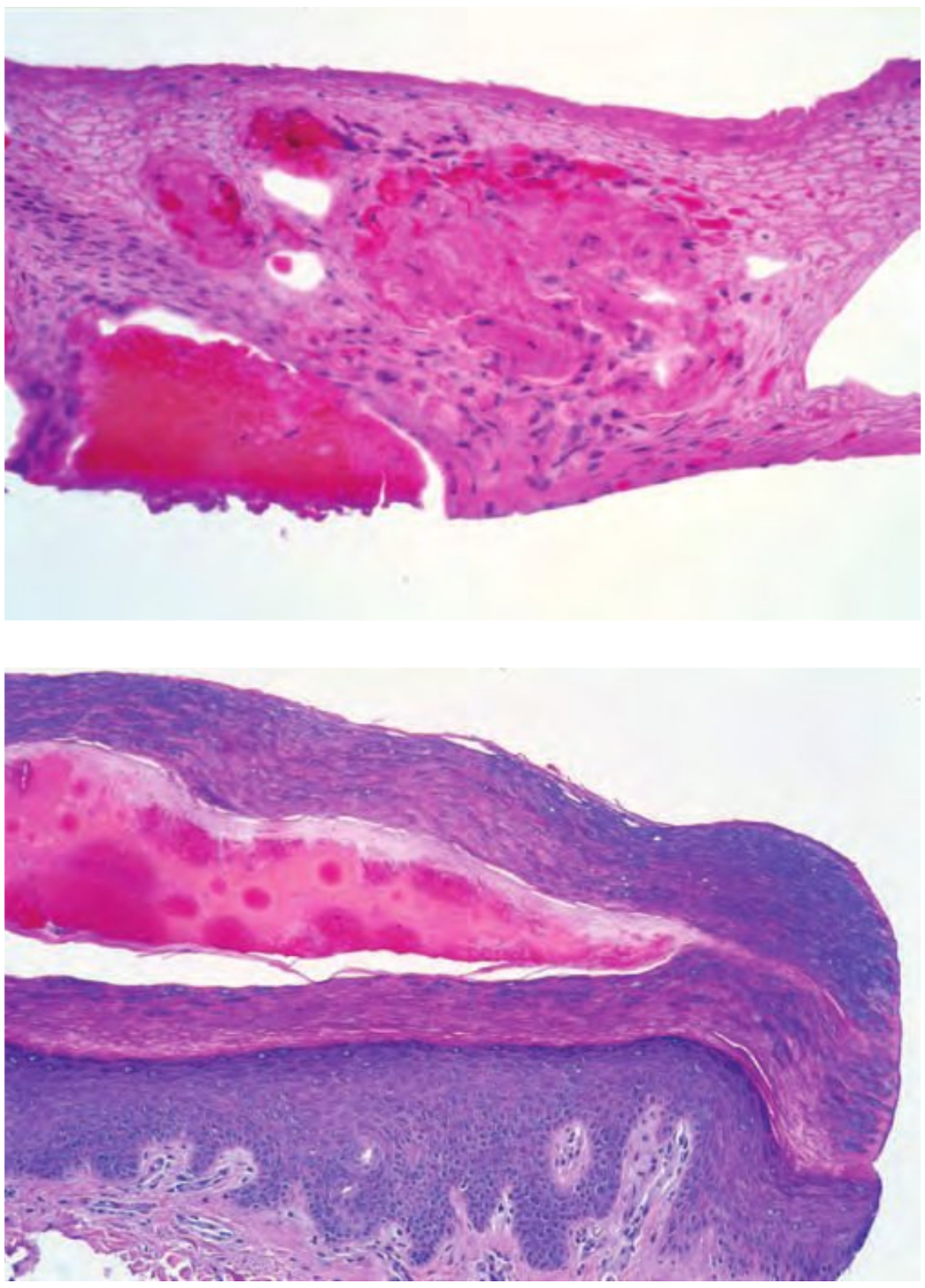
keratinocytes show pallor and loss of the cell outline. The edge of the blister cavity shows a jagged outline. The dermis does not show significant alteration or inflammation.

Differential Diagnosis. Other causes of paucicellular blister should be differentiated from friction blisters. Suction blisters and porphyria cutanea tarda have their plane of separation in a subepidermal location. Epidermolysis bullosa and epidermolysis bullosa acquisita may be acrally located but show a subepidermal bulla and characteristic electron microscopic and immunofluorescence features, respectively (see Chapter 9). Although diabetic bullae are also acral-located noninflammatory blisters and may have a partially intraepidermal plane, they tend to show a more prominently subepidermal split, without cytolytic keratinocytic changes.

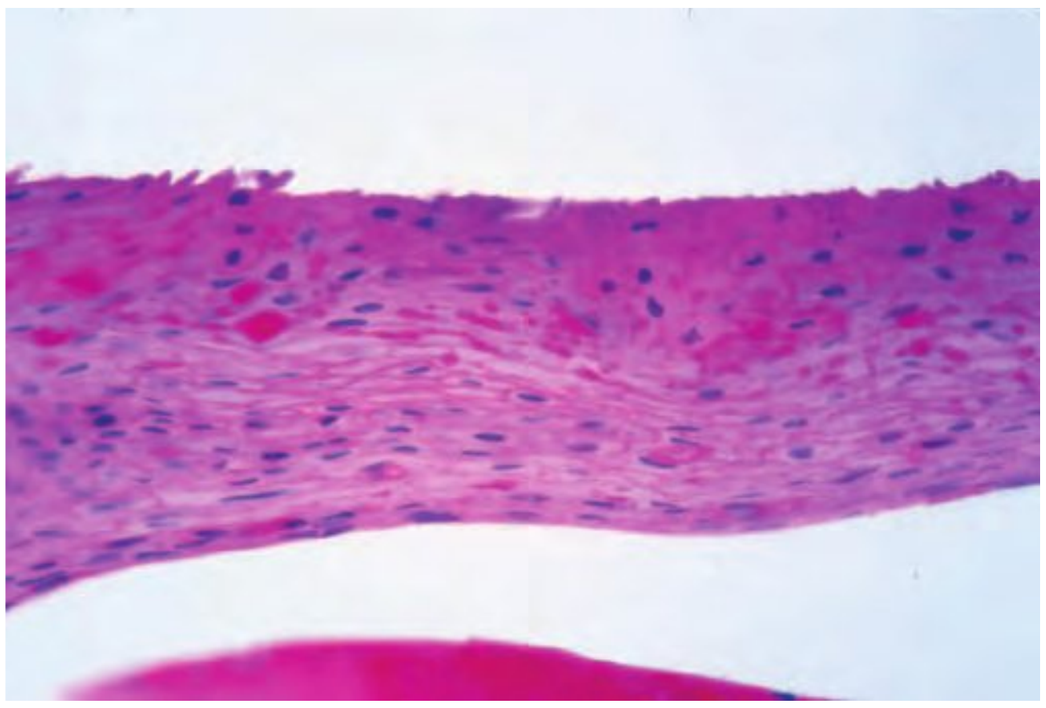
Talon Noir (Black Heel, Calcaneal Petechiae)

Talon noir typically presents as an irregular black macule on thickly keratinized acral sites, such as the heels and toes. These are often biopsied to exclude acral melanoma. Talon noir often occurs in association with athletic activity and results from shearing forces that lead to stratum corneal hemorrhage (77).

Histopathology. Often, only the stratum corneum is sampled and shows erythrocytes within layers of a thickened orthokeratotic stratum corneum (Fig. 13-10). Frequently there is parakeratosis. There may be associated serosanguinous fluid, with superficial blister formation. When dermis is incorporated in the biopsy, erythrocytes may be seen in the dermal papillae and epidermis. Iron staining does not highlight this process.



A



B

C

FIGURE 13-10. Talon noir (calcaneal petechiae). A: Talon noir occurs on acral skin due to shearing or rubbing trauma, and thus one sees a hyperkeratotic stratum corneum, often accompanied by parakeratosis. Often, only portions of the stratum corneum are sampled. The hemorrhage can be identified as loculated erythrocytes and serosanguinous fluid or as small collections of intracorneal erythrocytes, some of which show degeneration. B: The hemorrhage may present as solitary intact or degenerating erythrocytes within the corneal layers. Hemosiderin will not be apparent on hematoxylin or iron staining. C: There may be features of a friction blister, with intracorneal hemorrhage accompanied by serosanguinous fluid, forming an intracorneal hemorrhagic bulla.

Acanthoma Fissuratum (Granuloma Fissuratum)

Acanthoma fissuratum occurs at the site of chronic low-grade pressure or rubbing trauma at the site where eyeglasses sit on the nose or ear. Clinically, there is a pink- to flesh-colored plaque or nodule with a central depression located on the lateral bridge of the nose near the medial canthus or near the cheek or at the crease between the postauricular scalp and posterior ear, where the eyeglass stem lies. This may be biopsied to exclude nonmelanoma skin cancer.

Histopathology. The epidermis shows prominent nonatypical acanthosis with mild orthohyperkeratosis and hypergranulosis. The rete is wide and blunt ended, and centrally there is attenuation of the rete, corresponding to the clinical depression (Fig. 13-11). Spongiosis and parakeratosis may be seen. The dermis shows a proliferation of small, slightly dilated vessels with a fibrotic stroma and variable patchy chronic inflammation.

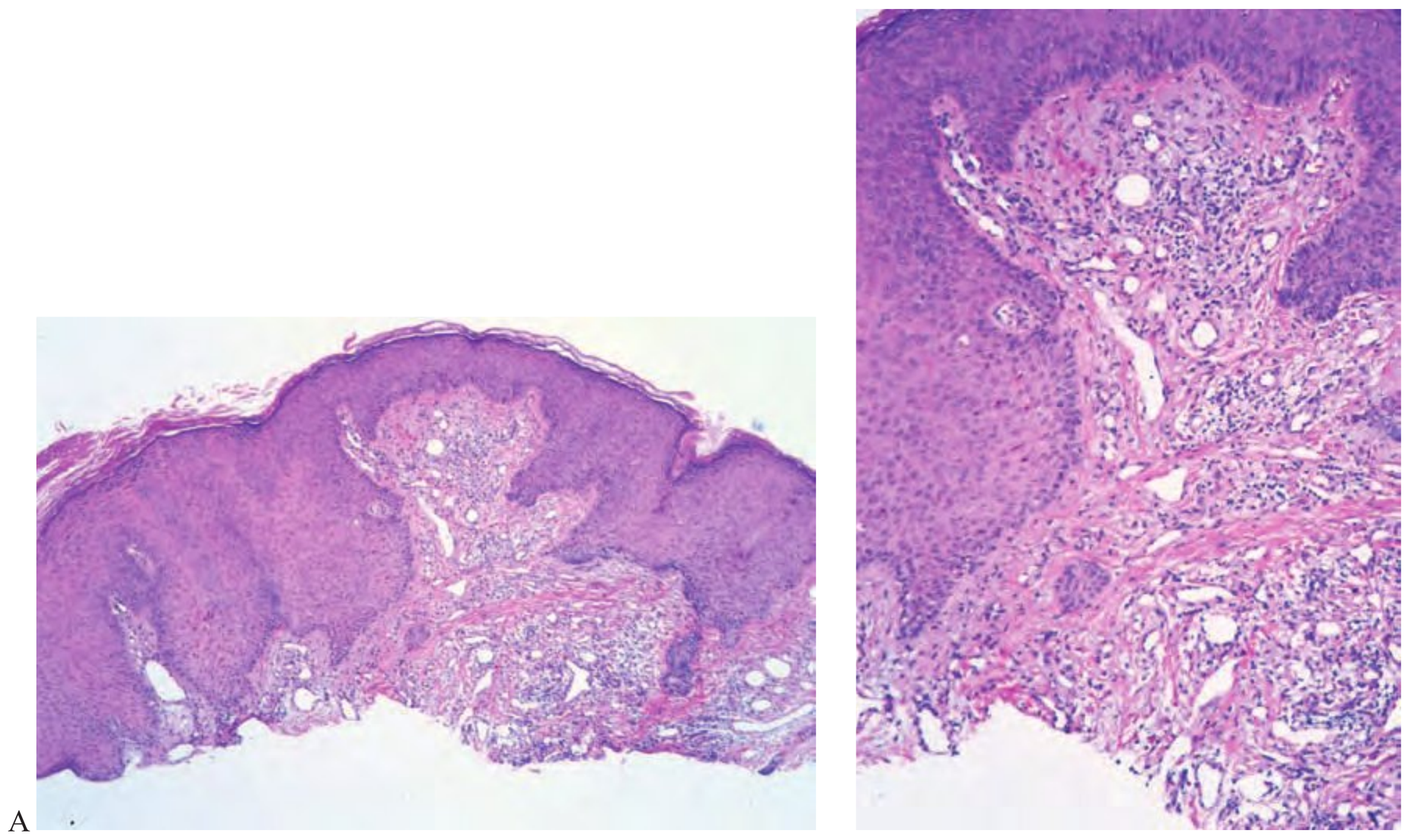
Differential Diagnosis. The epidermal and fibrovascular changes noted in acanthoma fissuratum are similar to those seen in chondrodermatitis nodularis helicis (see Chapter 18). The latter is differentiated by the location on the auricle and the presence of fibrinoid dermal necrosis and cartilaginous changes. Lichen simplex chronicus has some similar features but shows more dermal fibrosis and vertical orientation of the vessels in the dermal papillae.

Surgery-Associated Injury

Curettage surgery is frequently performed by dermatologists to biopsy, treat, or "define" a superficial basal or squamous cell carcinoma before excision. Curettage is frequently followed by electrodesiccation to further destroy remaining tumor and/or to assist in hemostasis.

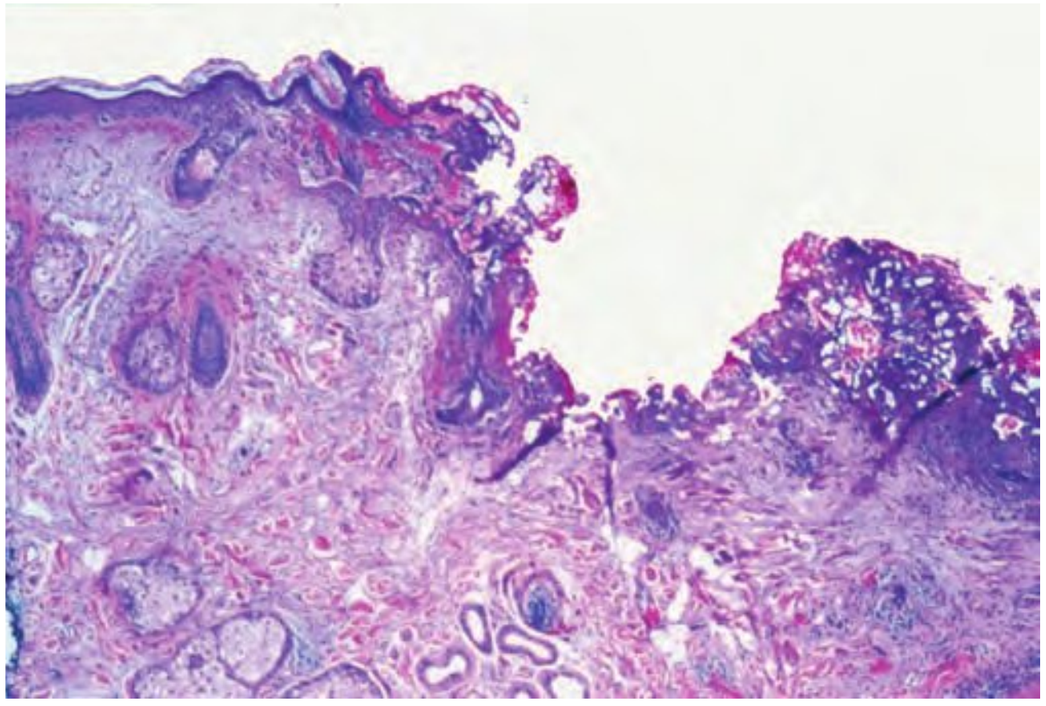
Histopathology. Electrodesiccation-induced injury results in elongation and stretch distortion of the epithelial nuclei (Fig. 13-12). Basophilic collagen necrosis can be seen beneath a recent electrodesiccation-induced surgical ulcer or scar. This may present with lacelike coagulation necrosis of the collagen and epidermis. At a healing biopsy site, foci of this injured collagen may be seen engulfed by multinucleated giant cells. The dermis beneath a recent curettage ulcer base shows edema, vascular dilation, and congestion without coagulation necrosis (Fig. 13-13). Dermal inflammation will be minimal, unless there are residual biopsy-site changes. The epidermis is usually denuded, but there may be partial remnants of attached epidermis without the stretch artifact typical of electrodesiccation.

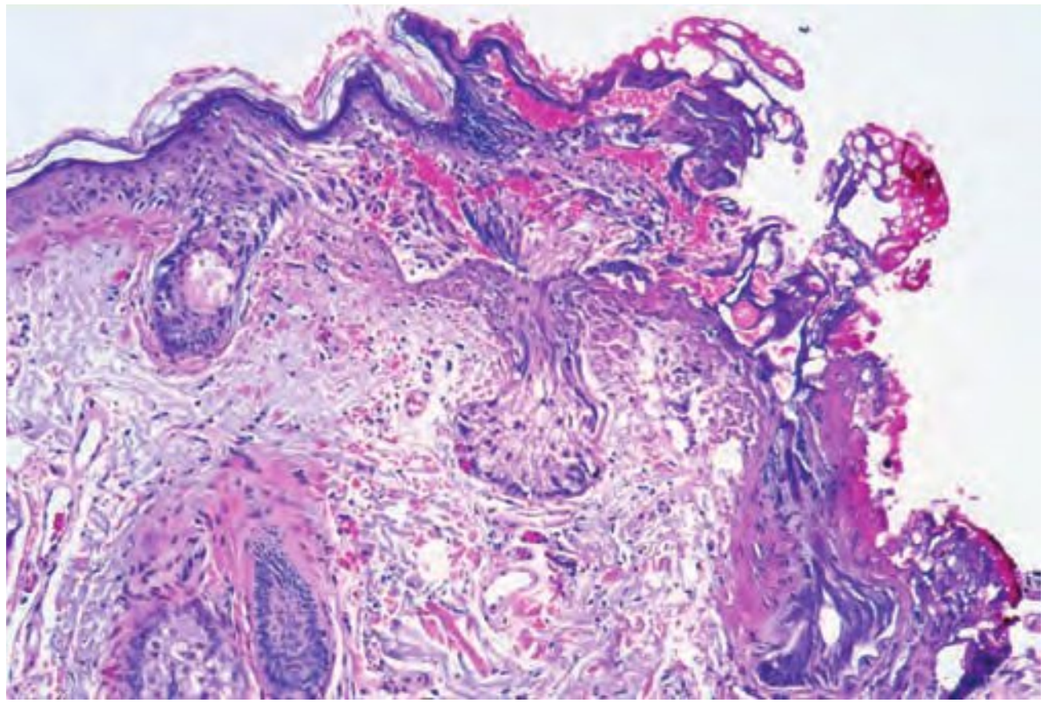
Differential Diagnosis. The nuclei elongation of electrodesiccation injury should be differentiated from atypia of an actinic keratosis. Atypical melanocytic hyperplasia may show overlap features, but this can be differentiated with immunohistochemical stains for melanocytes (see Chapter 28).

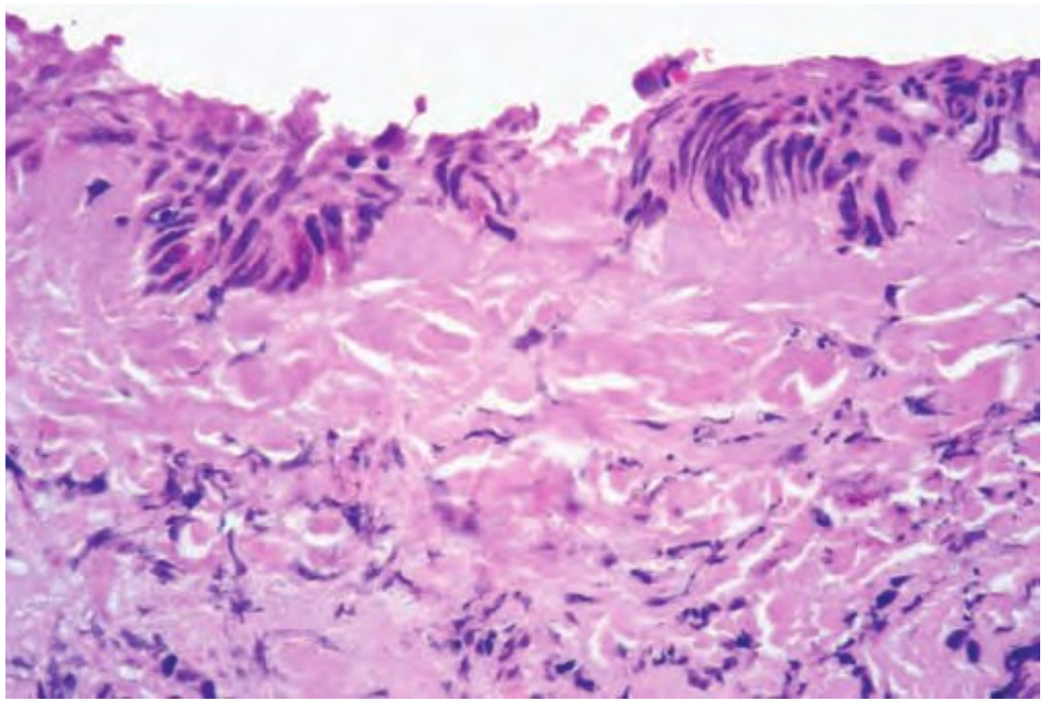


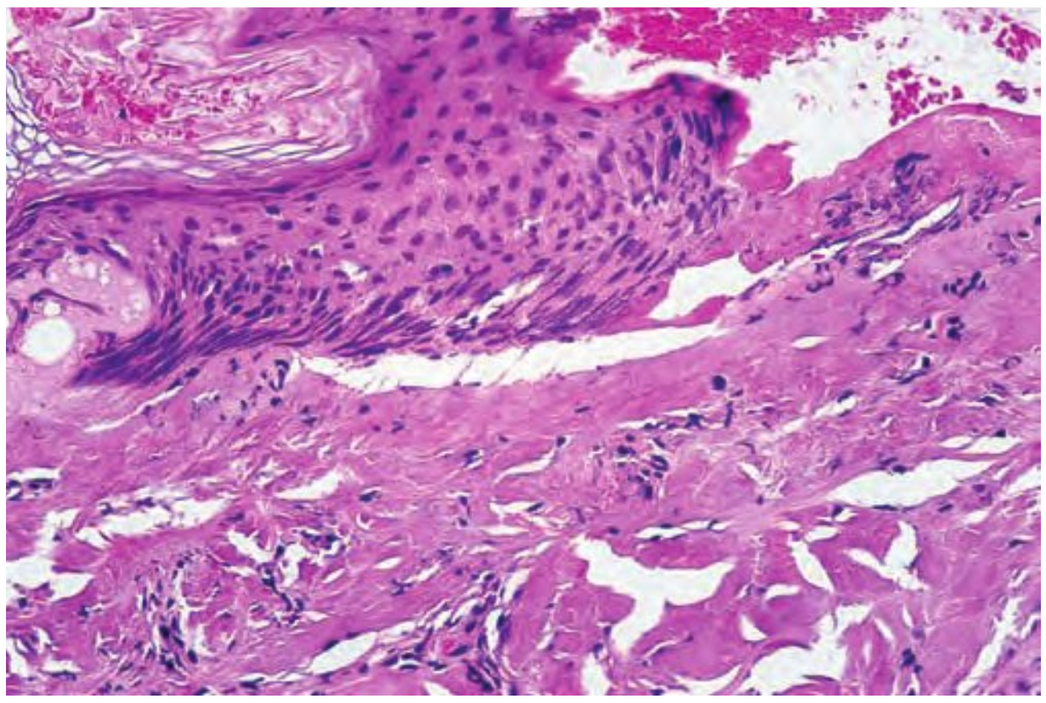
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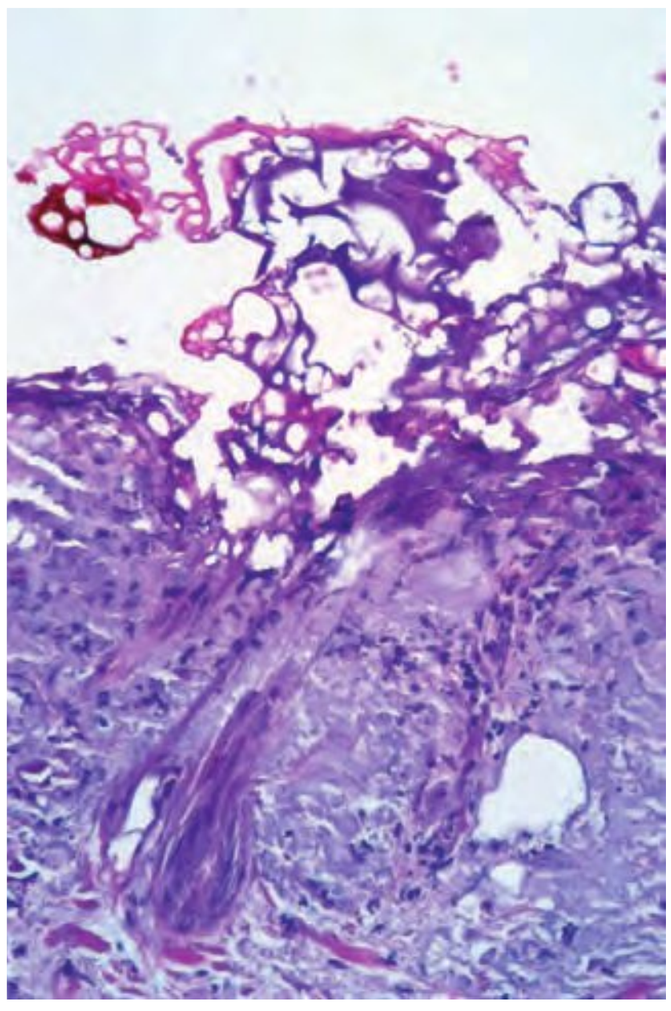
FIGURE 13-11. Acanthoma fissuratum (granuloma fissuratum). A: There is nonatypical acanthosis of the epidermis, with attenuation of the rete centrally. B: Within the dermis, there is a proliferation of slightly dilated small vessels, associated with fibrosis and a variable chronic inflammatory infiltrate. The term "granuloma" is a misnomer because a granulomatous infiltrate is not seen.

A 

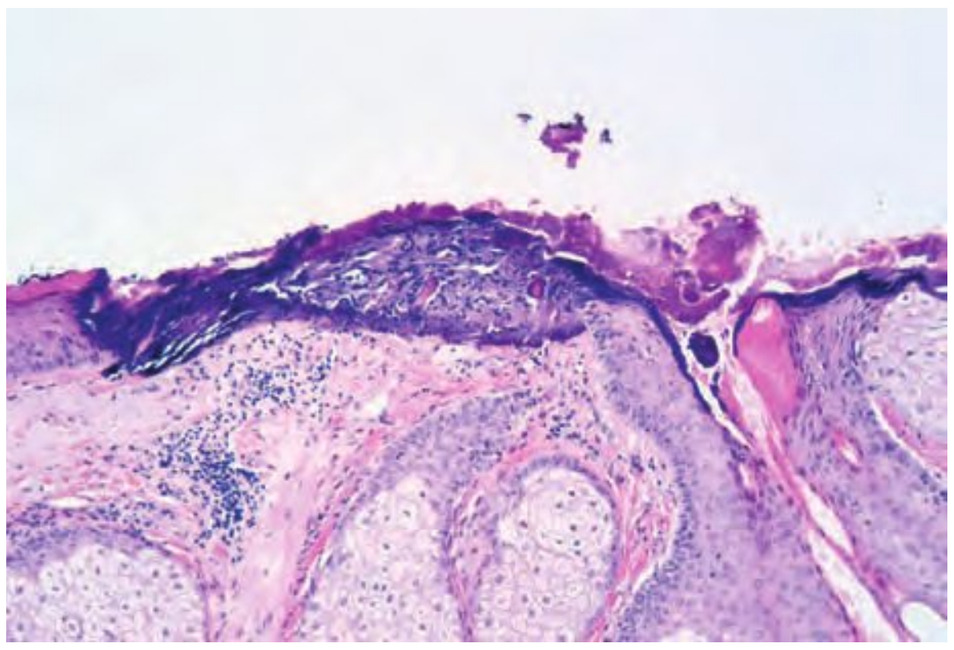
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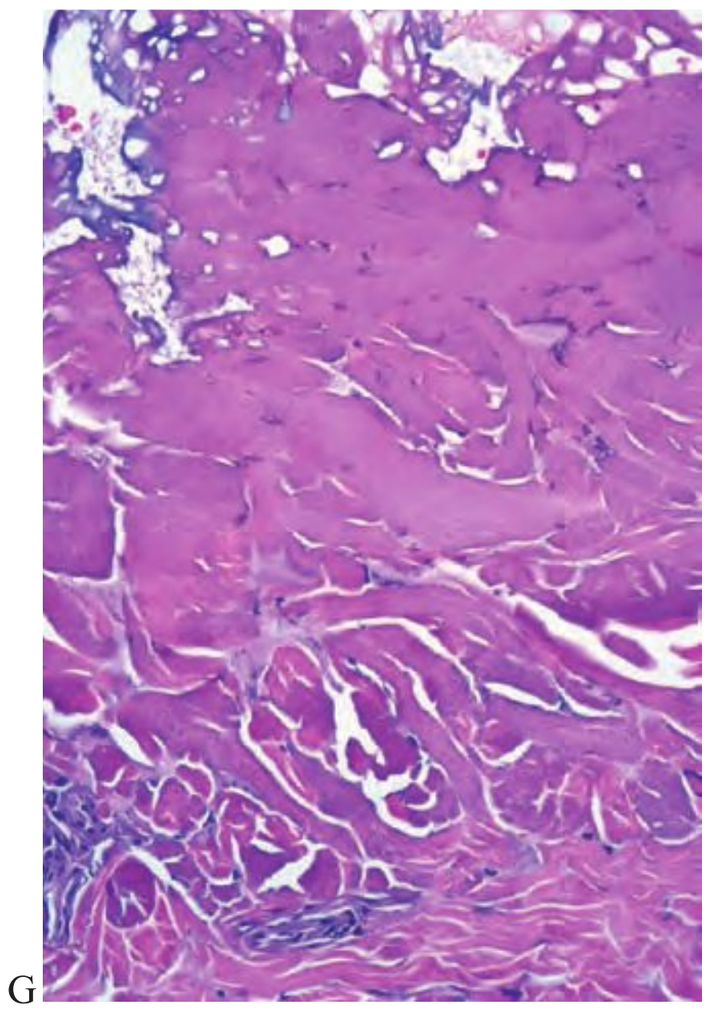


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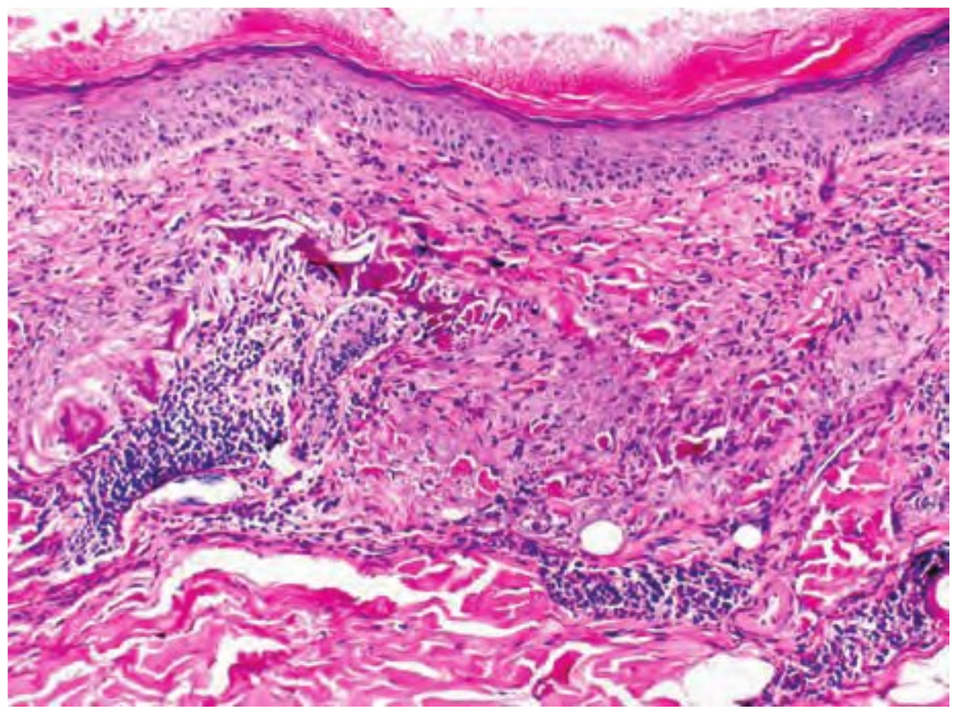


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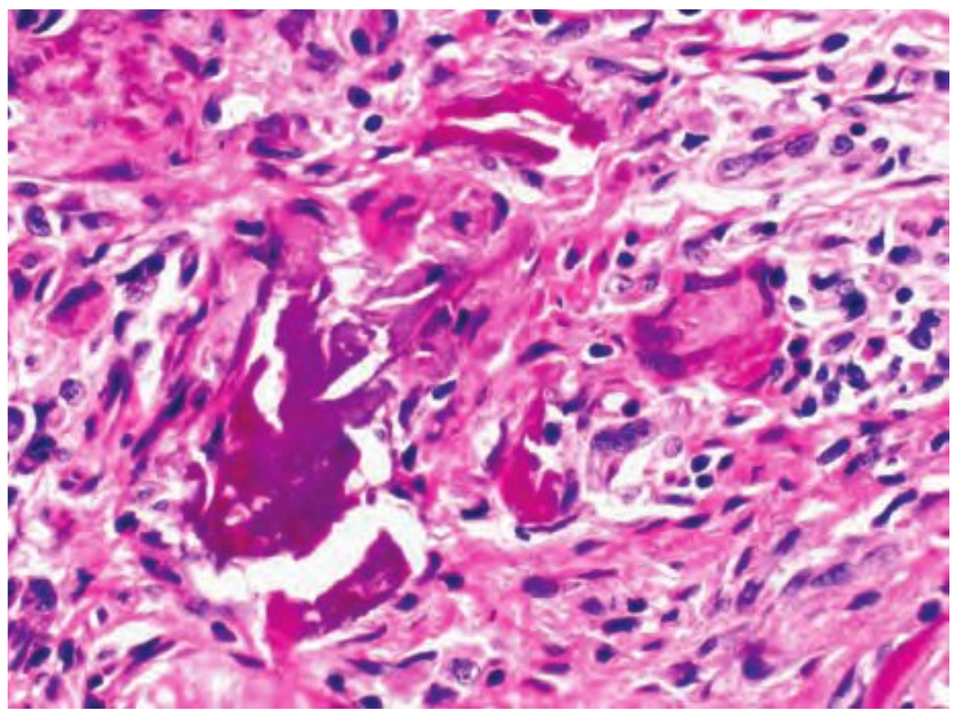
FIGURE 13-12. Electrodesiccation injury. A: There is ulceration of the epidermis and dermis with reticulated lacelike hemorrhagic and basophilic coagulation necrosis of the epidermis and superficial dermis. B: Near the edge of the ulcer, the epidermis and follicular epithelium show elongated alteration of the nuclei, with disassociation and blister formation. C: The epithelial cells typically show elongation of nuclei in electrodesiccation injury. Hyperchromasia of nuclei may be seen, simulating atypia, but the stretch artifact and absence of parakeratosis differentiate this from an actinic keratosis. D: Incipient blister formation can be seen in association with elongation cytolysis of keratinocytes and/or coagulation necrosis of the dermis due to electrodesiccation heat injury. E: Electrodesiccation elongation effects on the follicular epithelium are similar to those seen in the epidermis. This higher-power view highlights the lacelike pattern of coagulation necrosis seen in some cases of electrodesiccation injury. F: Another pattern of electrodesiccation injury, characterized by abrupt basophilic alteration of the collagen and epithelium. (continued)



G



H



I

FIGURE 13-12. Continued. G: The dermal changes of electrodesiccation injury are characterized by homogenized basophilic coagulation necrosis and loss of the distinction between collagen bundles. In contrast, the deeper tissue shows minimally damaged collagen, with distinct separation of the collagen bundles. Superficially there is mild lacelike change. H: Within a healing surgical biopsy site, foci of basophilic desiccated collagen are noted beneath the reparative fibrosis. I: A foreign body reaction to altered collagen is noted, with engulfment of the basophilic injured collagen.

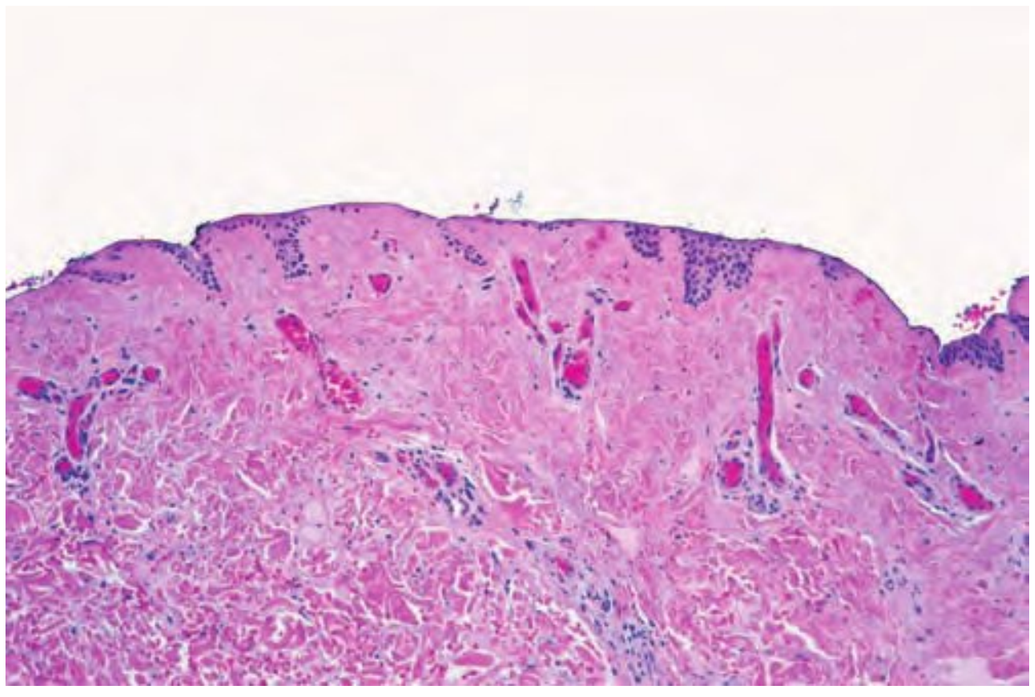


FIGURE 13-13. Curettage-induced ulceration. In contrast to desiccation-induced injury, there is no dermal collagen reaction. The ulcer base typically shows vascular congestion.

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CHAPTER 14

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Noninfectious Granulomas

GRANULOMA ANNULARE

Granuloma annulare is an idiopathic, palisaded, granulomatous condition that is frequently encountered by dermatopathologists. It occurs most commonly in children and young adults but may affect all age groups. Females are affected somewhat more commonly than males. The lesions of granuloma annulare consist of small, firm, asymptomatic papules that are flesh colored or pale red and are often grouped in an annular or circinate fashion (Fig. 14-1). There usually are several lesions, but there may be just one, or there may be many. The lesions are found most commonly on the arms, hands, legs, and feet. The trunk may also be involved, and rare sites of involvement include the palms, penis, ear, and periocular regions (1). Although chronic, the lesions usually subside after a number of years. Unusual variants of granuloma annulare include (a) a generalized form, consisting of hundreds of papules that are either discrete or confluent but only rarely show an annular arrangement (2,3), (b) perforating granuloma annulare, with umbilicated lesions occurring usually in a localized distribution (4–6) and, rarely, in a generalized distribution (7–9), (c) erythematous or patch granuloma annulare, showing large, slightly infiltrated erythematous patches, with a palpable border, on which scattered papules may subsequently arise (10,11), and (d) subcutaneous/deep granuloma annulare, in which subcutaneous nodules occur, especially in children, either alone or in association with intradermal lesions (12–19). The subcutaneous nodules have a clinical appearance similar to that of rheumatoid nodules, although there is no history of arthritis, and there is a greater tendency to occur on the legs, feet, and, occasionally, the head (15,20,21). In adults, similar lesions may be found near the small joints of the hands (22). A very rare, deep, destructive form of granuloma annulare has also been described (23,24).

A correlation between generalized papular granuloma annulare and diabetes mellitus has been observed by several authors (3,23,25). Granuloma annulare has been reported in at least 60 patients with HIV or AIDS, with a greater incidence of generalized disease in this population (27–31). Granuloma annulare–like lesions have also been reported to develop at sites of resolved herpes zoster (32,33) and occasionally in association with tattoos (34), necrobiosis lipoidica (35), and sarcoidosis (36).

Histopathology. Histologically, granuloma annulare shows an infiltrate of histiocytes and a perivascular infiltrate of lymphocytes that is usually sparse. The histiocytes may be present in an interstitial pattern without apparent organization or in palisades surrounding areas with prominent mucin (Figs. 14-2 to 14-5). Patterns between these two extremes occur, and typically a single biopsy will show histiocytes that are not palisaded, are slightly palisaded, and are well palisaded. Although degenerated collagen or small quantities of fibrin may be present (37), increased mucin is the hallmark of granuloma annulare. Increased mucin is almost always apparent on routinely stained sections as faint blue material with a stringy, finely granular appearance. Stains such as colloidal iron and Alcian blue can be used to highlight mucin if it is not clearly apparent. Occasionally, sections will not reveal increased mucin, particularly those lacking a palisaded arrangement of histiocytes. In biopsies with well-developed palisades, the central mucinous area is commonly accompanied by a few nuclear fragments or neutrophils. Plasma cells are present rarely. A sparse infiltrate of eosinophils is seen in approximately half of cases, and occasional biopsies show abundant eosinophils (38,39). Multinucleated histiocytes are present more often than not, but they are usually few and often subtle. They can occasionally be seen to have engulfed short, thick, blue-gray elastic fibers (40). The histiocytic infiltrate is usually present throughout the full thickness of the dermis or the middle and upper dermis, but occasionally just the superficial or the deep dermis is involved (41). Mitotic figures are usually rare (fewer than 1 per 10 high-power fields) but may be as frequent as 7 per 10 high-power fields in rare examples (42).

Rare examples of granuloma annulare show aggregates of epithelioid histiocytes, usually with some giant cells and a rim of lymphoid cells, which resemble the granulomas of sarcoidosis (36,37,41). These usually differ from sarcoidal granulomas, however, by showing poorer circumscription and by lacking asteroid bodies. Vascular changes in granuloma annulare are variable but generally inconspicuous (43). In some instances, however, there are fibrinoid deposits in vessel walls and occlusion of vascular lumina (44).

Among the variants of granuloma annulare mentioned, the usual histologic picture of palisaded and interstitial pattern is found in the generalized form (2). An interstitial pattern predominates in the erythematous and patch variants (10,11).

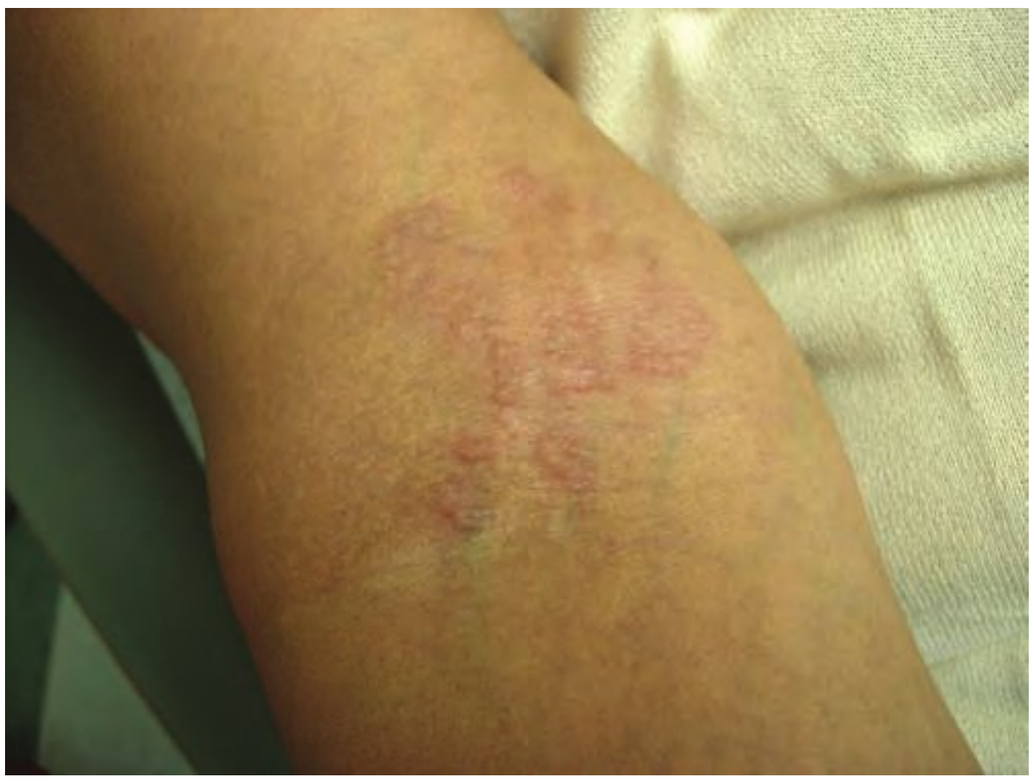


FIGURE 14-1. Granuloma annulare. Raised pink papules in an annular configuration in the antecubital fossa.

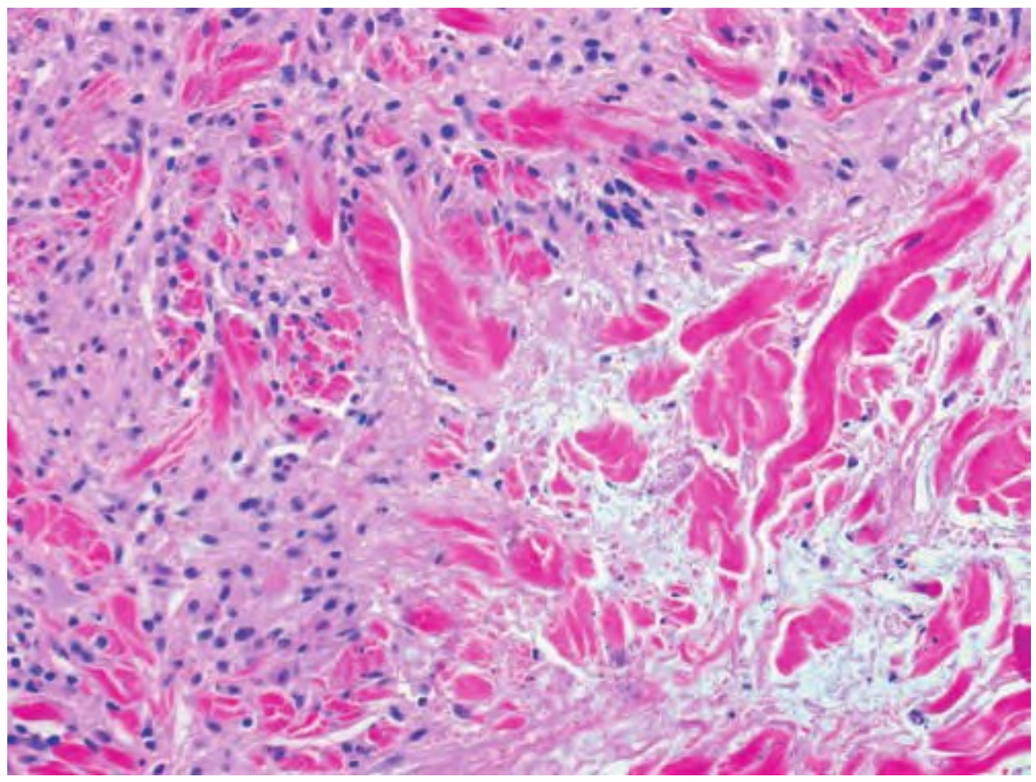


FIGURE 14-3. Granuloma annulare. Histiocytes surround mucin, which shows a feathery blue appearance, and a few fragments of neutrophils.

In perforating granuloma annulare, at least part of the palisading granulomatous process is located superficially and is associated with disruption of the epidermis (4,5,7,8).

The subcutaneous nodules of deep granuloma annulare usually show large histiocytic palisades surrounding mucin and degenerated collagen (Fig. 14-5). These central, degenerated foci exhibit a pale appearance (45); however, examples in which mucin was not apparent or in which the central area appeared more fibrinoid have also been reported (20,21). Thus, subcutaneous granuloma annulare may be histologically indistinguishable from rheumatoid nodule, an appearance that has led to the term *pseudorheumatoid nodule*.

Pathogenesis. The cause of granuloma annulare is unknown. Possible precipitating events in small subsets of patients have included insect bites, warts, erythema multiforme, herpes zoster, exposure to sunlight, hepatitis B vaccine, and tuberculin skin tests (46–49). There is likely an increased incidence and increased disease severity in patients with diabetes mellitus. Thrombi or vasculitic changes have been noted in some examples, and it is possible that what we term granuloma annulare may represent a variety of disease processes.

Electron microscopic examination reveals degeneration of both collagen and elastic fibers in granuloma annulare (37). The macrophages (histiocytes) show a high content of primary lysosomes and considerable cytoplasmic activity with release of lysosomal enzymes into the extracellular space (50). Synthesis of types I and III collagen also occurs, probably as a reparative response (51). A cell-mediated immune response also appears

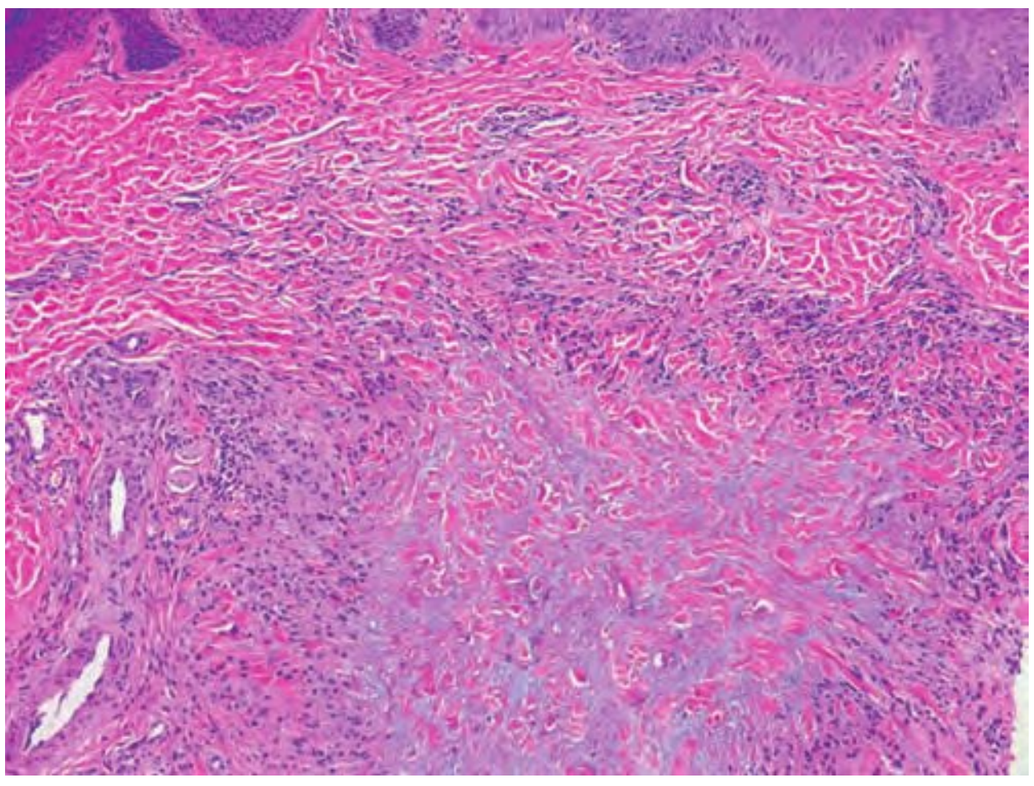


FIGURE 14-2. Granuloma annulare. A palisade of histiocytes surrounds mucin in the upper dermis.

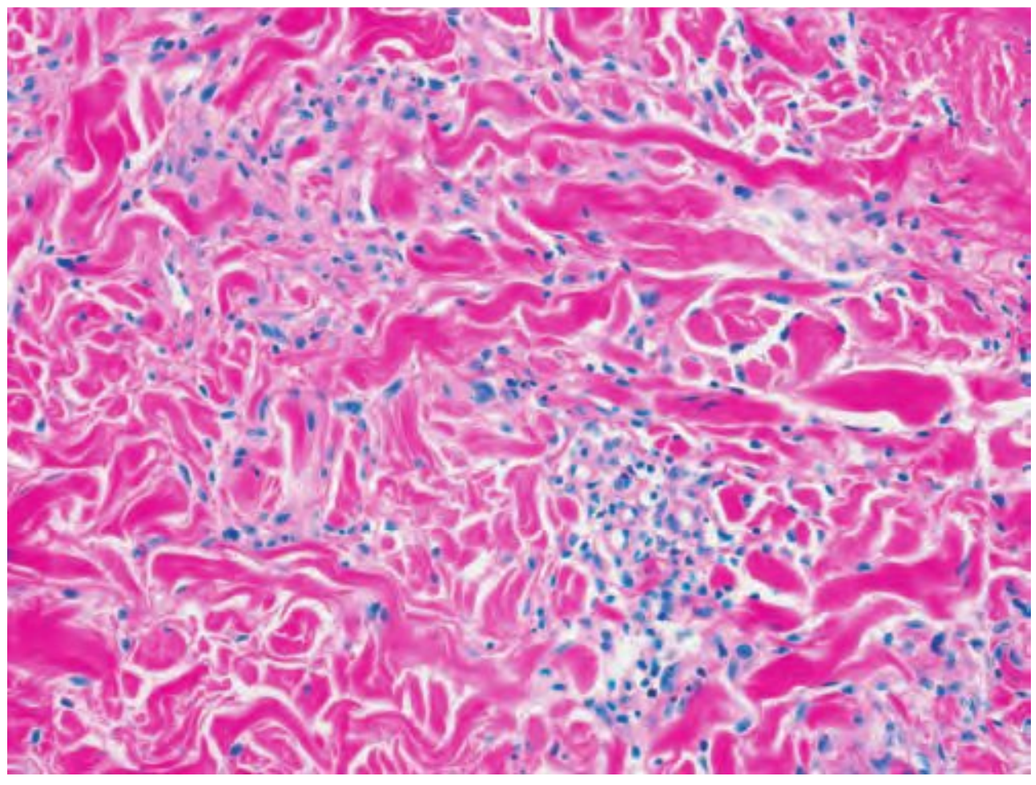


FIGURE 14-4. Granuloma annulare. Interstitial pattern granuloma annulare exhibits histiocytes between collagen bundles and perivascular lymphocytes.

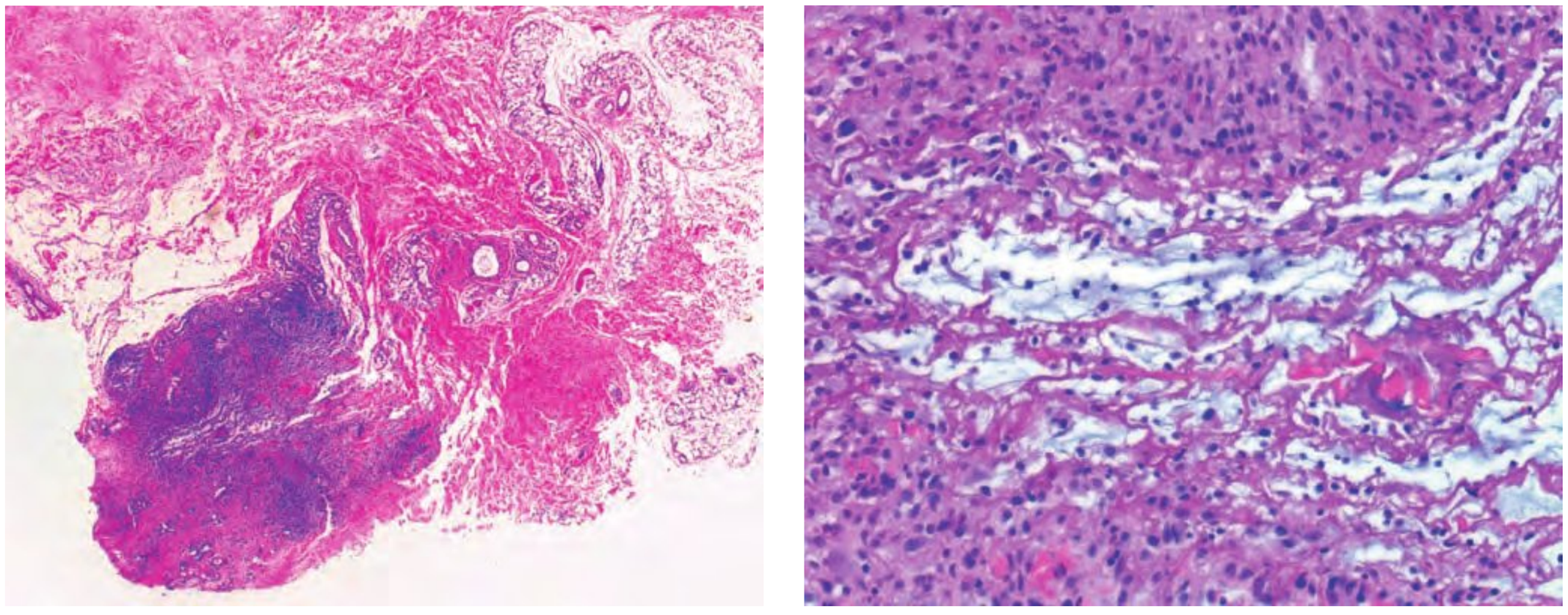


FIGURE 14-5. Deep granuloma annulare. A: A well-circumscribed subcutaneous nodule shows palisaded histiocytes surrounding mucin and fibrinoid material. B: Histiocytes in a palisade surround mucin and fibrinoid material.

to be involved, marked by prominent activated helper T cells (52–54). One immunoperoxidase study of the histiocytic population showed staining for lysozyme but not for other macrophage markers such as HAM 56 or CD-68 (55). Another demonstrated positivity for these two markers (42).

Blood vessel deposits of immunoglobulin M and the third component of complement (C3) have been observed by some investigators (53), but others have found them only rarely (56) or not at all (57). Thus the existence of an immune complex vasculitis in granuloma annulare (53) appears unlikely.

Differential Diagnosis. Granuloma annulare and necrobiosis lipoidica may resemble one another histologically. Although much has been written about the difficulty of separating these disorders histologically (43), the distinction can be easily accomplished clinically in most circumstances (58). Furthermore, although it is true that histologic distinction may be impossible, usually it can be accomplished by using the following criteria: (a) Although either disease may involve the dermis diffusely, necrobiosis lipoidica rarely involves just one focus of the dermis or predominantly the upper half of the dermis, whereas granuloma annulare often does. (b) Histiocytes in palisades that completely encircle altered connective tissue are more common in granuloma annulare, whereas histiocytes in linear array that are horizontally oriented in a somewhat tiered fashion are more typical of necrobiosis lipoidica. (c) Abundant mucin is typical of granuloma annulare and distinctly uncommon in necrobiosis lipoidica. (d) Necrobiosis lipoidica often shows dermal sclerosis and thickened subcutaneous septa, whereas granuloma annulare does not (the sclerosis often produces a straight edge to the sides of a punch biopsy, in contrast to the inward retraction and/or more irregular edge seen in biopsies without sclerosis). Other features that are more characteristic of necrobiosis lipoidica include the presence of a larger number of giant cells, prominent deep dermal plasma cells, and more pronounced vascular changes, including thickened blood vessel walls. Furthermore, necrobiosis lipoidica is more likely to show extensive deposits of lipids or nodular lymphocytic infiltrates in the deep dermis or subcutis (59), although neither feature is commonly seen.

The interstitial type of granuloma annulare, in which palisades of histiocytes are not well developed, is less likely to be confused with necrobiosis lipoidica. This pattern is more likely to be mistaken for a process that can also show a superficial and deep lymphocytic infiltrate, such as the inflammatory stage of morphea, but the subtle presence of histiocytes in an interstitial pattern usually allows a definitive diagnosis of granuloma annulare. Mycosis fungoides can have a granulomatous infiltrate with a granuloma annulare–like pattern (60,61). Such examples of this cutaneous T-cell lymphoma can usually be recognized by the presence of at least some intraepidermal lymphocytes, a dermal lymphocytic infiltrate that is more dense around the superficial plexus than the deep one, and/or a lichenoid component to the infiltrate. The interstitial type of granuloma annulare may also resemble a xanthoma. Distinction is usually possible because in granuloma annulare a foamy appearance to the histiocytes is either completely lacking or very subtle; in xanthoma, at least some of the histiocytes are obviously foamy. In addition, granuloma annulare tends to show an obvious perivascular lymphocytic infiltrate, whereas most xanthomas do not (62). Drug reactions may also mimic granuloma annulare, but these usually show interface changes that allow for their distinction (63). Rarely, infection with *Mycobacterium marinum* may have few neutrophils and may produce a histologic picture resembling interstitial granuloma annulare (64).

Differentiation of subcutaneous granuloma annulare from a rheumatoid nodule is not always possible on histologic grounds, but subcutaneous granuloma annulare is more likely than rheumatoid nodule to show prominent mucin and less likely to show foreign-body giant cells or prominent stromal fibrosis (45).

Finally, it should be remembered that granuloma annulare and other palisading granulomas may be simulated by epithelioid sarcoma, a lesion that may also contain mucin. Clues to epithelioid sarcoma include ulceration, cytologic atypia, necrotic foci that include necrotic epithelioid cells, and history of recurrence. Although atypia tends not to be striking, the epithelioid cells in epithelioid sarcoma usually show more nuclear hyperchromasia and pleomorphism, more mitotic figures, larger size, and redder cytoplasm than do the histiocytes of granuloma annulare (65). Immunohistochemically, epithelioid sarcoma can be distinguished from granuloma annulare by positivity for epithelial membrane antigen and keratins. Whereas a variety of keratins may be present in epithelioid sarcoma, the most common is cytokeratin 8/CAM 5.2, present in 94% of cases (66).

ANNULAR ELASTOLYTIC GIANT-CELL GRANULOMA

Annular elastolytic giant-cell granuloma is the name that is currently in vogue for a condition with unclear nosologic status, and it is uncertain whether it is truly distinct from granuloma annulare (67–69). It almost always occurs on sun-exposed skin, such as the face, neck, dorsum of hand, forearm, and arm, hence the previous name *actinic granuloma* (70,71) (Fig. 14-6). The appearance of lesions after prolonged tanning bed use has been reported (72). However, there are a few reports of similar lesions involving sun-protected sites (73–76). The lesions clinically resemble granuloma annulare. They are typically large, somewhat annular plaques. The border may be serpiginous and is slightly raised, approximately 3 mm wide, and pearly or slightly red or brown. The central zone may show depigmentation and/or atrophy. Smaller papules may also occur, and lesions may be solitary, few, or numerous (70,77,78). Other names under which these lesions have been described include *atypical necrobiosis lipoidica of the face and scalp* (79), *Miescher's granuloma of the face* (78), and *granuloma multiforme* (77). A possibly related process occurs on the conjunctiva (80).

Histopathology. The histologic features are best appreciated in a radial biopsy that contains the central zone, the elevated border, and the skin peripheral to the ring (70,77,78). The central zone shows the hallmark of the disease, that is, near or total absence of elastic fibers, best appreciated with an elastic tissue stain (e.g., Verhoeff-van Gieson) (Figs. 14-7 to 14-9). The collagen in this zone may show horizontally oriented fibers producing a slight scarlike appearance (Fig. 14-7). By contrast, the zone peripheral to the annulus shows an increased amount of thick elastotic material with the staining properties of elastic tissue. The transitional zone at the raised border shows a granulomatous infiltrate with either of the patterns seen in granuloma annulare, that is, histiocytes arranged interstitially between collagen bundles or, less commonly, in a palisade. Occasionally, there are contiguous epithelioid histiocytes in small clusters. Multinucleated histiocytes are conspicuous, usually being large and containing as many as a dozen nuclei, mostly in haphazard arrangement, but sometimes in ringed array. Elastotic fibers are present adjacent to and within the giant cells (Fig. 14-8). Asteroid bodies that stain like elastic fibers may be found in the giant cells (78). The infiltrate also contains lymphocytes and often some plasma cells. Mucin is not present.

Differential Diagnosis. The principal differential diagnosis is granuloma annulare, which may in fact be an artificial distinction.



FIGURE 14-6. Annular elastolytic granuloma. Annular pink plaques, with somewhat serpiginous borders, of the forehead.

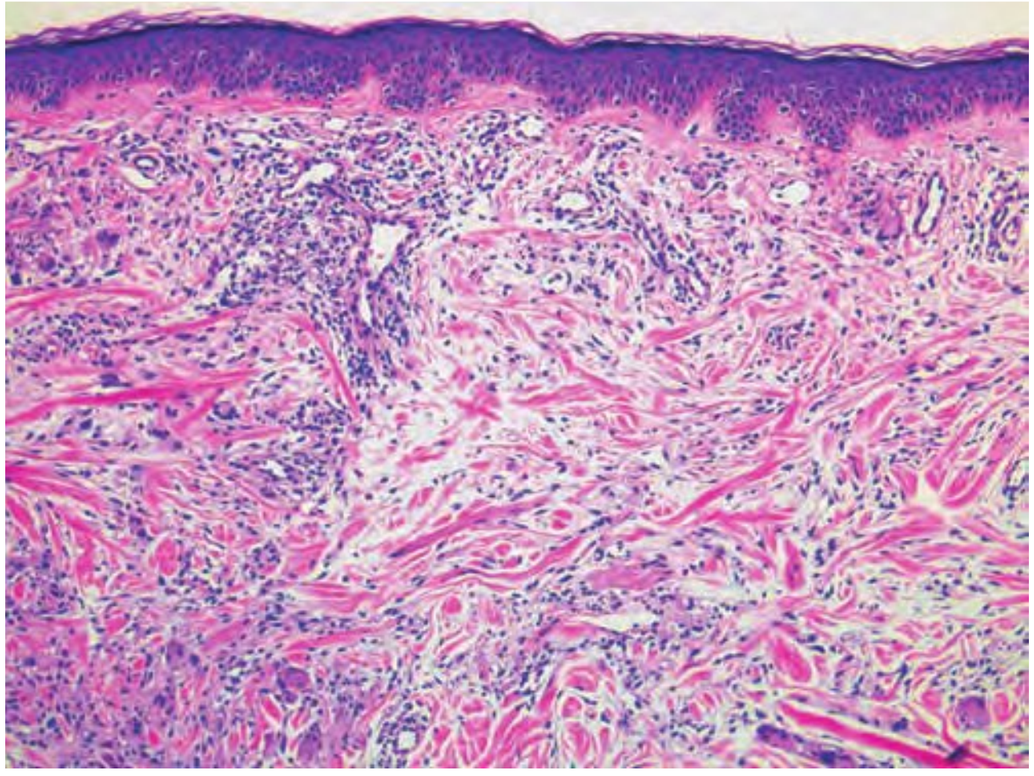


FIGURE 14-7. Annular elastolytic granuloma. Multinucleated histiocytes at left abut connective tissue at the center of the lesion that is slightly fibrotic; mucin is not apparent.

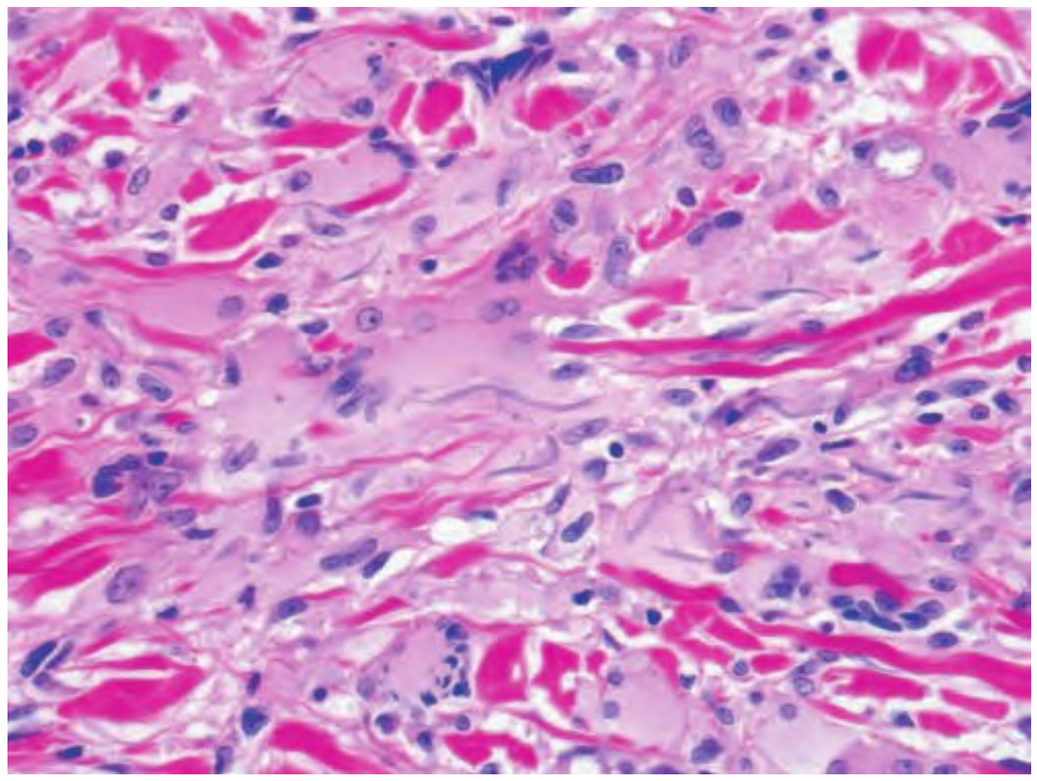


FIGURE 14-8. Annular elastolytic granuloma. Some multinucleated histiocytes have ingested blue-gray elastic fibers.

Because engulfment of abnormal elastic fibers can also occur in granuloma annulare (40) as well as in other granulomatous processes, it has been argued that the elastophagocytosis of annular elastolytic giant-cell granuloma does not qualify it as a distinct entity different from granuloma annulare of sun-damaged skin (68). Although some elastolysis has also been described in granuloma annulare (77), it is the complete loss of elastic tissue in the central zone that has been used as the primary basis for separating the diseases. Other features that have been evoked for distinguishing them are the presence of larger and more numerous giant cells, the absence of mucin in annular elastolytic giant-cell granuloma (70,81), and sparing of areas that lack elastic tissue, such as scars (76).

Necrobiosis lipoidica differs by the lack of a central zone of elastolysis and the presence of degenerated collagen, sclerosis, and, in some circumstances, lipids and vascular changes. Furthermore, annular elastolytic giant-cell granuloma involves mostly the upper and middle dermis, whereas necrobiosis lipoidica tends to affect the deep dermis and sometimes the subcutis at least as much as the upper dermis. Foreign-body granulomas generally have more distinct collections of epithelioid histiocytes, lack zonation in density of elastic fibers, and often have identifiable foreign material.

NECROBIOSIS LIPOIDICA

Necrobiosis lipoidica is an idiopathic disorder typified by indurated plaques of the shins (Fig. 14-10). In 1966, in a large series, Muller and Winkelman reported that two thirds of patients with necrobiosis lipoidica had overt diabetes at the time of diagnosis (82). Of the rest, all but 10% developed diabetes within 5 years, had abnormal glucose tolerance, or had a history of diabetes in at least one parent (26). In a more recent series, only 11% of patients had diabetes at presentation, with an additional 11% developing diabetes or impaired glucose tolerance over 15 years (83). Of all patients with diabetes, fewer than 1% develop necrobiosis lipoidica (26,83). Some reports have suggested that necrobiosis lipoidica heralds more rapid progression of diabetes in patients with that disorder (84).

In well-developed necrobiosis lipoidica, one observes one or several sharply but irregularly demarcated patches or plaques, usually on the shins (85). Usually they are bilateral, and the condition is more often present in women (26). The lesions appear yellow-brown in the center and purplish at the periphery. Whereas the periphery of the lesions may show slight induration, the center of the lesions gradually becomes atrophic, shows telangiectases, and may ulcerate. When lesions first begin, red-brown papules can be observed. In addition to the shins, lesions may be present elsewhere on the lower

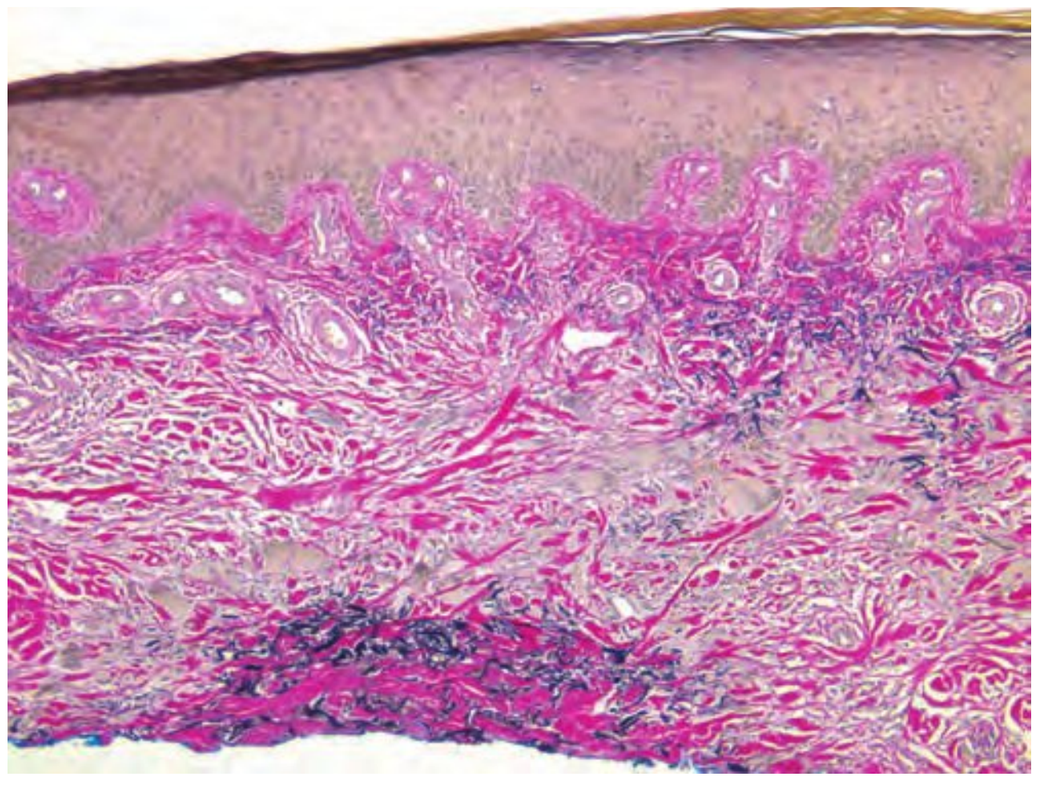


FIGURE 14-9. Annular elastolytic granuloma. Elastic tissue stain shows absence of elastic fibers in the center of the lesion.



FIGURE 14-10. Necrobiosis lipoidica. Waxy, red-brown plaque with central fine telangiectasia on the shin.

extremities, including the ankles, calves, thighs, popliteal areas, and feet. In about 15% of the cases, lesions are present also in areas other than the legs, especially on the dorsa of the hands, fingers, and forearms. Rarely, the head and abdomen are affected. Necrobiosis lipoidica with lesions exclusively outside the legs is extremely rare; it is reported to occur in 1% of patients with necrobiosis lipoidica (82).

Lesions located in areas other than the legs may appear raised and firm and may have a papular, nodular, or plaquelike appearance without atrophy. Clinically they may resemble granuloma annulare (82). Involvement of the scalp by large, atrophic patches occurs occasionally. This is usually seen in association with lesions on the shins and elsewhere (86,87) but also, rarely, in isolation (88–90).

In rare instances, transfollicular elimination of necrotic material takes place in necrobiosis lipoidica, producing small hyperkeratotic plugs within a plaque (91,92). Necrobiosis lipoidica occasionally coexists with sarcoid (93) or granuloma annulare (35). Rare examples of squamous cell carcinoma arising in lesions of necrobiosis lipoidica have been reported (94,95).

Histopathology: On histologic examination, the epidermis may be normal, atrophic, or hyperkeratotic. In some instances, the surface of the biopsy shows ulceration. Usually the entire thickness of the dermis or its lower two thirds is affected by a process that exhibits a variable degree of granulomatous inflammation, degeneration of collagen, and sclerosis (Figs. 14-11 and 14-12). Histologic changes of necrobiosis lipoidica may be seen in subcutaneous septae (96,97). Occasionally only the upper dermis is affected (41,43,58,82). The granulomatous component is usually conspicuous, and the histiocytes may or may not be arranged in a palisade. Occasionally there are just a few scattered epithelioid histiocytes and giant cells. The latter picture is more likely to occur in sections in which sclerosis is extensive, and occasionally in such biopsies several sections must be examined before a granulomatous component becomes apparent. Giant cells are usually of the Langhans or foreign-body type; occasionally, Touton cells or asteroid bodies (98) are seen. If the histiocytes are arranged in a palisade, the palisades tend to be somewhat horizontally oriented and/or vaguely tiered. Occasionally, histiocytes may be seen completely to encircle altered connective tissue, particularly degenerated collagen, but, more commonly, altered connective tissue is incompletely surrounded by histiocytes. This alteration of connective tissue has also been referred to as "necrobiosis." The altered collagen appears different from normal collagen by having a paler, grayer hue and by appearing more fragmented and haphazardly arranged; it may also appear more compact or smudged (Fig. 14-12). Areas of sclerosis with a diminished number of fibroblasts can be seen. A clue to the presence of sclerosis can be found by looking at the edges of the biopsy specimen, which tend to be straight with less of the inward retraction of the dermis ordinarily associated with punch biopsies (Fig. 14-11). Increased mucin is usually inapparent or subtle in contrast to granuloma annulare. Other findings include a sparse to moderately dense, primarily perivascular lymphocytic infiltrate, plasma cells in the deep dermis in some biopsies (Fig. 14-13), involvement of the upper subcutis with thickened fibrous septa, and lipids which may be present in foamy histiocytes (99), which may be inferred from the presence of cholesterol clefts or can be detected extracellularly with special stains on fresh tissue. Cholesterol clefts are rare, seen in less than 1% of cases (100). Deep lymphoid follicles may be present in up to 10% of cases (59). Older lesions show telangiectases superficially. Blood vessels, particularly in the middle and lower dermis, often exhibit thickening of their walls with proliferation of their endothelial cells. The process may lead to partial and rarely to complete occlusion of the lumen. The thickened walls may be infiltrated with periodic acid-Schiff (PAS)–positive, diastase-resistant material (43). Vascular changes of this type are seen particularly near foci containing thickened, hyalinized collagen

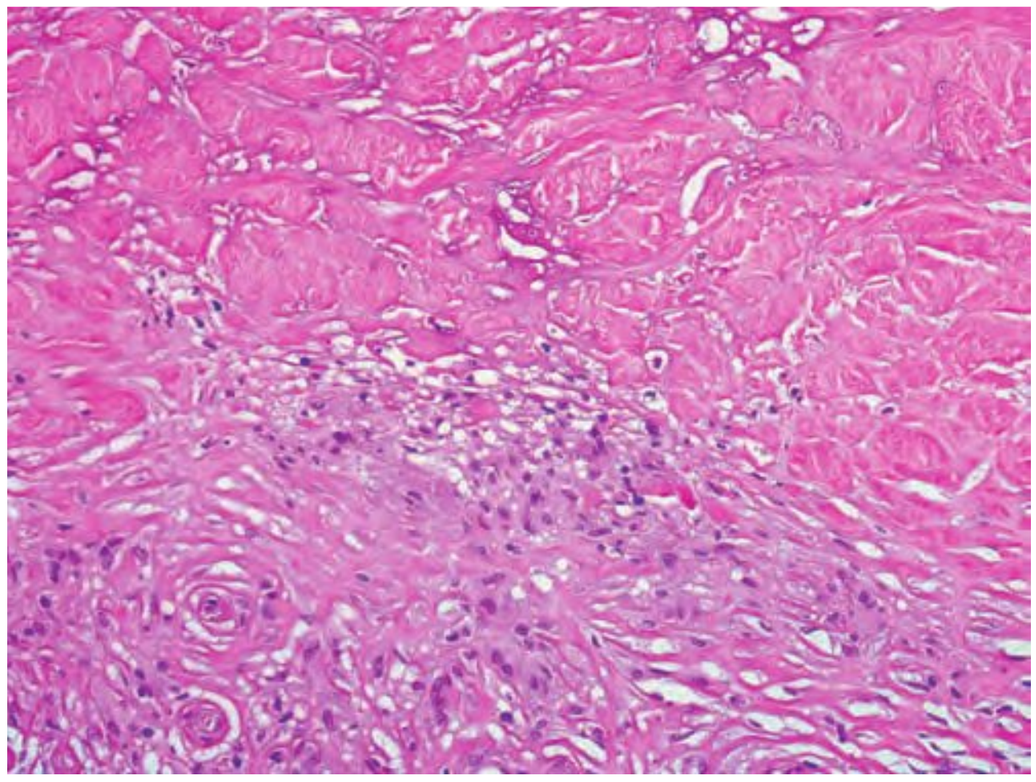


FIGURE 14-12. Necrobiosis lipoidica. Histiocytes, lymphocytes, and degenerated collagen are present.

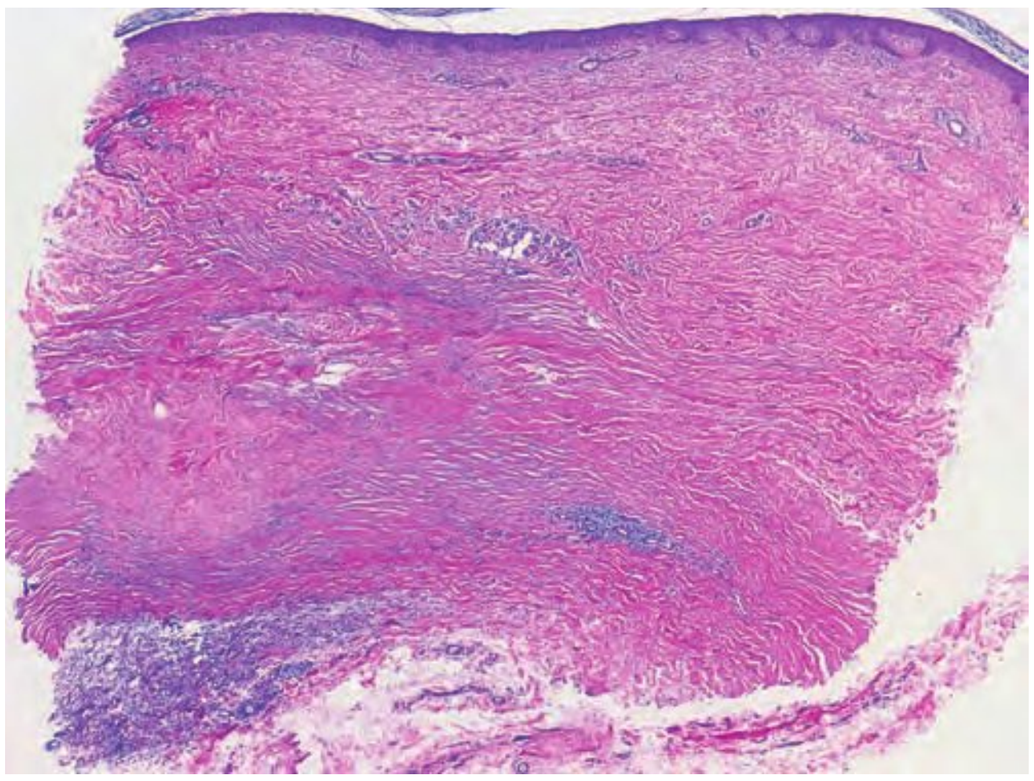


FIGURE 14-11. Necrobiosis lipoidica. The presence of sclerosis can be identified by the relatively straight edges of the punch biopsy. The infiltrate involves the full thickness of the dermis and is arranged in a tierlike fashion.

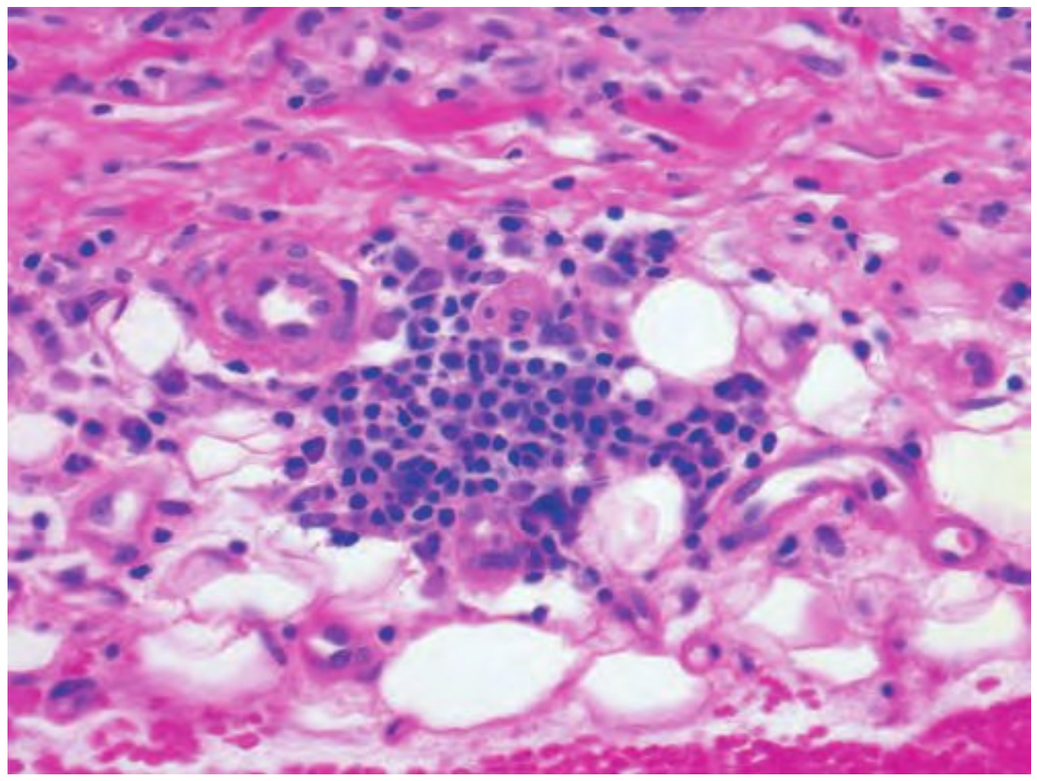


FIGURE 14-13. Necrobiosis lipoidica. Plasma cells at the dermal–subcutaneous junction are a typical finding.

bundles. Whereas the vascular changes often are conspicuous in lesions of the lower legs, they usually are mild or absent elsewhere (89). Histologic findings that are possibly correlated with the clinical presence of diabetes include florid palisading around degeneration of collagen (82) and cholesterol clefts (100).

Pathogenesis. The cause of necrobiosis lipoidica is unknown, and it is unclear whether the degeneration of collagen is a primary or a secondary event (85). Some authors have postulated that the degeneration of collagen is the result of vascular changes secondary to clinical or latent diabetes (101). However, evidence against a vascular cause includes the absence of vascular pathology in approximately one third of biopsies examined (82) and the fact that vessels that are affected are often situated in the lower dermis and are of a larger caliber than the vessels affected by diabetic microangiopathy. Abnormal glucose transport by fibroblasts has also been implicated (102).

Electron microscopic examination shows degenerative changes in collagen and elastin with loss of cross-striation in collagen fibrils. Collagen synthesis by fibroblasts is diminished (103).

Direct immunofluorescence studies have shown that necrobiotic foci contain fibrinogen. Deposits of immunoglobulin and C3 have been found in the vessel walls (104,105), but this is not a consistent finding (106).

Differential Diagnosis. Differentiation of necrobiosis lipoidica from granuloma annulare was discussed in the section on granuloma annulare.

Occasionally, necrobiosis lipoidica shows discrete collections of epithelioid cells that may resemble those seen in sarcoidosis (86). However, significant alteration of the collagen is usually present in necrobiosis lipoidica and absent in sarcoidosis (86).

Necrobiotic xanthogranuloma with paraproteinemia can simulate necrobiosis lipoidica but differs by showing a denser, more diffuse infiltrate with a greater number of foamy histiocytes, Touton giant cells, more extensive inflammation of the subcutis, and greater disruption of normal subcutaneous architecture. Lymphoid follicles and cholesterol clefts are more commonly seen in necrobiotic xanthogranuloma than in necrobiosis lipoidica (107).

Differentiation of necrobiosis lipoidica from annular elastolytic granuloma was discussed in the section on annular elastolytic granuloma.

RHEUMATOID NODULES

Rheumatoid nodules are deeply seated firm masses that occur in patients with rheumatoid arthritis, particularly over extensor prominences, such as the proximal ulna, the olecranon process, and the metacarpophalangeal and proximal interphalangeal joints (108). They may occur elsewhere, such as the back of the hands, over amputation stumps (109), and, rarely, in extracutaneous sites, such as the lung and heart (110,111). The nodules vary in size from a few millimeters to 5 cm and may be solitary or numerous (110). Rarely, rheumatoid nodules show a central draining perforation (112). Rheumatoid factor is almost always found in high titer. Rarely, nodules may precede apparent joint disease (108). The rapid appearance of many small rheumatoid nodules has been reported in some patients treated with methotrexate. This presentation has been termed accelerated rheumatoid nodulosis (113,114). The term rheumatoid nodulosis has been proposed for the clinical presentation of multiple nodules on the hands/elbows with intermittent arthralgias/arthritis but no evidence of systemic rheumatoid arthritis (115). Rheumatoid nodules also occur in occasional patients with systemic lupus erythematosus who do not exhibit rheumatoid arthritis (116–118).

Pseudorheumatoid nodule is a term that has been applied to nodules in the subcutis that mimic rheumatoid nodules histologically but that develop in the absence of joint pain, rheumatoid arthritis, or systemic lupus erythematosus (13,14,21). These occur in children or adults. The subsequent development of rheumatoid arthritis occurs infrequently in adults and rarely, if ever, in children. Because some of these nodules occur in patients with other lesions that are typical of intradermal granuloma annulare (13,14), the nodules are now generally considered to represent a subcutaneous variant of granuloma annulare.

Histopathology. Rheumatoid nodules occur in the subcutis and deep dermis. They exhibit one or several areas of fibrinoid degeneration of collagen that stain homogeneously red (Fig. 14-14). Nuclear fragments and basophilic material are often present, but mucin is almost always minimal or absent (45). These foci of degenerative change are surrounded by histiocytes in a palisade. Foreign-body giant cells are present in approximately 50% of biopsies (45). In the surrounding stroma, there is a proliferation of blood vessels associated with fibrosis. A sparse infiltrate of other inflammatory cells is associated with the histiocytes and surrounding stroma. Lymphocytes and neutrophils are most common, but mast cells, plasma cells, and eosinophils may be present. Occasionally, lipid is seen (13,45). Vasculitis has been described (119) but is

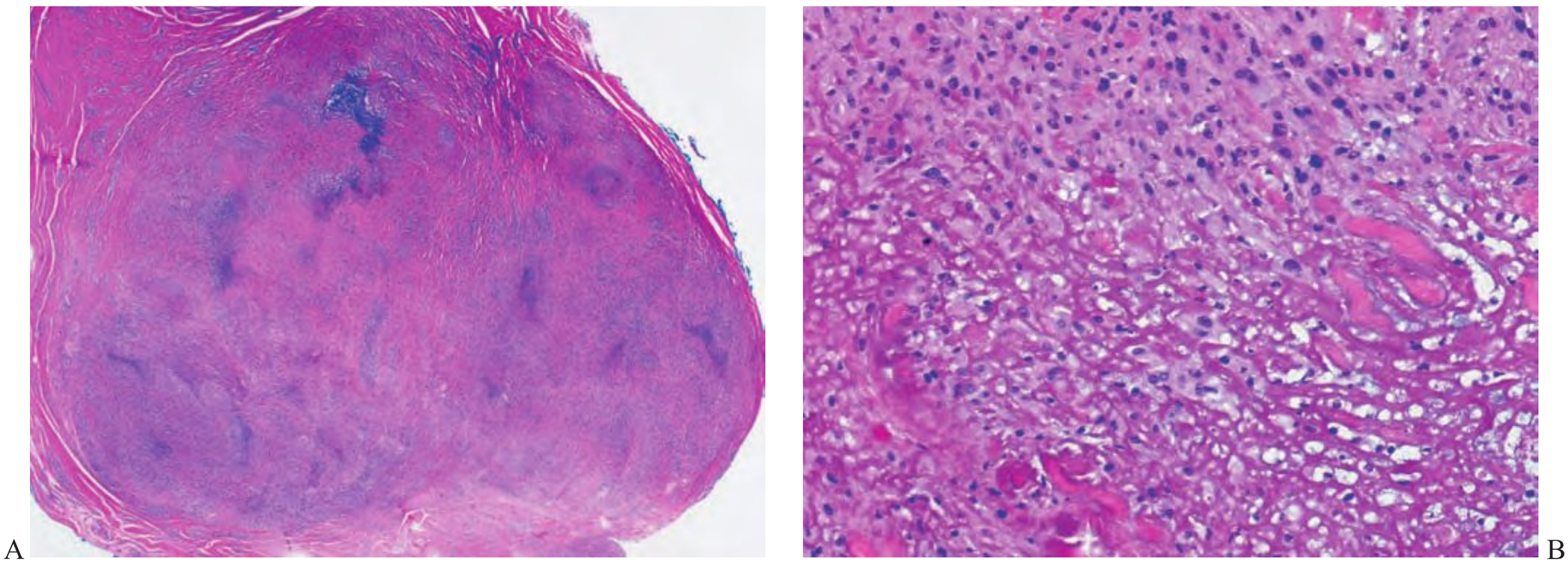


FIGURE 14-14. Rheumatoid nodule. A: A deeply seated, circumscribed nodule exhibits palisading around basophilic material. B: Fibrin is surrounded by histiocytes in a palisaded arrangement.

not usually encountered (45). In perforating rheumatoid nodules, the central fibrinoid material connects to the overlying skin surface (112).

Pathogenesis. Factors that have been implicated in the formation of rheumatoid nodules include trauma, vasculitis, and a specific T-cell–mediated immune reaction (108,120).

Differential Diagnosis. The principal differential diagnosis is subcutaneous granuloma annulare, which was discussed in the section on granuloma annulare. A distinction should be made from epithelioid sarcoma, which was also covered in that section. Nonabsorbable sutures or other foreign material may produce periarticular palisaded granulomas like those of rheumatoid nodule (121,122); in such instances, there should be a history of previous surgery or trauma, and birefringent material may be visible under polarized light. Rheumatic fever produces nodules (rheumatic nodules), especially over the elbows, knees, scalp, knuckles, ankles, and spine (123), which were confused with rheumatoid nodules in the early part of the 20th century. Histologically, a rheumatic fever nodule is less likely to show central, homogeneous fibrinoid necrosis. A palisade of histiocytes is usually not as well developed, and fibrosis is minimal or absent (110,124). Rarely, an infectious process, such as cryptococcosis, can produce a deep, palisaded granuloma. It can be differentiated from rheumatoid nodule because the palisade surrounds primarily necrotic debris and organisms rather than fibrinoid material.

PALISADED NEUTROPHILIC AND GRANULOMATOUS DERMATITIS

In 1983, Finan and Winkelmann reported on 27 patients with a variety of systemic disorders who had cutaneous lesions comprising a palisaded granulomatous infiltrate with prominent neutrophils. These patients often had umbilicated papules and nodules on the elbows and extensor surfaces of the digits (125) (Fig. 14-15). They termed this condition Churg-Strauss *granuloma* or cutaneous extravascular necrotizing granuloma. Of note, only a minority of these patients had Churg-Strauss *disease*, and many had a connective tissue disorder. Others observed similar lesions in patients with rheumatoid arthritis and described them under names such as *rheumatoid papules* (126,127) and *superficial ulcerating rheumatoid necrobiosis* (128,129). In 1994, Chu et al. reported on nine patients with connective tissue disorders and cutaneous lesions similar to those described in the foregoing (130). Biopsies from some of these patients showed histologic changes in early lesions that were judged to be a unique form of leukocytoclastic vasculitis (130). They proposed the term *palisaded neutrophilic and granulomatous dermatitis* to cover the spectrum of lesions in this



FIGURE 14-15. Palisaded, neutrophilic and granulomatous dermatitis. Umbilicated erythematous papules of the elbows.

disorder: early vasculitic lesions, later palisaded granulomatous lesions, and late stage lesions, which resembled necrobiosis lipoidica histologically (but not clinically). *Interstitial granulomatous dermatitis* likely represents a variant of palisaded neutrophilic and granulomatous dermatitis in which patients may present with long, linear, "ropelike" dermal lesions on the trunk, sometimes associated with more typical acral papules and nodules (131,132). Additional patients with similar histologic findings have been reported with other cutaneous manifestations such as plaques, which may be annular (133–135).

Histopathology. There are three, sometimes overlapping histologic patterns in this rare condition: (a) early lesions resembling leukocytoclastic vasculitis, (b) fully developed lesions with a granuloma annulare–like appearance but associated with prominent neutrophils, and (c) a fibrosing, necrobiosis lipoidica–like final stage.

Early lesions show a superficial and deep, diffuse infiltrate of neutrophils with leukocytoclasis, amorphous stringy basophilic debris, and degenerated collagen (130,136). There is vasculitis with unusually broad cuffs of fibrin that separate the vessels from the surrounding basophilic material and altered collagen. Extravasated red cells are scant. Papillary dermal edema is typical, and the epidermis may be ulcerated or hyperplastic.

The fully developed lesions of this condition are more often encountered. They show a palisaded, granulomatous infiltrate with some resemblance to granuloma annulare (130,136) (Figs. 14-16 and 14-17). Whereas vasculitic changes are usually not conspicuous at this stage, neutrophilic dust and intact neutrophils are present in the centers of the palisades, accompanied by thickened, degenerated collagen bundles, fibrin, and mucin (Fig. 14-17).

The uncommonly encountered late or third-stage findings include histiocytes in a palisade around degenerated collagen,

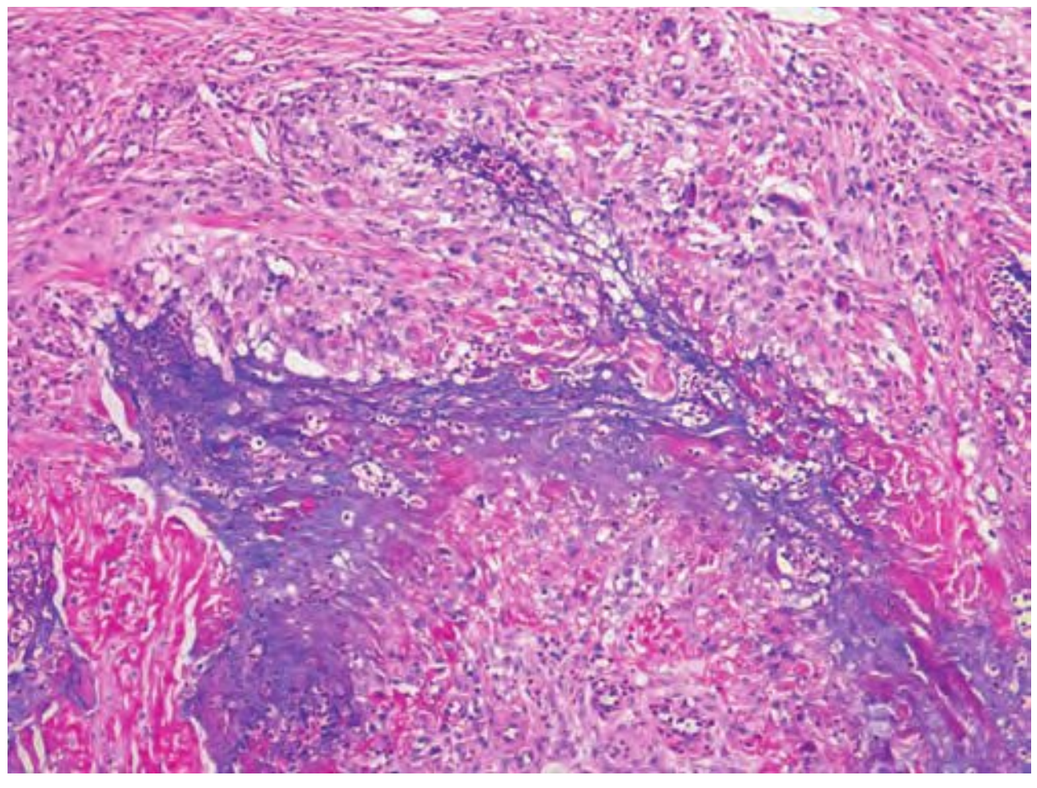


FIGURE 14-16. Palisaded, neutrophilic and granulomatous dermatitis. This fully developed lesion exhibits palisades of histiocytes, associated with neutrophils, basophilic debris, mucin, and degenerated collagen.

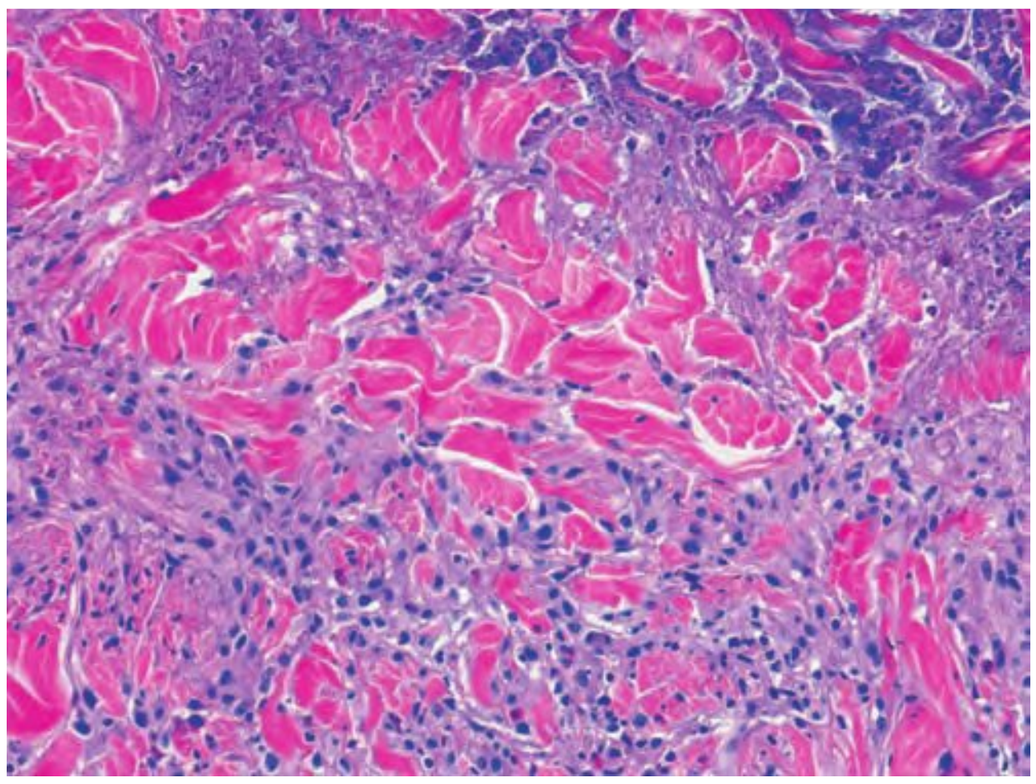


FIGURE 14-17. Palisaded, neutrophilic and granulomatous dermatitis. Neutrophilic dust and intact neutrophils are present in the centers of the palisades, accompanied by degenerated collagen bundles, fibrin, and mucin.

fibrin, and scattered neutrophils (130), with fibrosis in the dermis between the granulomas. Wisps of mucin may be present at the periphery of granulomas but not in their centers. There may also be a sparse, superficial, and deep perivascular infiltrate of lymphocytes and eosinophils.

Pathogenesis. Palisaded neutrophilic and granulomatous dermatitis has been associated with a wide variety of conditions. Whereas most are connective tissue disorders, such as rheumatoid arthritis or lupus erythematosus, others include lymphoproliferative disorders, bacterial endocarditis, inflammatory bowel disease, thyroid disease, diabetes mellitus, and infections (130,137). This condition is believed to represent an unusual immune complex–mediated vasculitis. Immunoglobulin M and C3 have been identified in small-vessel walls. The changes seen in fully developed lesions are believed to be a response to the vasculitic changes accompanying ischemia and enzymatic degradation by neutrophils.

Differential Diagnosis. Early lesions of palisaded neutrophilic and granulomatous dermatitis may be distinguished from other forms of leukocytoclastic vasculitis by the presence of unusually broad cuffs of fibrin around vessel walls, which separate the vessels from abundant basophilic nuclear debris. In addition, compared to most examples of leukocytoclastic vasculitis, early palisaded neutrophilic and granulomatous dermatitis shows a denser infiltrate of neutrophils and more nuclear debris diffusely throughout the dermis.

Fully developed lesions resemble *granuloma annulare* but differ from it by showing less prominent mucin, more fibrin, and thickening of collagen bundles. Whereas granuloma annulare may occasionally show nuclear debris, it is not as prominent as in palisaded neutrophilic and granulomatous dermatitis. This disorder also shows intact neutrophils, whereas

granuloma annulare only rarely does so. *Churg-Strauss disease* may show findings similar to palisaded neutrophilic and granulomatous dermatitis but differs by showing a predominance of eosinophils rather than neutrophils. Lesions of *Wegener's granulomatosis* are more likely to show active vasculitic changes concurrent with the palisaded granulomatous component. Drug eruptions (138) and infections with a palisaded and neutrophilic response may also be seen.

SARCOIDOSIS

Sarcoidosis is a granulomatous disease, often systemic, of undetermined cause. A distinction is made between the rare subacute, transient type of sarcoidosis and the usual chronic, persistent type.

In subacute, transient sarcoidosis, erythema nodosum is associated with hilar adenopathy, fever, and, in some cases, migrating polyarthritis and acute iritis. The disease subsides in almost all patients within a few months without sequelae. Cutaneous manifestations other than erythema nodosum do not occur (139,140). Occasionally, there is enlargement of some of the subcutaneous lymph nodes, such as the submental or cervical nodes (140,141).

In systemic sarcoidosis, cutaneous lesions are encountered in approximately one fourth of patients who are seen in medical departments (142). In contrast, cutaneous lesions are the only manifestation of sarcoidosis in about one fourth of patients with sarcoidosis seen in dermatologic departments (36,143,144).

In the United States, this disorder is much more common and is more severe in African Americans (145,146). It is rare in children (147–149). A rare genetic disorder, Blau's syndrome, may present in childhood and mimic sarcoidosis. This autosomal dominant disorder is marked by granulomatous inflammation of the skin, uveal tract, and joints, sparing the lungs (150,151).

The most common cutaneous lesions of sarcoidosis are brown-red or purple papules and plaques (152) (Fig. 14-18). Through central clearing, annular or circinate lesions may result. When papules or plaques of sarcoidosis are situated on the nose, cheeks, and ears, the term *lupus pernio* is applied (153). This presentation has been associated with upper respiratory involvement and greater disease severity (152,154).

A rare form of sarcoidosis is its lichenoid variant, in which small, papular lesions occur (155). Very rare manifestations of sarcoidosis include erythrodermic, ichthyosiform, atrophic, ulcerating, verrucous, angiolupoid, hypopigmented, alopecic, and morpheaform variants. In erythrodermic sarcoidosis, the erythroderma may be generalized (156) or may consist of extensive, sharply demarcated, brown-red, slightly scaling patches with little or no palpable infiltration (157). In ichthyosiform sarcoidosis, ichthyotic changes favor the lower extremities (158), but at times they also may be present elsewhere on the skin (159,160). Rarely, there are extensive atrophic lesions (161). They may undergo ulceration (162,163). Multiple ulcers have been described also in plaque-like lesions (164). Angiolupoid sarcoid is characterized by a prominent telangiectatic component (165). Lesions of hypopigmented sarcoid appear as macules with or without an associated papular or nodular component (166).

Subcutaneous nodules of sarcoidosis are also rare. Originally described by Darier and Roussy (167), they may occur in association with other cutaneous lesions (157,168) or alone (169). Up to 80% to 90% of patients with subcutaneous sarcoidosis may have associated systemic disease (170). Sarcoidosis has been described in AIDS patients (171), and a transient form of chronic sarcoidosis has been reported in patients with hepatitis C undergoing treatment with interferon alfa and ribavirin (172).

Systemic sarcoidosis occasionally coexists with granuloma annulare (36). Cutaneous lesions of sarcoidosis may localize to areas of scarring, as in herpes zoster scars (173,174). Tattoos (175,176), exogenous ochronosis (177), or other exogenous materials in the skin (178) may serve as a nidus for cutaneous lesions in patients with sarcoidosis. Two studies demonstrated polarizable foreign material in approximately 20% of cutaneous sarcoidal lesions from patients with systemic sarcoidosis (179,180).



FIGURE 14-18. Sarcoid. Pink-brown papules in clusters on the neck.

Histopathology. The lesions of erythema nodosum occurring in subacute, transient sarcoidosis have the same histologic appearance as "idiopathic" erythema nodosum (141).

Like lesions in other organs, the cutaneous lesions of chronic, persistent sarcoidosis are characterized by the presence of circumscribed collections of epithelioid histiocytes—so-called epithelioid cell tubercles—which show little or no necrosis (Figs. 14-19 and 14-20).

The papules, plaques, and lupus pernio–type lesions show variously sized aggregates of epithelioid cells scattered irregularly through the dermis with occasional extension into the subcutis (181). In the erythrodermic form, the infiltrate shows small granulomas in the upper dermis intermingled with numerous lymphocytes (157,182) and, rarely, also giant cells (183). Typical sarcoidal granulomas are found in the ichthyosiform lesions (159), in ulcerated areas (164), and in atrophic lesions (184,185). Verrucous sarcoid exhibits prominent associated acanthosis and hyperkeratosis (186,187). Biopsies of

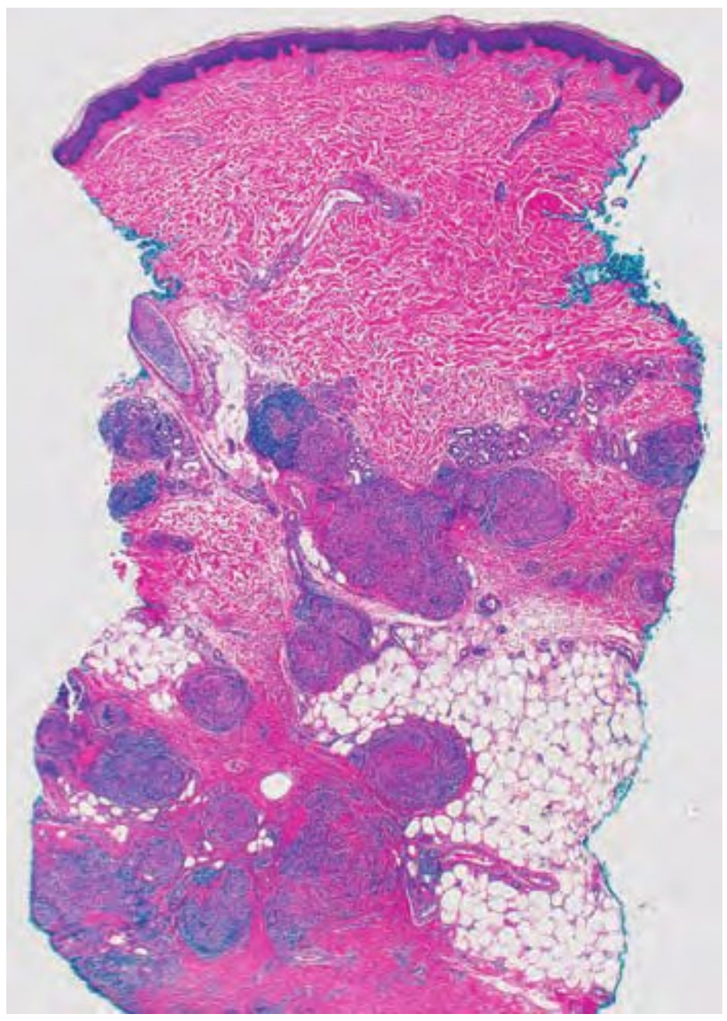


FIGURE 14-19. Sarcoid. There are well-circumscribed, nodular collections of epithelioid histiocytes in the dermis. This example also shows subcutaneous involvement, which is less common than purely dermal involvement.

hypopigmented sarcoid may reveal granulomas, which may have a perineural component or fail to reveal granulomas (188). In subcutaneous nodules, larger epithelioid cell tubercles lie in the subcutaneous fat (169).

In typical cutaneous lesions of sarcoidosis, the well-demarcated islands of epithelioid cells contain few, if any, giant cells. Those that are present are usually of the Langhans type. A moderate number of giant cells can be found in old lesions. These giant cells may be large and irregular in shape. In a minority of cases, giant cells contain asteroid bodies or Schaumann bodies

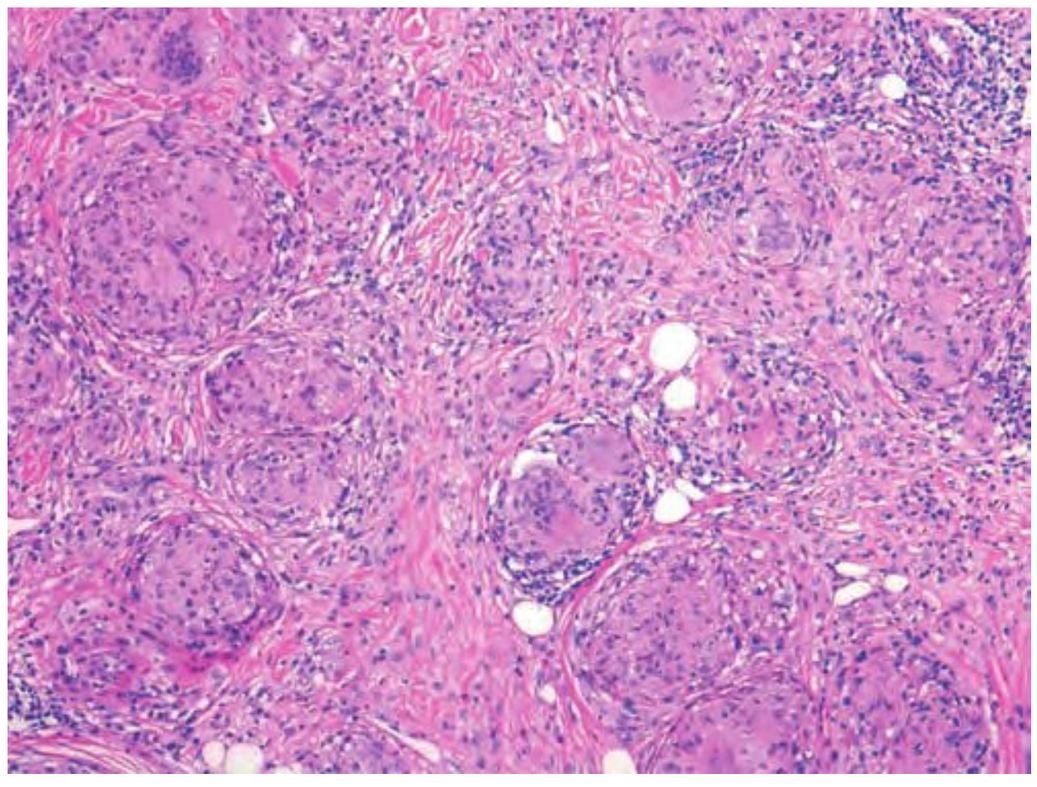


FIGURE 14-20. Sarcoid. Well-circumscribed, roundish collections of epithelioid histiocytes, some multinucleated, with few lymphocytes.

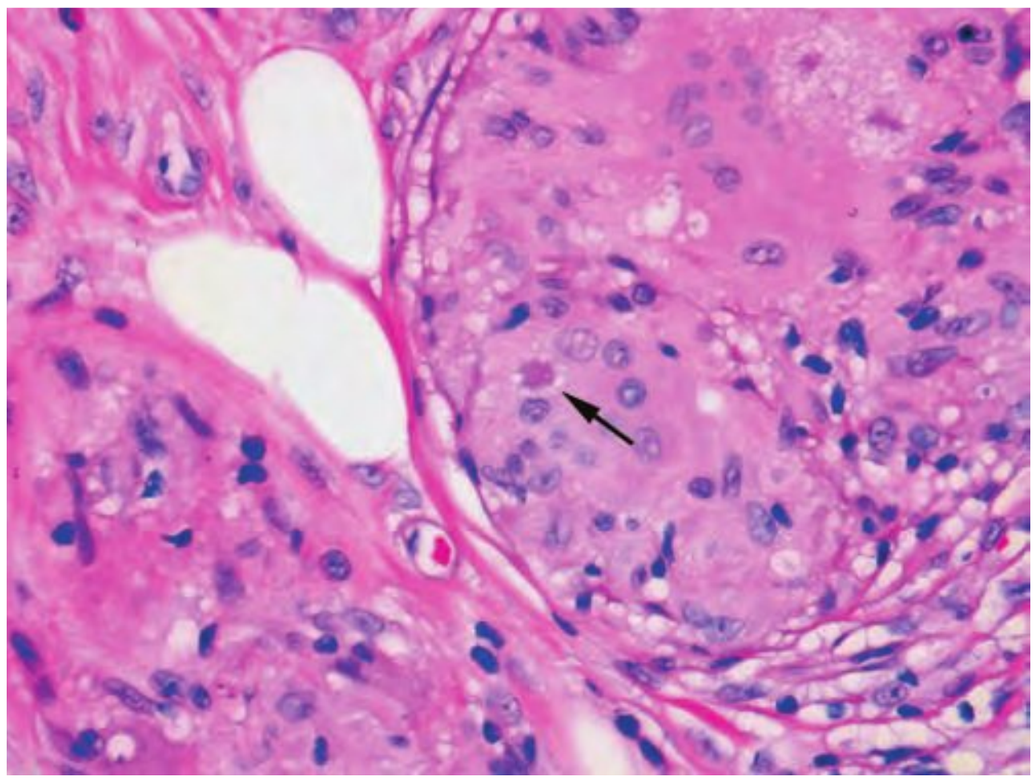


FIGURE 14-21. Sarcoid. Three star-shaped, eosinophilic asteroid bodies are present, one at the arrow and two in the upper right.

(189). Asteroid bodies (Fig. 14-21), which are more common, are star-shaped eosinophilic structures that, when stained with phosphotungstic acid–hematoxylin, produce a center that is brown-red with radiating blue spikes (157). Schaumann bodies are round or oval, laminated, and calcified, especially at their periphery. They stain dark blue because of the presence of calcium. Neither of these two bodies is specific for sarcoidosis: They have been observed in a variety of other granulomas, including those of leprosy, tuberculosis, foreign-body reactions, and necrobiotic xanthogranuloma (190).

Classically, sarcoid has been associated with only a sparse lymphocytic infiltrate, particularly at the margins of the epithelioid cell granulomas (Fig. 14-20). Because of the scarcity of lymphocytes, the granulomas have been referred to as "naked" tubercles. However, lymphocytic infiltrates in sarcoid may occasionally be dense, as in tuberculosis (Fig. 14-22). Occasionally, small foci of fibrin or necrosis showing

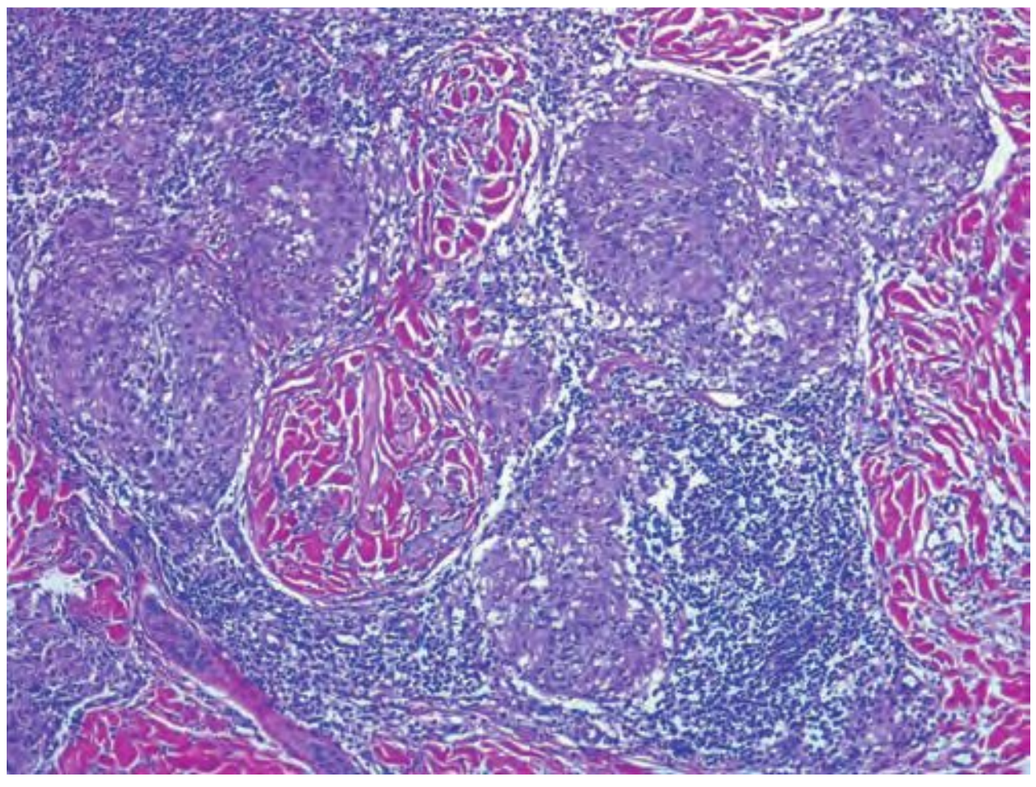


FIGURE 14-22. Sarcoid. A fairly dense lymphocytic infiltrate is associated with the epithelioid histiocytes, a less common finding than the usual "naked tubercles."

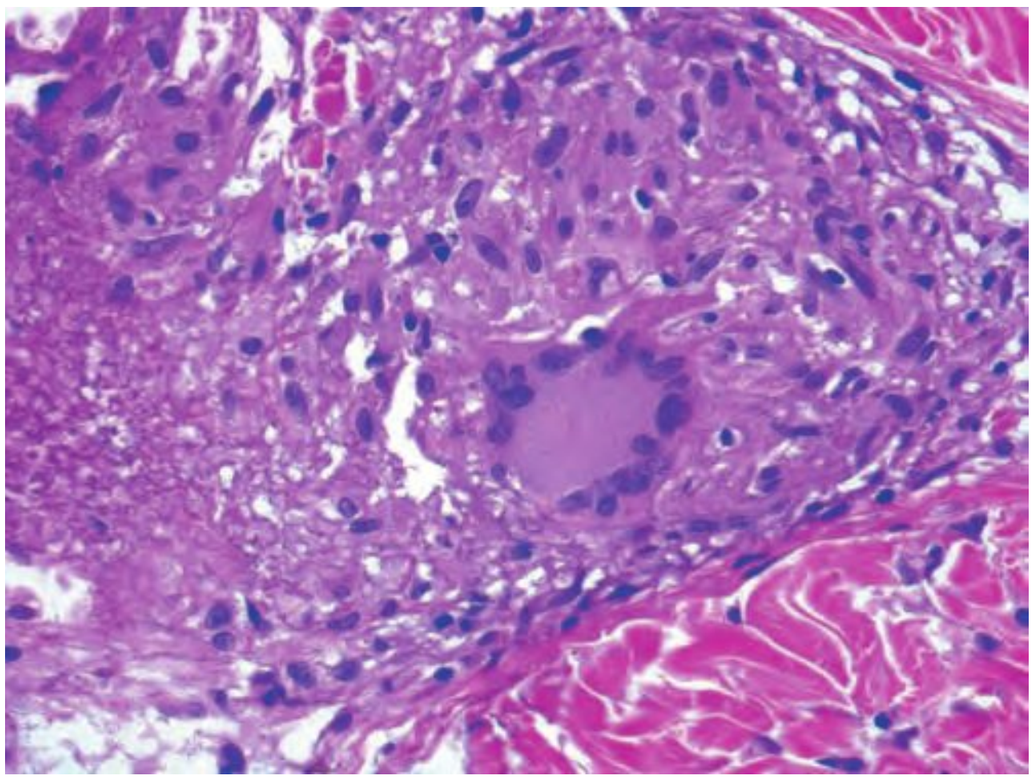


FIGURE 14-23. Sarcoid. On the left is fibrinoid material within the granulomatous component.

eosinophilic staining is found in the center of some of the granulomas (Fig. 14-23) (154,181). A reticulum stain of sarcoid reveals a network of reticulum fibers surrounding and permeating the epithelioid cell granulomas. If the granulomas of sarcoidosis involute, fibrosis extends from the periphery toward the center, with gradual disappearance of the epithelioid cells (181). Fibrosis, however, is minimal to absent in most examples of sarcoidosis, with the exception of the morpheaform variant, where it is prominent (191). Other features that may sometimes be seen include elastophagocytosis, increased dermal mucin, and lichenoid inflammation (192).

Systemic Lesions. The lungs are the most commonly involved organ in the chronic, persistent type of sarcoidosis, and respiratory symptoms are present in approximately 50% of patients (140). The lesions may be either nodular or diffuse with extensive parenchymal fibrosis.

In about 25% of the patients, ocular manifestations occur, most commonly chronic iridocyclitis. Splenomegaly is present in about 17%. In approximately12%, osseous granulomas are present, most commonly in the phalanges of the fingers and toes. Involved phalanges appear swollen and deformed, often sausage-shaped (193). The skull may show circumscribed lytic lesions (194). About 8% of the patients have involvement of large salivary glands, usually the parotid. In about 5%, one encounters paresis of a cranial nerve, most commonly of the facial nerve (140). Oral mucosal involvement occurs very rarely (195). Asymptomatic enlargement of the hilar lymph nodes is present in 70%, of peripheral lymph nodes in 30%, and of the liver in 20% of the patients (140,196).

Sarcoidosis, although usually a benign disease, is fatal in approximately 5% of patients (140,196). The most common cause of death from sarcoidosis is right ventricular failure resulting from massive pulmonary involvement. Pulmonary hemorrhage and superimposed tuberculosis are rare causes of death. Another potentially fatal complication is renal insufficiency resulting from hypercalcemia and hypercalciuria (197) or from sarcoidal glomerulonephritis (198). In very rare instances, death results from massive involvement of the myocardium (199) or liver (200). Hypopituitarism from involvement of either the pituitary gland or the hypothalamus is also a rare fatal complication (201).

The diagnosis of sarcoidosis in a patient with systemic disease is based on clinical presentation, biopsy findings, and exclusion of other granulomatous processes. If skin lesions are present, they are an obvious choice for biopsy. In the absence of skin lesions, a Kveim test was frequently used in the past. The Kveim test involves intradermal injection of antigen derived from heat-sterilized suspension of sarcoidal tissue, particularly spleen or lymph node. The site is sampled 6 weeks later, with a positive result being the formation of a sarcoid-like granuloma (202,203). The test has a sensitivity of about 80%, with false-positive reactions occurring in less than 2% of cases (204). However, Kveim antigen is neither widely available nor approved by the U.S. Food and Drug Administration. It is infrequently used (145). The most accepted alternative approach for confirming a presumptive diagnosis of systemic sarcoidosis is fiberoptic bronchoscopy with transbronchial lung biopsy (205). Endobronchial biopsy has also been shown to be useful (206), as has asymptomatic gastrocnemius muscle biopsy (207). Less specific ancillary tests, such as serum angiotensin-converting enzyme levels, can provide supportive data (146).

Pathogenesis. The cause of sarcoidosis is unknown, and the disease may not have the same pathogenesis in all individuals. Alterations in immunologic status have long been recognized, including hypergammaglobulinemia, impaired delayed-type hypersensitivity reactions to cutaneous antigens (anergy), and a shift of helper T lymphocytes from peripheral blood to sites of disease activity (208). However, these immunologic phenomena may represent a response to an as-yet-unidentified antigen (209). Mycobacteria, especially cell-wall–deficient forms, have been postulated to represent the antigen source (209–212). *Mycobacterium* tuberculosis has been implicated by some studies, whereas others have suggested atypical mycobacteria (212,213). Other infectious causes such as *Rickettsia* (214) have also been suggested.

Electron microscopic examination of epithelioid cells fails to show any evidence of bacterial fragments, unlike the macrophages seen in granulomas caused by mycobacteria, although the cells contain primary lysosomes, some autophagic vacuoles, and complex, laminated residual bodies (215). The giant cells form through the coalescence of epithelioid cells with partial fusion of their plasma membranes. Schaumann bodies likely arise from laminated residual bodies of lysosomes. Asteroid bodies consist of collagen showing the typical 64- to 70-nm periodicity. It seems likely that this collagen is trapped between epithelioid cells during the stage of giant-cell formation (215).

Differential Diagnosis. The histologic differentiation of sarcoidosis from lupus vulgaris may be very difficult, and it is

occasionally impossible. There is no absolute histologic criterion by which the two diseases can be differentiated with certainty. However, as a rule, the infiltrate in sarcoidosis lies scattered throughout the dermis, whereas the infiltrate in lupus vulgaris is located close to the epidermis. Furthermore, sarcoidosis usually shows few lymphoid cells at the periphery of the granulomas, giving them the appearance of "naked" granulomas. By contrast, lupus vulgaris often shows a marked inflammatory reaction around and between the granulomas. The granulomas of sarcoidosis usually show much less central necrosis than the granulomas of lupus vulgaris (216); however, not all biopsies of tuberculosis show necrosis, and some biopsies of sarcoid do. The epidermis in sarcoidosis is usually normal or atrophic. In lupus vulgaris, in addition to atrophy, areas of ulceration, acanthosis, and pseudocarcinomatous hyperplasia are not uncommon. The absence of identifiable mycobacteria with acid-fast stain cannot be used to exclude tuberculosis because the organisms in lupus vulgaris are scarce and may be difficult or impossible to find.

Foreign-body granulomas can also resemble sarcoidosis. Polariscopic examination in search of doubly refractile material, such as silica, should be performed on biopsies suspected of being sarcoidosis. The presence of foreign material does not exclude a concurrent diagnosis of sarcoidosis (189). The papular type of acne rosacea occasionally shows "naked" tubercles indistinguishable from those of sarcoidosis, but unlike sarcoid, they are usually perifollicular.

Tuberculoid leprosy, which may show granulomas in association with only a sparse lymphocytic infiltrate, can also be difficult to distinguish from sarcoidosis. Only 7% of cases of tuberculoid leprosy show acid-fast bacilli, and then only a few, so that they may easily be overlooked (217). The most likely place to find bacilli is within degenerated dermal nerves (the granulomas of tuberculoid leprosy form around dermal nerves that are undergoing necrosis). The granulomas of tuberculoid leprosy show small areas of central necrosis more often than those of sarcoidosis. In addition, the granulomas of tuberculoid leprosy, in contrast with those of sarcoidosis, follow nerves and therefore often appear elongated (218). Clinical correlation may be required to distinguish between these two diseases. For example, in the United States, leprosy virtually can be excluded if a patient has not been in an endemic area (either in a foreign country or where it is carried in armadillos domestically, e.g., Texas and Louisiana) or has not had prolonged close contact with another individual with the disease.

FOREIGN-BODY REACTIONS

Foreign substances, when injected or implanted accidentally into the skin, can produce a nonallergic foreign-body reaction or, in persons specifically sensitized to them, an allergic response (219). In addition, certain substances formed within the body may produce a nonallergic foreign-body reaction when deposited in the dermis or subcutis. Such endogenous foreign-body reactions are produced, for instance, by urates in gout and by keratinous material in pilomatricoma, as well as in ruptured epidermoid and trichilemmal cysts.

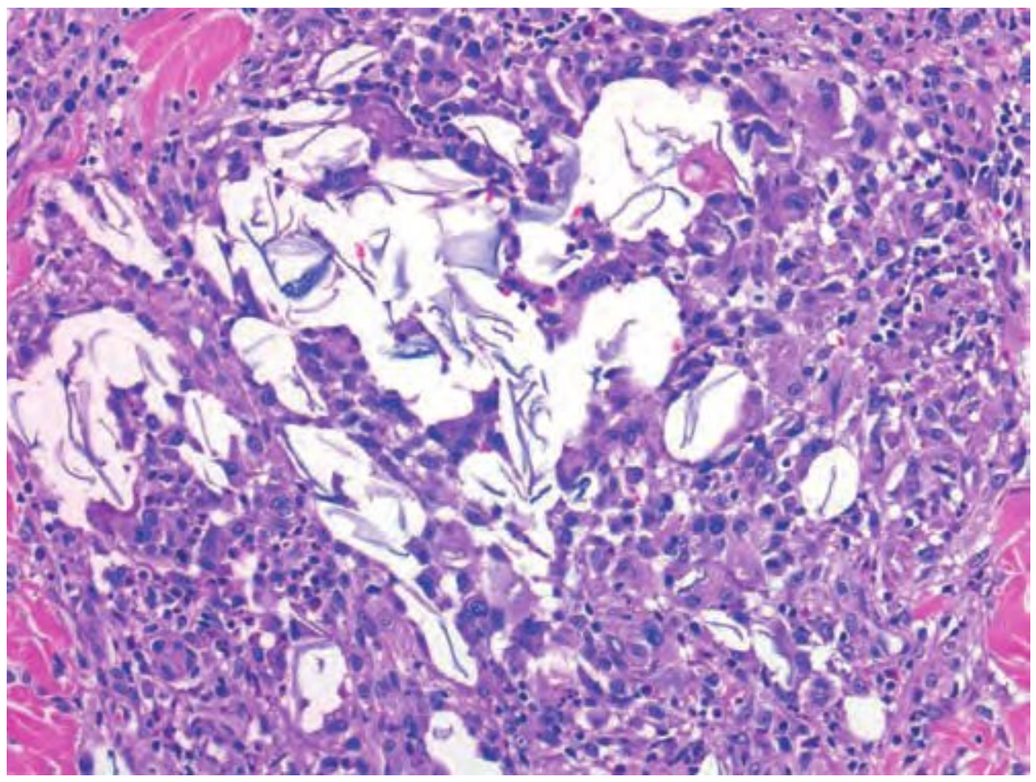


FIGURE 14-24. Ruptured epidermoid cyst. There are neutrophils and histiocytes surrounding cornified cells from the center of the cyst.

Histopathology. A *nonallergic* foreign-body reaction typically shows a granulomatous response marked by histiocytes and giant cells surrounding foreign material. Often, some of the giant cells are of the foreign-body type, in which the nuclei are in haphazard array. In addition, lymphocytes are usually present, as may be plasma cells and neutrophils. Frequently, some of the foreign material is seen within macrophages and giant cells, a finding that of course is of great diagnostic value. The most common cause of a foreign-body granuloma is rupture of a hair follicle or follicular cyst, and sometimes only the cyst contents, rather than residual cyst wall, is identifiable (Fig. 14-24). Exogenous substances producing nonallergic foreign-body reactions include silk and nylon sutures (Fig. 14-25),

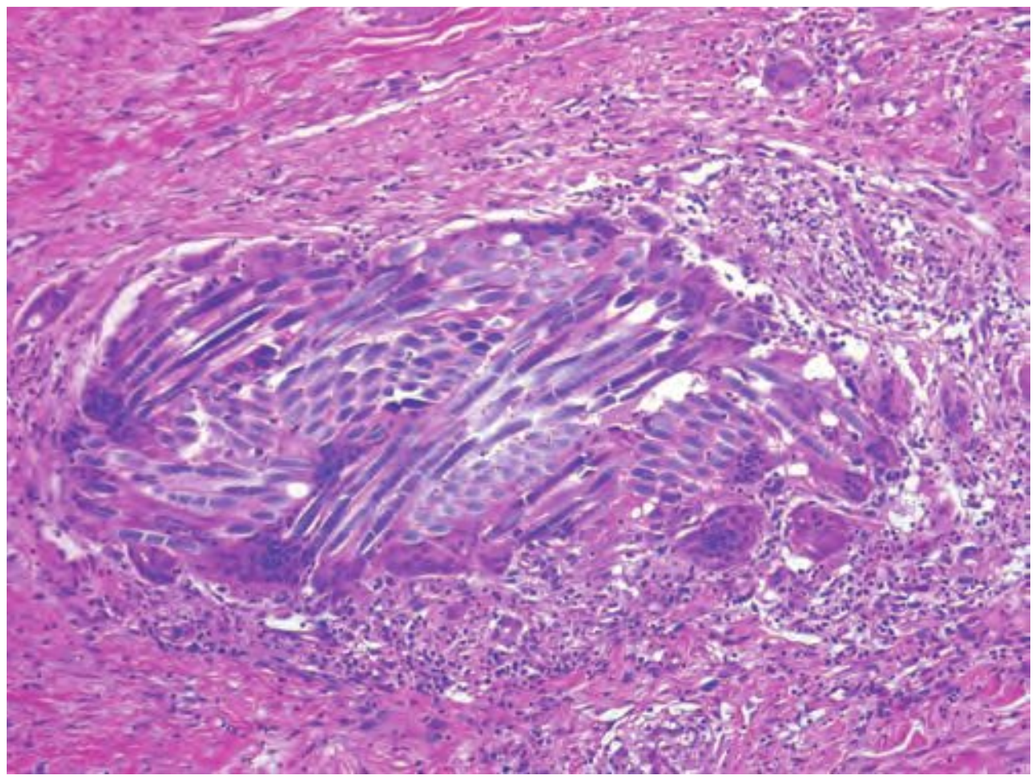


FIGURE 14-25. Foreign-body granuloma caused by nylon suture. The suture is composed of blue-gray, linear material and is surrounded by histiocytes, including many multinucleated foreign body–type giant cells.

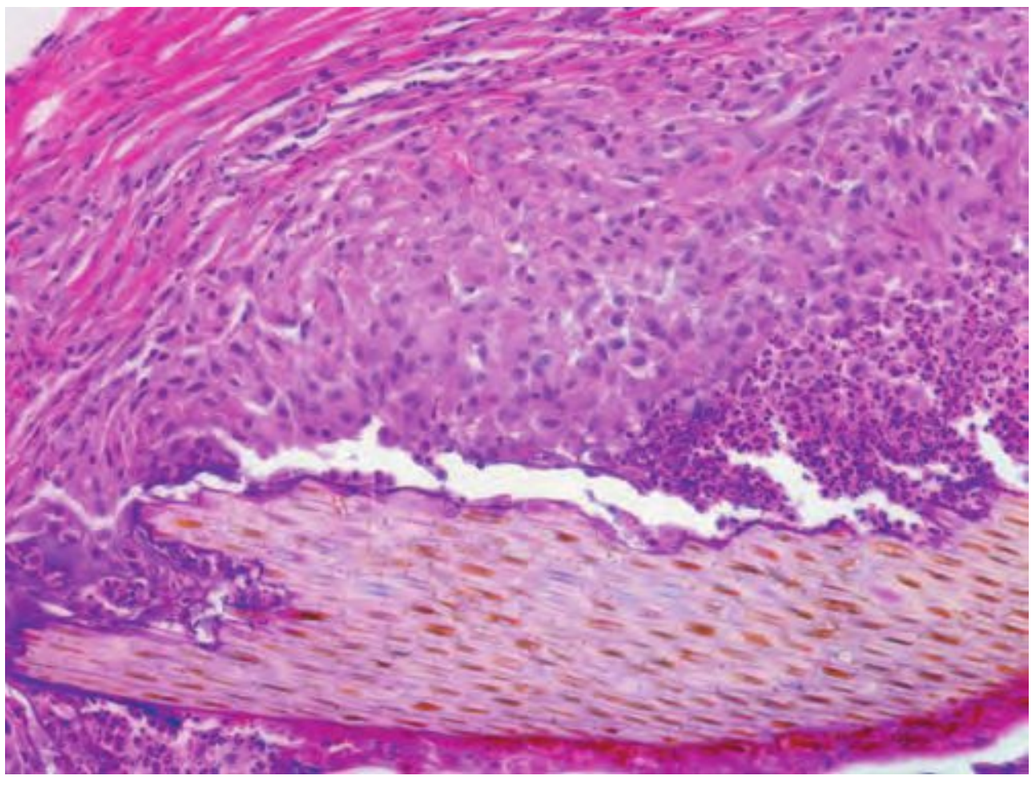


FIGURE 14-26. Foreign-body reaction to a wood splinter. The wood splinter shows an orderly arrangement of rectangular cells, typical of plant material, surrounded by a nodular infiltrate with histiocytes, including multinucleated histiocytes of the foreign-body type, and neutrophils.

wood or other plant material (Fig. 14-26), paraffin and other oily substances, silicone gel, talc, surgical glove starch powder, and cactus spines. Some of these substances—nylon sutures, wood, talc, surgical glove starch powder, and sea urchin spines—are doubly refractile on polarizing examination. Double refraction often is very helpful in localizing foreign substances. Knife marks in the section may be an additional clue to the presence of particulate foreign matter (Fig. 14-27).

An *allergic* granulomatous reaction to a foreign body typically shows a sarcoidal or tuberculoid pattern consisting of epithelioid cells with or without giant cells. Phagocytosis of the foreign substance is slight or absent. Substances that in sensitized persons produce an allergic granulomatous reaction include zirconium, beryllium, and certain dyes used in tattoos. Some substances that at first act as foreign material may later, after sensitization has occurred, act as allergens, as in the case of sea urchin spines and silica.

A histologic decision as to whether a granuloma is of the foreign-body type or of the allergic type is not always possible. A granuloma of the allergic type is more likely to show rounded, well-circumscribed collections of epithelioid histiocytes and less likely to have multinucleated histiocytes of the foreign-body type.

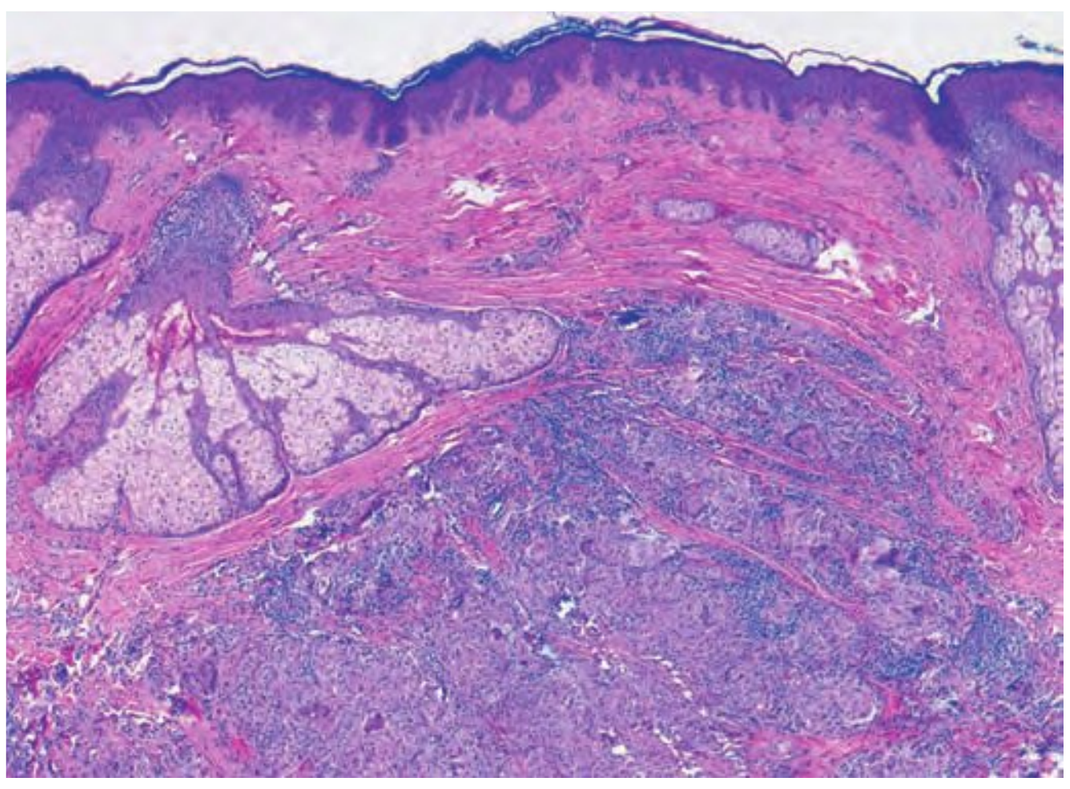


FIGURE 14-27. Foreign-body reaction. There are circumscribed, nodular collections of epithelioid histiocytes, similar to what may be seen in sarcoid, associated with knife marks (diagonally oriented in this photograph), which serve as a clue to the presence of the foreign material, which cannot be seen at this magnification.

Paraffinoma

Foreign-body reactions may occur following injections of oily substances such as mineral oil (paraffin) typically into the breasts (220), genitalia, or scalp (221) for cosmetic purposes. These occur as irregular, plaquelike indurations of the skin and subcutaneous tissue (222,223). Ulcers or abscesses may develop. The interval between the time of injection and the development of induration or ulceration may be many years.

The misleading term *sclerosing lipogranuloma* was given to paraffinoma of the male genitalia because of the disproved assumption that it was a local reactive process following injury to adipose tissue (224,225).

Histopathology. Paraffinomas have a "Swiss cheese" appearance because of the presence of numerous ovoid or round cavities that show great variation in size. These cavities represent spaces occupied by the oily substance (226). The spaces between the cavities are taken up in part by fibrotic connective tissue and in part by an infiltrate of macrophages and lymphocytes. Some of the macrophages have the appearance of foam cells. Variable numbers of multinucleated foreign-body giant cells are present.

In frozen sections of paraffinoma, the foreign material stains orange with Sudan IV or oil red O, although less so than neutral fat (226).

Silicone Granuloma

Reactions to medical-grade silicone have occurred after injection of its liquid form for cosmetic purposes or from leakage or rupture of silicone gel from breast implants. Leakage from silicone breast implants can cause development of subcutaneous nodules and plaques (227). Lesions containing silicone at sites adjacent to and, rarely, distant from areas of injection or implantation may occur (228,229). A localized reaction at injection sites by silicone-coated acupuncture or venepuncture needles has also been reported (230,231).

Histopathology. As in paraffinoma, numerous ovoid or round cavities of varying sizes are seen, resulting in a "Swiss cheese" appearance (Fig. 14-28). These spaces are what remain after the silicone has been removed during processing, although

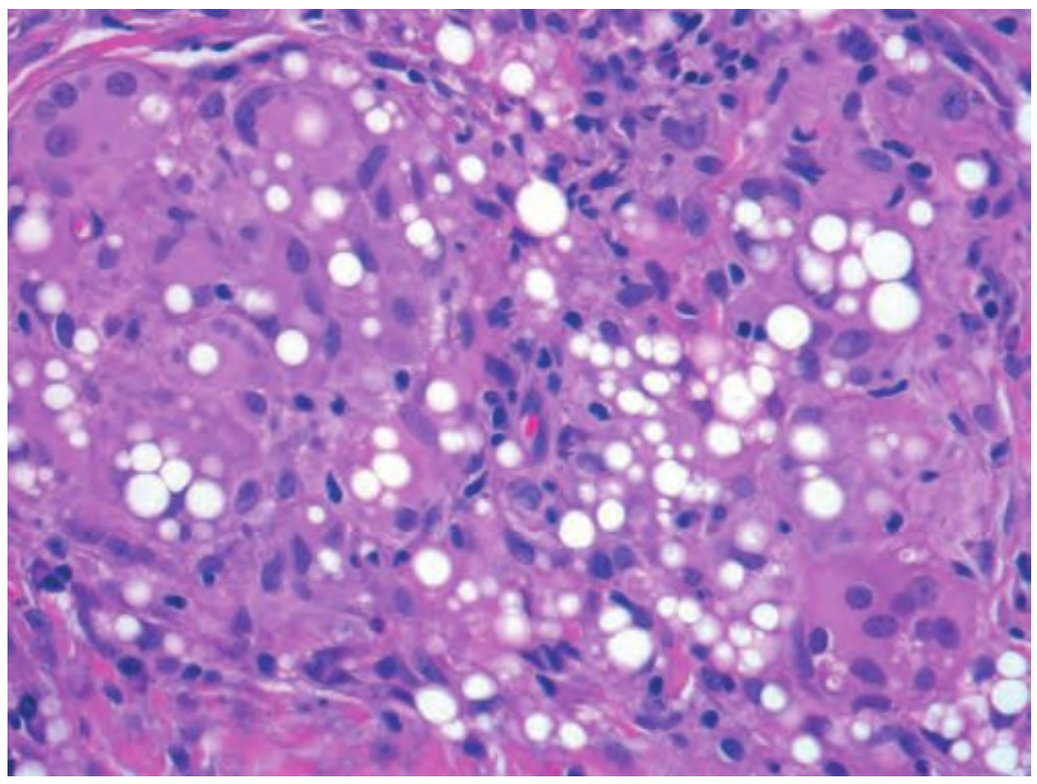


FIGURE 14-28. Silicone granuloma. Silicone used for cosmetic purposes may produce a granulomatous response with a "Swiss cheese" appearance. (Courtesy of John Walsh, MD.)

occasionally scant residual silicone is seen as colorless, irregularly shaped, refractile, nonpolarizable material within the spaces. Histiocytes may be present between the cavities; they can be foamy or multinucleated and accompanied by lymphocytes and eosinophils (227,232). In addition, varying degrees of fibrosis are present. The identification of silicone within a specimen can be facilitated via thick sectioning, dark-field microscopy, and other techniques (233).

Talc Granuloma

Talc (magnesium silicate) may produce granulomatous inflammation when introduced into open wounds. Historically, talc was used as powder on gloves, but this use has been abandoned for many years, and starch is now used for surgical dusting powder (234). However, talc may still be introduced into wounds either because of accidental contamination by a surgeon who uses talcum powder (234) or because talcum may be incorporated into the rubber glove during manufacturing (235). Talc may also be introduced into the skin through topical application of medications (236).

Histopathology. Histologic examination reveals histiocytes and multinucleated giant cells, some of which may contain visible particles of talc. Talc crystals can be needle shaped with a yellow-brown or blue-green hue and appear as white birefringent particles with polarized light (235). Their presence can be confirmed by x-ray diffraction studies (237) or energy-dispersive x-ray analysis (235).

Starch Granuloma

Granulomas may result from the contamination of wounds with surgical gloves powdered with corn starch (238).

Histopathology. A foreign-body reaction with multinucleated giant cells is present. Scattered through the infiltrate, one observes starch granules as ill-defined ovoid basophilic structures measuring 10 to 20 μm in diameter. Most of the granules are seen within foreign-body giant cells. They react with PAS and methenamine silver and, on examination in polarized light, are birefringent, showing a Maltese cross configuration (238).

Cactus Granuloma

Cactus granulomas show, within days or weeks after the injury, tender papules from which cactus spines may still protrude. They may be extruded spontaneously within a few months.

Histopathology. Early papules—a few days after the injury—show fragments of cactus spicules in the dermis that are associated with an intense, perivascular lymphohistiocytic infiltrate containing many eosinophils. After a few weeks, the infiltrate consists of lymphocytes, macrophages, and giant cells (239,240). Sharply marginated spicules are seen within giant cells and lying free in the dermis. The spicules are PAS positive (241).

Pilonidal Sinus

The pilonidal sinus is most often seen in young adult men over the sacrum (242). In barbers, the implantation of human hair in the interdigital web spaces may cause small, asymptomatic or tender sinus tracts (243,244). Similar lesions are even more common within web spaces or in other sites in dog groomers and other animal caretakers (245,246).

Histopathology. Histologic examination reveals a sinus tract lined by squamous epithelium containing one or several hairs, thus resembling a hair follicle. Either the sinus tract encases the hair completely, or, if the hair extends deeper than the sinus tract, one finds at the lower end of the hair a foreign-body giant-cell reaction intermingled with inflammatory cells (243,247).

Sea Urchin Granuloma

Injuries from the spines of sea urchins occur most commonly on the hands and feet. Even if the friable spines have been only incompletely removed, the wounds tend to heal after spontaneous extrusion of most of the foreign material (248,249). However, in some persons, violaceous nodules appear at the sites of injury after a latent period of 2 to 12 months (250).

Histopathology. The nodules are composed largely of epithelioid histiocytes and giant cells (248). Doubly refractile material is present in a minority of the granulomas (249). If remnants of a spine are still present, they are surrounded by leukocytes and many large foreign-body giant cells (249). A minority of patients show nongranulomatous findings, the most common of which is a neutrophilic infiltrate (251).

Pathogenesis. The appearance of sarcoid-like granulomas after a latent interval of months in only a small proportion of the injured patients suggests a delayed hypersensitivity reaction (250). The spines of sea urchins, in addition to the calcified material, contain remnants of epithelial cells (250). The double refraction that may be found in the granulomas may be due to the presence of a small amount of silica in the calcified spines (249).

Silica Granuloma

Silica (silicon dioxide) is present in rocks, soil, sand, and glass. It frequently contaminates accidental wounds, in which it sets up a foreign-body reaction of limited duration followed by fibrosis (252). In the vast majority of cases, silica causes no further sequelae. In exceptional cases, a granulomatous delayed hypersensitivity reaction occurs at the site of the old scar (253). The mean interval for this delayed hypersensitivity reaction is approximately 10 years, but it may be less than 1 year or more than 50 years after the original injury (254). When this reaction occurs, indurated papules or nodules develop at the site of injury.

Histopathology. In silica granuloma, there are groups of epithelioid histiocytes with a lymphocytic infiltrate that tends to be sparse (253–257). Foreign-body giant cells may be abundant or absent, and Langhans giant cells also may be present. If multinucleated histiocytes are not numerous, a picture resembling sarcoid is produced. However, the diagnosis of sarcoidosis may be excluded by clinical information and the presence, especially within giant cells, of crystalline particles varying in size from barely visible to 100 μm in length; they represent silica crystals. When examined with polarized light, these particles are doubly refractile (Fig. 14-29). The presence of silicon can be confirmed by x-ray spectrometric or energy-dispersive x-ray analysis (254,255).

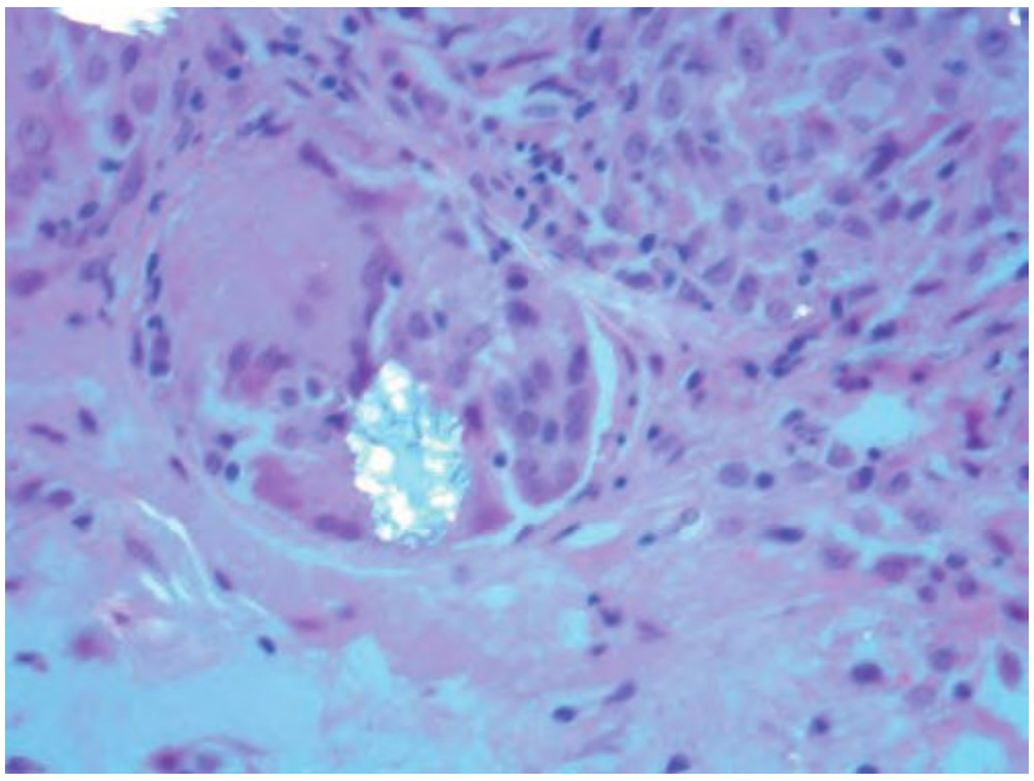


FIGURE 14-29. Silica. Silica, like other foreign materials with a crystalline structure, is doubly refractile when viewed under polarized light.

Pathogenesis. Evidence suggests that the sarcoid-like granulomatous response to silica that occurs long after initial injury represents a delayed-type hypersensitivity reaction (253,254,256,258).

Zirconium Granuloma

Deodorant sticks containing zirconium lactate and creams containing zirconium oxide may cause a persistent eruption composed of soft, red-brown papules in the areas to which they have been applied. Zirconium lactate is no longer present in antiperspirants sold in the United States; however, a granulomatous reaction has also been described in response to roll-on antiperspirant containing aluminum–zirconium complex (259,260).

Histopathology. Histologic examination shows large aggregates of epithelioid cells with a few giant cells and a sparse or moderately dense lymphocytic infiltrate, producing a picture that may be indistinguishable from sarcoidosis (261–263). Because of the small size of the zirconium particles, they cannot be detected on examination with polarized light (261). Their presence, however, can be demonstrated by spectrographic analysis (262) or energy-dispersive x-ray analysis (259).

Pathogenesis. Evidence that zirconium granulomas develop on the basis of an allergic sensitization to zirconium includes the following: (a) They occur only in persons sensitized to zirconium (264), (b) the pattern of granuloma inflammation is like that of other granulomatous dermatitides that have been attributed to delayed-type hypersensitivity reactions, and (c) autoradiographic analysis of experimentally induced lesions in sensitized individuals reveals no zirconium within histiocytes (265).

Reactions to Aluminum

Reactions to aluminum occur most often in the setting of surgical scars secondary to the use of aluminum chloride as a hemostatic agent, although these reactions are not clinically apparent. However, single or multiple persistent subcutaneous nodules may appear several months or even years after the subcutaneous injection of a variety of vaccines or allergen desensitization extracts that are aluminum adsorbed (266). The aluminum adjuvant is believed to prolong the period of activity of the vaccine or desensitization agent, thus increasing the immunologic response.

Histopathology. In surgical scars, the hemostatic agent aluminum chloride can be seen as granular violaceous-to-gray stippled deposits within macrophages (Fig. 14-30).

In subcutaneous nodules at injection sites, the most striking finding in some biopsy specimens is the presence of nodular aggregates of lymphocytes with lymphoid follicles and germinal centers within the dermis and subcutis. There is fibrosis, which may occur in bands that separate the lymphocytic nodules. Eosinophils may be prominent, and the condition may show a pseudolymphomatous appearance (267–269). The granulomatous component consists of histiocytes with ample cytoplasm and, in some cases, a few giant cells or large areas of

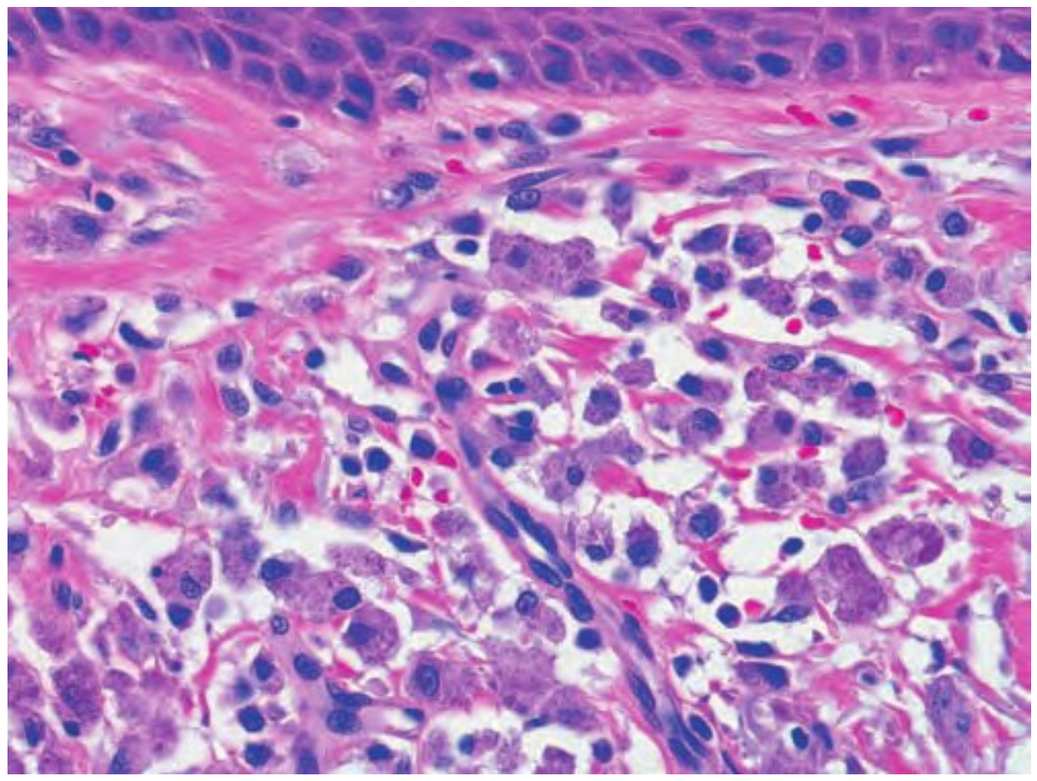


FIGURE 14-30. Aluminum chloride. Histiocytes with purplish granules as a consequence of aluminum chloride used for hemostasis during a previous procedure performed at this site.

eosinophilic necrosis surrounded by histiocytes in a palisade (268). Early lesions tend to show a reaction that is more purely granulomatous (266). Palisading granulomatous reactions have also been reported (270). There may be prominent septal and lobular inflammation of the panniculus (271). In any of the patterns that may occur, a key to making the diagnosis is the identification of histiocytes with abundant violaceous-to-gray granular cytoplasm; these granules contain aluminum and are PAS positive and diastase resistant (267).

Pathogenesis. This condition is believed to represent a delayed hypersensitivity reaction to aluminum. Electron microscopic examination reveals irregular membrane-bound, electron-dense material within macrophages. X-ray microanalysis has shown that the electron-dense material contains aluminum (267).

Titanium Granuloma

Titanium has been implicated rarely in the formation of granulomas, internally and in the skin, the latter as a consequence of body piercing (272).

Histopathology. An infiltrate of histiocytes, lymphocytes, and plasma cells is present, and some macrophages contain minute brown-black particles (272).

Zinc-Induced Granuloma

Local allergic reactions to insulin are not uncommon. However, the granulomatous response, which may occur with zinc-containing insulin preparations, is rare. It may begin with sterile furunculoid lesions (273,274).

Histopathology. The early furunculoid lesions show a dense neutrophilic infiltrate and many birefringent rhomboidal crystals of zinc insulin. Later, fibrosis and granulomatous inflammation develop (274).

Berylliosis

Beryllium granulomas are mostly of historical interest. Up to 1949, beryllium-containing compounds were widely used in the manufacture of fluorescent light tubes. Two diseases resulted from this: systemic berylliosis and local beryllium granulomas. Systemic berylliosis developed in some workers in plants manufacturing fluorescent tubes through inhalation of these compounds. Systemic berylliosis primarily shows pulmonary involvement, which results in death in about one third of the patients (275). Beryllium may reach the skin through blood circulation and cause cutaneous granulomas. However, this is a rare event, having been observed in one series in only 4 of 535 patients with systemic berylliosis (275). The granulomas consist of only a few papular lesions over which the skin remains intact.

Purely local beryllium granulomas occurred in persons who cut themselves on broken fluorescent tubes that were coated with a mixture containing zinc-beryllium silicate (276). The cutaneous granulomas after laceration show, as their first sign, incomplete healing of the laceration, followed by swelling, induration, tenderness, and, finally, central ulceration (277).

Histopathology. The cutaneous granulomas of systemic berylliosis, similar to those of sarcoidosis, show very slight or no caseation (275). The cutaneous granulomas following laceration, in contrast to the cutaneous granulomas of systemic berylliosis, show central necrosis, which may be pronounced (276). A moderately dense infiltrate of lymphocytes may be present, resembling the granulomas of tuberculosis. The epidermis shows acanthosis and possibly ulceration. No particles of beryllium are seen in histologic sections, but its presence in the lesions can be demonstrated by spectrographic analysis (277).

Pathogenesis. Systemic berylliosis develops on the basis of a delayed hypersensitivity reaction (278,279).

Tattoo Reactions

Clinically apparent inflammatory reactions to permanent tattoos, although uncommon, are now seen with greater frequency due to the rise in popularity of tattoos. They have been observed most commonly with red dyes containing mercuric sulfide, such as cinnabar (Chinese red). More recently, there has been a move away from using mercury-containing dyes toward the use of dyes containing other red pigments, such as ferric hydrate (sienna or red ochre), cadmium selenide (cadmium red), and organic dyes, but such mercury-free red dyes may also produce adverse reactions (280,281). Reactions have also been reported with chrome green (282), cobalt blue (283), purple manganese salts (284), yellow cadmium sulfide (285), and iron oxide (286). In some instances, an allergic response to the pigment has been suggested by a positive patch test.

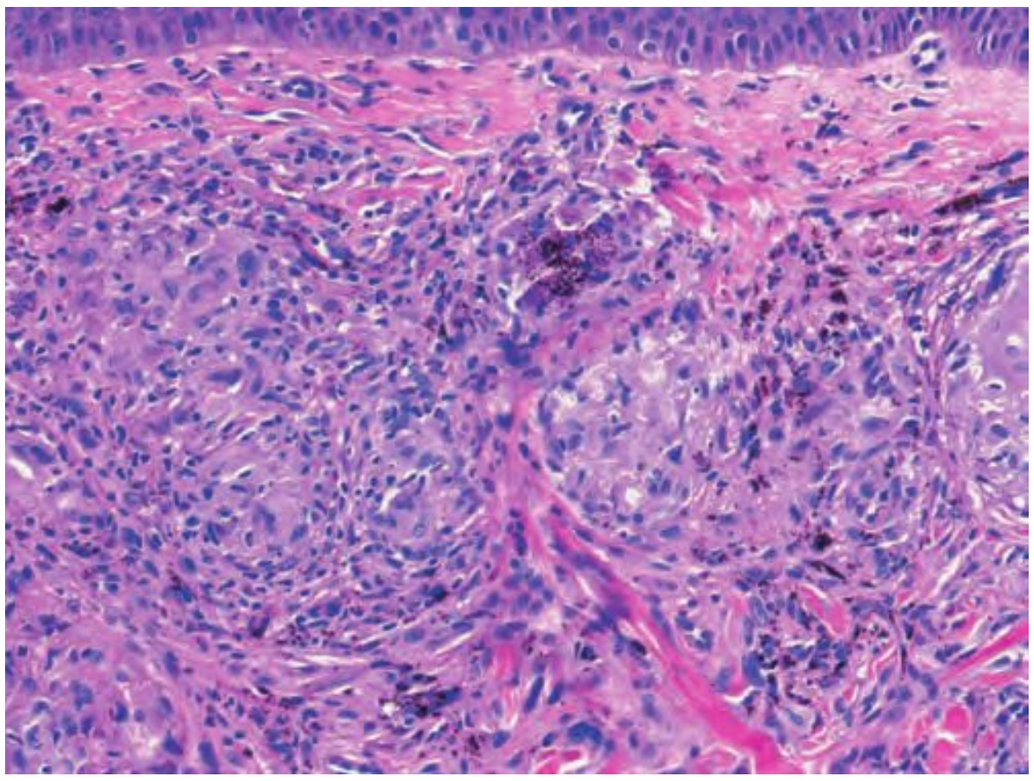


FIGURE 14-31. Decorative tattoo. Granulomatous inflammation in response to pigment used for a tattoo.

Reactions to "temporary" tattoos are rare. Usually comprised of black commercial henna, these tattoos are painted onto the skin surface. The most common reaction is allergic contact dermatitis, but a lichenoid dermatitis, a scarring reaction, and hypopigmentation have been reported (287–291).

Tattoos may also occur due to pigmented materials accidentally implanted in the skin, such as graphite, or due to solutions employed for hemostasis (292,293), particularly Monsel's solution (ferric subsulfate).

Histopathology. Permanent tattoos that are not clinically inflamed show irregularly shaped granules of dye that are located within macrophages and extracellularly in the dermis (294).

Inflammatory reactions in clinically inflamed permanent tattoos may or may not be granulomatous. Photoexacerbation has been described with reactions to red pigments (280,281) and yellow pigments (285). Nongranulomatous reactions include a perivascular lymphocytic infiltrate with pigment-containing macrophages (280,294), a lichenoid response, which in some instances may resemble lichen planus or hypertrophic lichen planus (280,281,295,296), and a pseudolymphomatous picture with a dense, nodular or diffuse, predominantly lymphocytic infiltrate that also contains histiocytes and coarse tattoo pigment granules (297,298).

Granulomatous reactions may be either of the sarcoidal type (282,299,300) or the foreign-body type (282,286). A tuberculoid pattern has also been described in response to cobalt blue, but this may have been due to a mycobacterial infection (301). The granulomatous responses show tattoo granules scattered throughout the infiltrate. In the sarcoidal type, the infiltrate contains nodules of epithelioid histiocytes (Figs. 14-31 and 14-32), and in the foreign-body type, there are obvious multinucleated histiocytes of the foreign-body type. A sparse or dense lymphocytic infiltrate may be present. In the sarcoidal type of reaction, regional lymph nodes may also show tattoo granules (302). There are some reports of patients with sarcoidal granulomas in their tattoos who also had pulmonary disease (175,299,300,303), uveitis (283,304), or erythema nodosum (299), suggesting a systemic hypersensitivity response to the tattoo, or true sarcoidosis.

Traumatic graphite tattoos show black granules free in the dermis and sometimes within histiocytes (Fig. 14-33). Monsel's tattoos, also typically seen in conjunction with scars, show multinucleate histiocytes containing coarse, brown, refractile pigment (Fig. 14-34), which is positive on staining for iron. Larger, brown, extracellular jagged aggregates of pigment are suggestive of Monsel's tattoo (305). Ferruginization of collagen bundles is typical, and a proliferation of spindled fibrohistiocytic cells may also occur.

Electron microscopic examination of tattoos without an allergic reaction shows that most tattoo granules are located within macrophages, where they often lie within membrane-bound lysosomes. In addition, some tattoo granules are found free in the dermis (306).

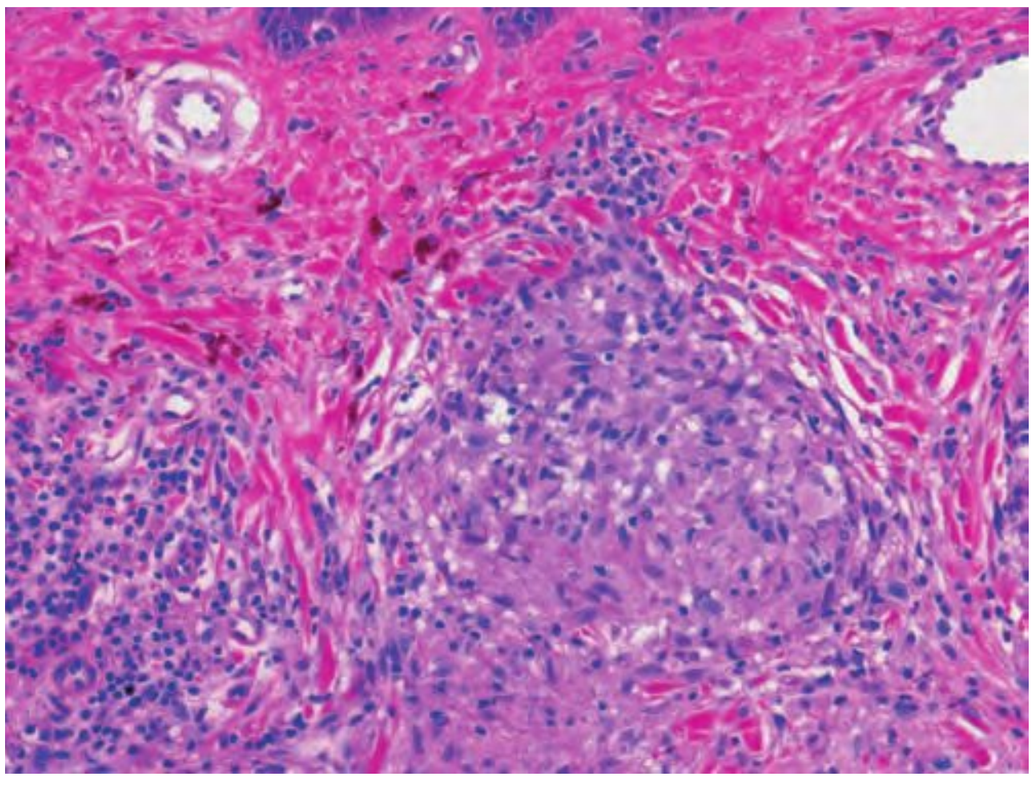
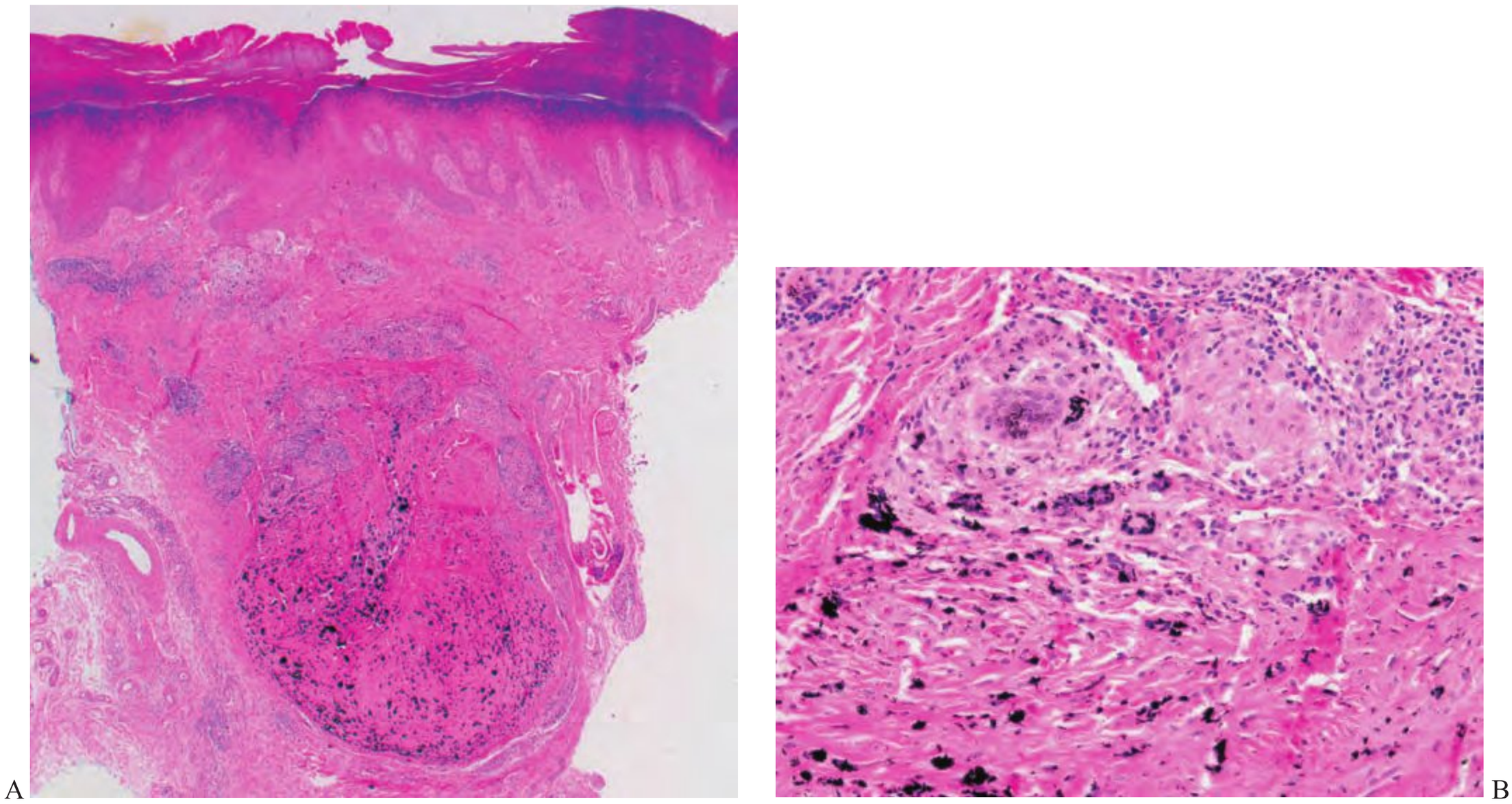


FIGURE 14-32. Decorative tattoo. Granulomatous response to a red tattoo.

Bovine Collagen Implant and Other Tissue Augmentation Materials

Injectable bovine collagen is used for cosmetic purposes, principally on the face to diminish "wrinkles," such as glabellar creases and prominent nasolabial folds. A small minority of patients develop an allergic granulomatous response at the site of injection. This response usually develops within 1 month of injection, is manifested by induration and erythema, and usually resolves spontaneously in less than 1 year (232,307). Hyaluronic acid has also been used for similar cosmetic purposes. Although it is less immunogenic, reactions to this injected material have been reported in approximately 3% of patients (308,309). Recent additions to the soft tissue augmentation armamentarium include synthetic substances such



A B

FIGURE 14-33. Traumatic tattoo from graphite. A: A circumscribed collection of black material is present in the dermis. B: The black material is darker than melanin, and the clumps have irregular shapes and sizes; some are intracellular and some are extracellular. There are also knife marks from the foreign material.

as polymethylmethacrylate (ArteFill, ArteColl) and polydimethylsiloxane (Bioplastique). Adverse reactions to these materials have been reported (310–312), with polymethylmethacrylate and silicone probably being the fillers to which reactions are most commonly encountered.

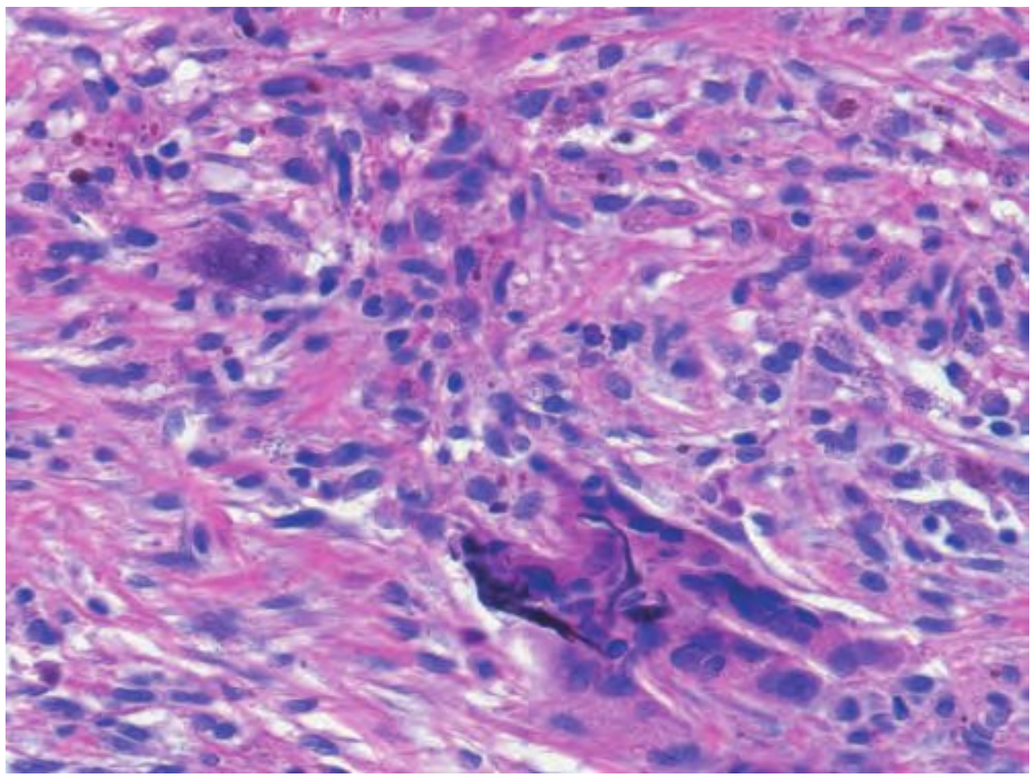


FIGURE 14-34. Monsel's tattoo. Monsel's solution may produce a granulomatous response associated with pigment that is gray-brown, with pigment sometimes in larger clumps.

Histopathology. Bovine collagen differs from native collagen by exhibiting a paler, less fibrillar appearance and by its nonbirefringence when examined with polarized light. It may lie within the center of a palisaded granuloma containing many foreign-body giant cells, or it may be associated with a more diffuse granulomatous reaction. There is a variable associated infiltrate of lymphocytes, eosinophils, plasma cells, and neutrophils that tends to spare the implanted collagen (232).

Biopsies of patients with erythematous raised areas at sites of hyaluronic acid injections have revealed a granulomatous infiltrate with prominent giant cells in most patients. A mild lymphohistiocytic infiltrate without granulomas appears to be less common (308). Polymethylmethacrylate granuloma shows numerous sharply circumscribed, seemingly empty round spaces, uniform in size and shape, mimicking normal adipocytes (310). Epithelioid histiocytes with occasional giant cells surround these spaces. Within them, on lowering the microscope condenser, one notes vaguely visible round, sharply circumscribed, translucent, nonbirefringent foreign bodies. Polydimethylsiloxane granuloma exhibits numerous irregularly shaped spaces distributed diffusely throughout a sclerotic stroma (310). At higher power, nonbirefringent foreign material is apparent within these irregularly shaped spaces, which are outlined by multinucleate giant cells. The histologic findings of other currently used fillers have been described (313–315).

Corticosteroid Deposits

Corticosteroid preparations for intralesional use are suspensions of insoluble crystalline chemicals; soluble corticosteroids are not effective for intralesional use. These suspensions may be identified histologically after injection of triamcinolone or other steroids. Sites where these deposits have been described include the skin (e.g., in keloids), the nasal mucosa, and the Achilles tendon. The material may persist at the site of injection for months or years (232,316).

Histopathology. Corticosteroid deposits are recognizable by their acellular, amphophilic, granular appearance in association with clear spaces. The spaces may represent the sites of dissolved crystals. Uncommonly, birefringent crystals can be seen with polarized light. Inflammation tends to be absent or sparse, but a palisaded granuloma may develop (316–319).

CHEILITIS GRANULOMATOSA (MIESCHER-MELKERSSON-ROSENTHAL SYNDROME)

The classic triad of Miescher-Melkersson-Rosenthal syndrome consists of recurrent labial edema, relapsing facial paralysis, and fissured tongue (320). However, not all patients have the classic triad. In a review of 220 patients, labial swelling was seen in 84%, facial palsy in 23%, and fissured tongue in 60% (320). Whereas monosymptomatic labial edema is recognized as part of the syndrome, lingua plicata by itself is not, because this is not uncommon in the general population. One occasionally observes, either in addition to or in place of swelling of the lips, swelling of the forehead, chin, cheeks, eyelids, or tongue (321,322). Submandibular or submental lymph nodes may be enlarged (323). Swelling of the buccal mucosa, gingiva, and palate also can occur (320). Chronic swelling of the vulva or of the foreskin has been described as a genital counterpart of cheilitis granulomatosa (324,325).

Histopathology. Granulomatous inflammation is not present in all biopsies of clinically involved lips (326). Sections may show simply edema, lymphangiectasia, and a predominately perivascular lymphoplasmacytic infiltrate. The infiltrate is often sparse but may be dense, producing a nodular appearance. If granulomas are present, they are noncaseating and tend to be small and scattered (Fig. 14-35). Collections of epithelioid histiocytes may be poorly circumscribed and are often associated with lymphocytes, but occasionally larger and/or "naked" tubercles are present, producing an appearance similar to that of sarcoidosis (322,323,326–330). Affected lymph nodes may also show granulomatous inflammation (331).

Pathogenesis. The cause of cheilitis granulomatosa is unknown. Idiosyncratic reactions to exogenous factors, such as food additives, have been postulated to be causal in some cases (332,333). A relationship to sarcoidosis, originally assumed by some authors (331), appears unsubstantiated. Likewise, this syndrome appears to be distinct from Crohn's disease, which may also produce granulomatous inflammation of the lip (333,334).

CHEILITIS GLANDULARIS

Cheilitis glandularis is a rare condition marked by persistent enlargement and eversion of the lower lip. Labial salivary ducts appear to be dilated and exude mucoid material or clear fluid that may be accentuated by gentle squeezing (335,336). A papular component may be present (337). Diagnosis is based primarily on clinical features (335). It has been described mostly in adults but also in children.

Histopathology. Various histologic findings have been reported, none consistently, and this condition may not represent a specific disease (see section on pathogenesis).

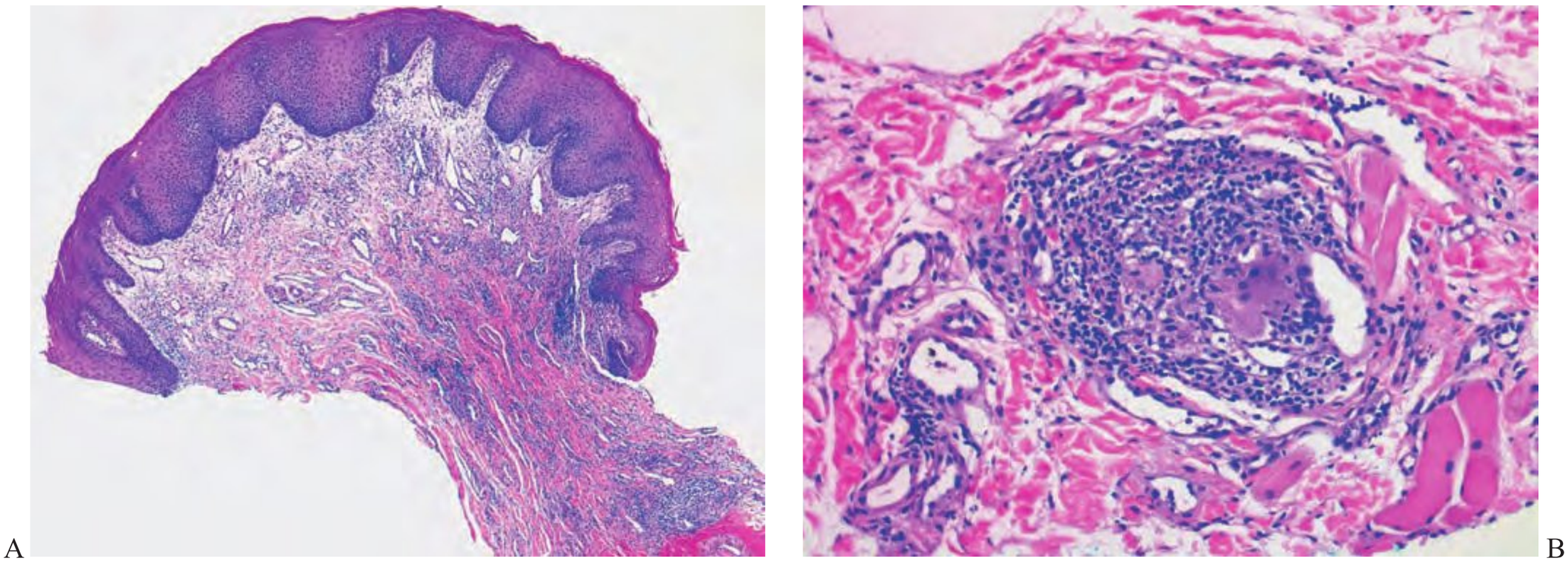


FIGURE 14-35. Cheilitis granulomatosa. A: Biopsy of lip mucosa showing slight vascular ectasia, edema, and a sparse inflammatory infiltrate including lymphocytes. B: A subtle granulomatous component.

Salivary gland hyperplasia, duct ectasia, fibrosis, and inflammation comprising lymphocytes, plasma cells, and histiocytes have been described (336,337). However, any or all of these features may be absent (335). Hyperkeratosis can also occur (335).

Pathogenesis. Cheilitis glandularis is probably caused by several different factors. Marked, chronic sun and wind exposure has been implicated as a common cause, and it has been suggested that this is not truly a disorder of salivary glands because they may appear histologically normal (335). An atopic diathesis, factitious cheilitis, and hereditary factors have also been implicated (335,337). There are older reports in the literature that describe an increased incidence of squamous cell carcinoma in association with cheilitis glandularis (338). This is probably a consequence of actinic damage, which tends to be associated with this condition and may be exacerbated by the eversion of the lip (338).

GRANULOMA GLUTEALE INFANTUM

Granuloma gluteale infantum, first described in 1971 (339), shows asymptomatic, round to oval, smooth papules and nodules irregularly distributed over regions covered by diapers (339–342). The lesions are typically reddish blue in color, ranging from a few millimeters to a few centimeters in diameter. Although usually seen in infants, this condition has also been described in incontinent adults (342,343), and a similar process with an erosive component has been reported in adults with extensive use of benzocaine (344). Although clinically this disorder may appear similar to a granulomatous condition, histologically it is not.

Histopathology. Acanthosis is usually present. A dense, mixed infiltrate is seen throughout the dermis. Lymphocytes, histiocytes, plasma cells, neutrophils, and eosinophils may all be seen (341). In addition, there may be microabscesses composed of neutrophils and eosinophils, as well as extravasation of erythrocytes together with a proliferation of capillaries (339,345). Multinucleated histiocytes or well-developed granulomas are not a feature of the infiltrate. In a few instances, staining with the PAS reaction has revealed spores and pseudohyphae consistent with the presence of *Candida albicans* in the stratum corneum (346), but fungi are often not detected.

Pathogenesis. In nearly all patients described in the literature, the development of granuloma gluteale infantum has been preceded by a diaper dermatitis, which only in some instances has been associated with a *C. albicans* infection (340,345). Topical applications of fluorinated corticosteroid preparations for a prolonged period of time and prolonged wearing of plastic diapers have been implicated, but a consistent cause has not been identified (347). It appears very likely that exogenous factors including irritants and external trauma contribute to this eruption (339,344).

MISCELLANEOUS GRANULOMATOUS LESIONS

Interstitial Granulomatous Drug Reaction

A limited number of patients have been described with annular to solid erythematous plaques on the inner arms, proximal thighs, and intertriginous areas. Implicated agents include antihypertensives, antihyperlipidemics, antihistamines, anticonvulsants, antidepressants (63), tumor necrosis factor-α inhibitors (348), and herbal medications (349).

Histopathology. An interstitial infiltrate of lymphocytes and histiocytes with slight fragmentation of collagen is reported, in conjunction with variable numbers of eosinophils and neutrophils and vacuolar interface change.

Differential Diagnosis Clinical presentation and the presence of vacuolar interface change may be helpful in distinguishing this condition from granuloma annulare and palisaded neutrophilic and granulomatous dermatitis (130).

Zoster-Related Granulomas

Following herpes zoster, patients may present with persistent reddish papules in a zosteriform distribution.

Histopathology. A variety of reaction patterns may be found in zoster-related scars. The most common granulomatous patterns are granuloma annulare–like (350) and sarcoid-like patterns.

Common Variable Immunodeficiency

Patients with common variable immunodeficiency often have multiple cutaneous warts and systemic signs and symptoms that include diarrhea, chronic/recurrent bacterial infections, hepatosplenomegaly, and lymphadenopathy. Patients may also develop periarticular subcutaneous nodules.

Histopathology. Biopsy of the nodules may show granuloma annulare-like (351), tuberculoid leprosy-like (352), sarcoid-like, and/or tuberculosis-like (353,354) granulomas.

Paraneoplastic Phenomena

Patients with hematologic malignancy may sometimes present with granulomatous lesions.

Histopathology. A spectrum of histologic findings has been described, including granuloma annulare–like, annular elastolytic–like, sarcoid-like, and tuberculoid patterns (355,356).

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CHAPTER 15

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Degenerative Diseases and Perforating Disorders

SOLAR (ACTINIC) ELASTOSIS

Senescent changes in areas of the skin not regularly exposed to sunlight manifest themselves clinically only in thinning of the skin and a decrease in the amount of subcutaneous fat. In contrast, there are often pronounced changes in the appearance of the exposed skin of elderly persons, especially those with fair complexions. These changes, however, are the result of chronic sun exposure (photoaging) rather than of intrinsic (chronologic) aging. In exposed areas, especially on the face, the skin shows wrinkling, furrowing, and thinning. In addition, there may be an irregular distribution of pigment.

Histopathology. In skin not regularly exposed to sunlight, there is a progressive loss of elastic tissue in the papillary dermis with age. Elastic fibers in the papillary dermis are composed of elaunin and oxytalin fibers. Elaunin fibers, which consist of microfibrils and a small amount of elastin, run parallel to the dermal–epidermal junction. Overlying oxytalan fibers, composed solely of microfibrils, form a thin, superficial network perpendicular to the dermal-epidermal junction that ends at the basement membrane zone (see Chapter 3). In middle age, the oxytalan fibers in the papillary dermis are split and fewer than at a young age; in old age, they may be absent (1). Mature elastic fibers in the reticular dermis also undergo changes due to intrinsic aging, becoming fragmented and porous (2).

In the skin of the face exposed to the sun, especially in persons with fair complexions, hyperplasia of the elastic tissue is usually evident on histologic examination by the age of 30 years, even though clinically the skin may appear normal. No white person past 40 years of age has normal elastic tissue in the skin of the face (3). The elastic fibers of the reticular dermis are increased in number, and they are thicker, curled, and tangled.

In patients with clinically evident solar elastosis of the exposed skin, staining with hematoxylin-eosin reveals, in the upper dermis, basophilic degeneration of the collagen separated from a somewhat atrophic epidermis by a narrow band of normal collagen. In the areas of basophilic degeneration, the bundles of eosinophilic collagen have been replaced by amorphous basophilic granular material.

With elastic tissue stains, the areas of basophilic degeneration stain like elastic tissue and therefore are referred to as *elastotic material*. The elastotic material usually consists of aggregates of thick, interwoven bands in the upper dermis (4) (Fig. 15-1A); but in areas of severe solar degeneration, the elastotic material may have an amorphous rather than a fibrous appearance (Fig. 15-1B) and may extend into the lower portions of the dermis rather than being confined to the upper dermis (5).

On staining with silver nitrate, the distribution of melanin in the basal cell layer may appear irregular in that areas of hyperpigmentation alternate with areas of hypopigmentation (5).

Histogenesis. Electron microscopic examination of areas of solar elastosis shows elastotic material as the main component (EM 13). Even though this elastotic material resembles elastic tissue in its chemical composition, it differs significantly in appearance from aged elastic fibers in unexposed, aged skin. Instead of showing amorphous electron-lucent elastin and aggregates of electron-dense microfibrils (see Chapter 3), the thick fibers of elastotic material show two structural components: a fine granular matrix of medium electron density and, within this matrix, homogeneous, electron-dense, irregularly shaped inclusions (6). Microfibrils such as those observed in normal or aged elastic fibers are absent. Immunoelectron microscopy shows that the elastotic material has retained its antigenicity for elastin but not for microfibrils (7). The number and size of elastotic fibers are greatly increased over the number and size of elastic fibers found in normal or aged skin. Extensive amorphous material can be seen around the elastotic fibers and also among the collagen fibrils. Collagen fibrils are diminished in number, with those present often showing a diminished electron density, a diminished contrast in cross striation, and a splitting up into filaments at their ends (8).

Elastotic material is not regarded as a degeneration product of preexisting elastic fibers. Most current findings indicate that elastotic material is composed primarily of elastic tissue, much of which may be newly formed as the result of an altered function of fibroblasts. Evidence of transcriptional activation of the elastin gene in biopsied tissue and fibroblast cultures from sun-damaged skin further supports this. Additional accumulation of elastotic material may be secondary to a disruption of the balance between synthesis and degradation of elastin in photodamaged skin (9).

The elastotic material that histochemically stains like elastic tissue resembles elastic tissue in its chemical composition and its physical and enzymatic reactions. Thus, the amino acid composition of the elastotic tissue resembles that of elastin and differs significantly from that of collagen. In particular, the

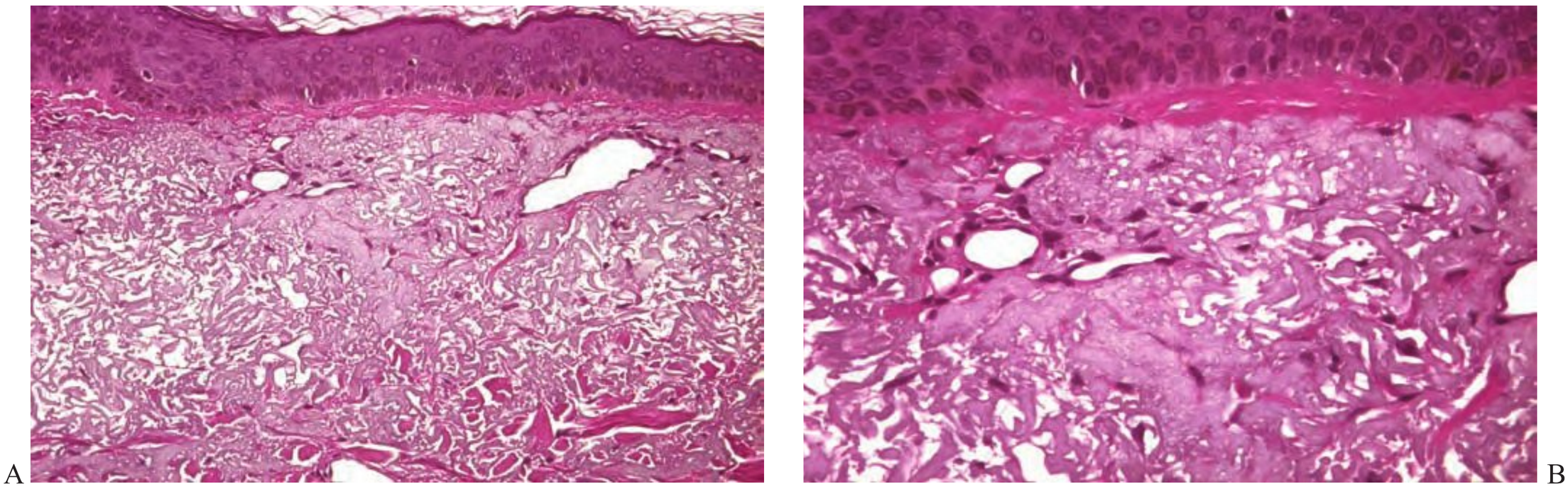


FIGURE 15-1. Solar (actinic) degeneration. A: In the upper dermis, separated from the epidermis by a narrow band of normal collagen, there are aggregates of thick, interwoven bands of the elastotic material. B: Extensive amorphous material can be seen around and among elastic and collagen fibers.

elastotic material, like elastic tissue, has a much lower content of hydroxyproline than collagen (10). Moreover, the elastotic material in unfixed sections shows the same brilliant autofluorescence as do elastic fibers on examination with the fluorescence microscope (11), and both the elastotic material and elastic tissue are susceptible to elastase digestion (12). The elastotic material contains a large amount of acid mucopolysaccharides, as indicated by staining with Alcian blue. A significant portion of these acid mucopolysaccharides may be sulfated because prior incubation with hyaluronidase removes only 50% to 75% of the Alcian blue–positive staining. The basophilia of the elastotic material, however, is not affected by incubation with hyaluronidase (13).

The irregular distribution of melanin in the epidermis observed in some patients with solar degeneration, when studied by electron microscopy, is found to be caused largely by an impairment of pigment transfer from melanocytes to keratinocytes. Although some keratinocytes contain many melanosomes, others contain few or no melanosomes. The latter are surrounded by dendrites laden with melanosomes (14).

Differential Diagnosis. For a discussion of differentiation of solar elastosis from pseudoxanthoma elasticum (PXE), see Chapter 3 and 6.

LOCALIZED EXPRESSIONS OF SOLAR ELASTOSIS

Several clinically distinct forms of localized solar elastosis have been described. In the nuchal region, the skin, after many years of exposure to the sun, may appear thickened and furrowed. This is referred to as *cutis rhomboidalis nuchae*. *Elastotic nodules of the ears* are localized papular and nodular forms of solar elastosis that usually occur on the antihelix (15–18). Severe solar elastosis may also occur as yellowish plaques associated with small cysts and comedones. *Favre-Racouchot syndrome (nodular elastosis with cysts and comedones)* is an example occurring on facial skin lateral to the eyes (19,20). A similar condition occurring on the arms has been termed *actinic comedonal plaques* (21–23). Two other types of circumscribed solar elastosis occurring on the upper extremities are *solar elastotic bands of the forearm* (4,24) and *collagenous and elastotic marginal plaques of the hands* (25–32).

Elastotic Nodules of the Ears

Elastotic nodules are most often seen on the anterior crus of the antihelix (15,16,18) and occasionally on the helix of the ears (17). They are often bilateral. Clinically, they may mimic basal cell carcinomas, amyloidosis, gouty tophi, or chondrodermatitis nodularis helicis (15–18).

Histopathology. Irregular elastotic fibers and clumps of elastotic material are seen in the background of marked dermal solar elastosis (Fig. 15-2A). The fibers and clumps can be highlighted with a Verhoeff–van Gieson elastic stain (17) (Fig. 15-2B).

Favre-Racouchot Syndrome (Nodular Elastosis with Cysts and Comedones)

Favre-Racouchot syndrome is characterized by yellow plaques with multiple open and cystically dilated comedones. The condition typically affects the skin lateral to the eyes in elderly males (19,20,41). However, a case has also been documented on the shoulder (33). Although the condition is usually bilateral, it may be unilateral (34–36). It is thought to be primarily secondary to prolonged solar exposure with the formation of comedones facilitated by an extracellular matrix of compromised structural integrity (2). Smoking may also be a contributing factor in its development (37).

Histopathology. Dilated pilosebaceous openings and large, round, cystlike spaces are lined by a flattened epithelium and

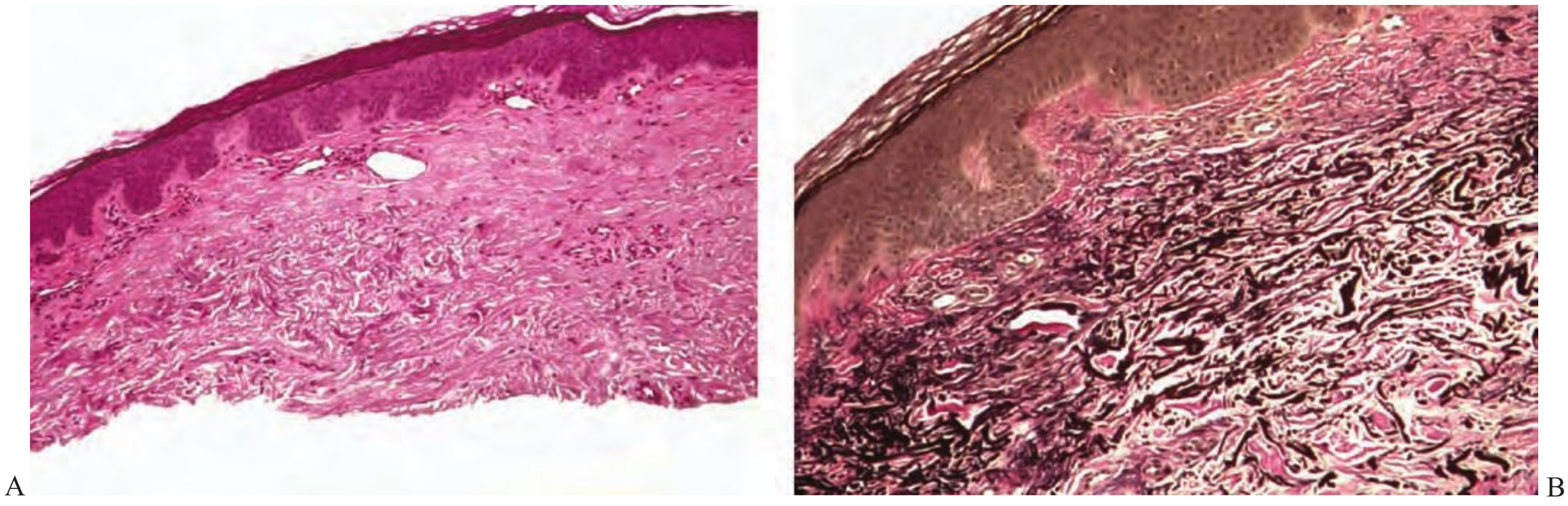


FIGURE 15-2. Elastotic nodule of the ear. A: A dome-shaped papule with marked solar elastosis in the dermis and clumped and irregular eosinophilic material representing degenerated elastic fibers. B: The coarse, clumped material is highlighted with an elastic stain.

represent greatly distended hair follicles (19,20). Both the dilated pilosebaceous openings and the cystlike spaces are filled with layered horny material. Vellus hair shafts and bacteria have been demonstrated within the spaces as well, suggesting that the cystlike spaces may represent closed comedones rather than true infundibular cysts (38). The sebaceous glands are atrophic. Solar elastosis often is pronounced (19), but it may be slight or absent (39). Because the comedones are open, they do not tend to become inflamed (40) (see section on acne vulgaris, Chapter 18).

Actinic Comedonal Plaques

In actinic comedonal plaques, solitary nodular plaques with a cribriform appearance and comedone-like structures occur, often unilaterally, on the arms or forearms (21–23). The plaques are composed of confluent erythematous to bluish papules and nodules. The condition has been described in fair-skinned individuals with a history of chronic sun exposure. They can be found in association with Favre-Racouchot syndrome and may in fact represent an ectopic expression of this entity (22).

Histopathology. Dilated corneocyte-filled follicular lumina are present within areas of elastotic, amorphous material. The overlying epidermis is usually dyskeratotic and atrophic. The histologic findings are quite similar to those seen in Favre-Racouchot syndrome (21,22).

Solar Elastotic Bands of the Forearm

Solar elastotic bands of the forearm consist of soft cordlike plaques across the flexor surface of the forearms (4,24). The bands occur in areas of actinic damage and usually with senile purpura.

Histopathology. Nodular collections of basophilic homogenous amorphous material underlying an atrophic epidermis are conspicuous features. Thickened degenerated elastic fibers within the homogenous material are also observed. Stellate fibroblasts and a perivascular infiltrate of lymphocytes and hemosiderin-laden macrophages are found in close apposition to the elastic fibers. The nodular collections and thickened elastic fibers stain positively with Verhoeff–van Gieson elastic stain (4).

Collagenous and Elastotic Marginal Plaques of the Hands

Collagenous and elastotic marginal plaques of the hands have been described by several names: *elasto-collagenous plaques of the hands* (25), *degenerative collagenous plaques of the hands* (26,28), and *keratoelastoidosis marginalis* (27). This acquired, slowly progressive condition is usually seen in elderly males and consists of groups of linear confluent papules along the medial and lateral aspects of the hands at the juncture of the palmar and dorsal surfaces. The medial aspect of the thumb and radial aspect of the index finger are most commonly affected. The condition closely resembles the genodermatosis, *acrokeratoelastoidosis* (30). However, there is no familial predisposition or involvement of the plantar surfaces. Actinic damage and chronic repetitive pressure or trauma has been implicated in its pathogenesis (27,42,43).

Histopathology. The reticular dermis displays an acellular zone of haphazardly arranged collagen with some bundles running perpendicular to the epidermis (28). The bundles of collagen are admixed with fragmented elastic fibers and distinctive angulated amorphous "basophilic elastotic masses" in the upper dermis. These masses can be demonstrated to contain degenerating elastic fibers and calcium (29).

PERFORATING DISORDERS

The perforating disorders comprise a group of disorders sharing the common characteristic of transepidermal elimination

(TEE). This phenomenon is characterized by the elimination or extrusion of altered dermal substances and, in some cases, by such material behaving as foreign material.

Traditionally, four diseases have been included in this group: *Kyrle's disease* (hyperkeratosis follicularis et parafollicularis in cutem penetrans), *perforating folliculitis*, *elastosis perforans serpiginosa* (EPS), and *reactive perforating collagenosis* (RPC). A fifth entity, acquired perforating dermatosis (APD), which is usually associated with renal disease and/or diabetes mellitus, in which clinical and histologic findings may resemble any of these four diseases, has been added to this group (44). Although TEE is a prominent feature in all of these conditions, it has also been described as a secondary phenomenon in other entities, including such inflammatory disorders as granuloma annulare, one variant of PXE, and chondrodermatitis nodularis helicis. Elastic fibers can be transepidermally eliminated overlying sites of healing wounds. Collagen may be eliminated through keratoacanthomas (45). Needless to say, there is a long list of other conditions that can exhibit TEE as an associated reaction pattern.

Kyrle's Disease

Kyrle's disease is a rare disorder, described by Kyrle in 1916 (46). There is controversy as to whether it represents a distinct entity, an exaggerated form of perforating folliculitis (46,47), or actually comprises a group of disorders with similar epidermal–dermal reaction patterns associated with chronic renal failure, diabetes, prurigo nodularis, and even keratosis pilaris. Therefore, the discussion of Kyrle's disease and perforating disorders seen in chronic renal disease and/or diabetes has a very broad overlap in terms of their clinical and pathologic features.

Clinical Features. This eruption presents with a large number of papules, some coalescing into plaques, numbering in the hundreds and often distributed on the extremities. Although some may appear to involve the follicular units, these lesions are more likely to be extrafollicular. The typical patient is young to middle aged and often has a history of diabetes mellitus. The papules are dome shaped, 2 to 8 mm in diameter, with a central keratotic plug. Excoriations often are found in the vicinity of these lesions. Linear lesions related to possible koebnerization have been described.

Histopathology. The essential histopathologic findings include (a) a follicular or extrafollicular cornified plug with focal parakeratosis embedded in an epidermal invagination, (b) basophilic degenerated material identified in small collections throughout the plug with absence of demonstrable collagen and elastin, (c) abnormal vacuolated and/or dyskeratotic keratinization of the epithelial cells extending to the basal cell zone, (d) irregular epithelial hyperplasia, and (e) an inflammatory component that is typically granulomatous with small foci of suppuration (Fig. 15-3). In most instances, it is important to perform elastic tissue stains and even trichrome stains to exclude perforating elastic fibers, as in elastosis perforans serpiginosa, or collagen fibers, as in RPC (48).



FIGURE 15-3. Kyrle's disease. A large parakeratotic plug containing basophilic debris lies within an invagination of the epidermis. The underlying dermis displays acute and chronic inflammation.

Histogenesis. The primary event is claimed to be a disturbance of epidermal keratinization characterized by the formation of dyskeratotic foci and acceleration of the process of keratinization. This leads to the formation of keratotic plugs with areas of parakeratosis (49–51). Because the rapid rate of differentiation and keratinization exceeds the rate of cell proliferation, the parakeratotic column gradually extends deeper into the abnormal epidermis, leading in most cases to perforation of the parakeratotic column into the dermis. Perforation is not the cause of Kyrle's disease, as originally thought (46), but rather represents the consequence or final event of the abnormally sped-up keratinization. This rapid production of abnormal keratin forms a plug that acts as a foreign body, penetrating the epidermis and inciting a granulomatous inflammatory reaction. A certain similarity exists between the parakeratotic column in Kyrle's disease and that observed in porokeratosis of Mibelli (50). In both conditions, a parakeratotic column forms as the result of rapid and faulty keratinization of dyskeratotic cells, but, whereas in Kyrle's disease the dyskeratotic cells are often used up so that disruption of the epithelium occurs, the clone of dyskeratotic cells can maintain itself in porokeratosis Mibelli by extending peripherally.

Differential Diagnosis. See Table 15-1.

Perforating Folliculitis

Perforating folliculitis is a perforating disorder that has many features overlapping with Kyrle's disease and also comprises one of the clinical and histologic patterns seen in APD. As

TABLE 15-1 Differential Diagnoses of Perforating Disorders

Disease	Primary defect	Distinctive features	Histogenesis
Kyrle's disease	Focus of dyskeratotic rapidly proliferating cells in the epidermis	Follicular or extrafollicular cornified plug embedded in an epidermal invagination associated with epithelial hyperplasia and absence of demonstrable collagen and elastin	Disturbance of keratinization, forming a plug that acts as a foreign body penetrating the epidermis and inciting a granulomatous inflammatory reaction
Perforating folliculitis	Hyperkeratotic plug in follicular unit containing a retained hair	Compact ortho- and parakeratotic plug with degenerated collagen, altered elastin, and mixed inflammatory cell infiltrate including neutrophils	A primary irritant causing follicular hyperkeratosis resulting in a mechanical breakdown of the follicle wall by the hair shaft
Elastosis perforans serpiginosum	Formation of numerous coarse elastic fibers in the superficial dermis	Formation of narrow channel through an acanthotic epidermis with elimination of eosinophilic elastic fibers	Thickened elastic fibers act as mechanical irritants or "foreign bodies"
Reactive perforating collagenosis	Subepidermal focus of altered collagen caused by trauma	Formation of cup-shaped vertically oriented channel with transepidermal elimination of degenerated collagen	Histochemically altered collagen acts as "foreign body"
Acquired perforating disorder	Chronic rubbing due to pruritis, resulting in hyperkeratosis, keratosis, and perforation, possibly in association with other factors such as accumulation of poorly dialyzable substances	A combination of features similar to any of the above disorders	Exogenously altered skin in pruritic diabetics and patients with chronic renal disease

described by Mehregan and Coskey (52), this is a relatively uncommon disorder that usually is observed in the second to fourth decades of life and is characterized by erythematous follicular papules with central keratotic plugs. The lesions are 2 to 8 mm in diameter and tend to be localized to the extensor surfaces of the extremities and the buttocks. The key to making this diagnosis is the clinical and histologic identification of a follicular unit as the primary site for the inflammatory process.

Histopathology. The main pathologic abnormalities consist of (a) a dilated follicular infundibulum filled with compact ortho and parakeratotic cornified cells (Fig. 15-4A); (b) degenerated basophilic staining material, comprised of granular nuclear debris from nuclear neutrophils, other inflammatory cells, and degenerated collagen bundles (Fig. 15-4B); (c) one or more perforations through the follicular epithelium; and (d) an associated perifollicular inflammatory cell infiltrate composed of lymphocytes, histiocytes, and neutrophils. Additionally, altered collagen and refractile eosinophilically altered elastic fibers are found adjacent to the sites of perforation. When serial sections through the specimen are examined, a remnant of the hair shaft can sometimes be found.

Histogenesis. Perforating folliculitis is the end result of abnormal follicular keratinization that most likely is caused by irritation, either chemical or physical, and even chronic rubbing. A portion of a curled-up hair is often seen close to or within the area of perforation or even in the dermis, surrounded by a foreign body granuloma (51).

Differential Diagnosis. In Kyrle's disease, the keratinous plug may be extrafollicular, the perforation usually is present deep in the invagination at the bottom of the keratinous plug, and no eosinophilic degeneration of elastic fibers is found. In addition, epithelial hyperplasia is a significant feature. For a discussion of the differential diagnosis of perforating folliculitis from EPS, see the following section on differential diagnosis for EPS. See also Table 15-1.

Elastosis Perforans Serpiginosa

EPS is the most distinctive of the perforating disorders because it demonstrates the best example of TEE. In EPS, increased numbers of thickened elastic fibers are present in the upper dermis, and altered elastic fibers are extruded through the epidermis. It is a rare disorder that affects young individuals, with a peak incidence in the second decade. Men are affected more often than women. EPS is primarily a papular eruption localized to one anatomic site and most commonly affecting the nape of the neck, the face, or the upper extremities. The

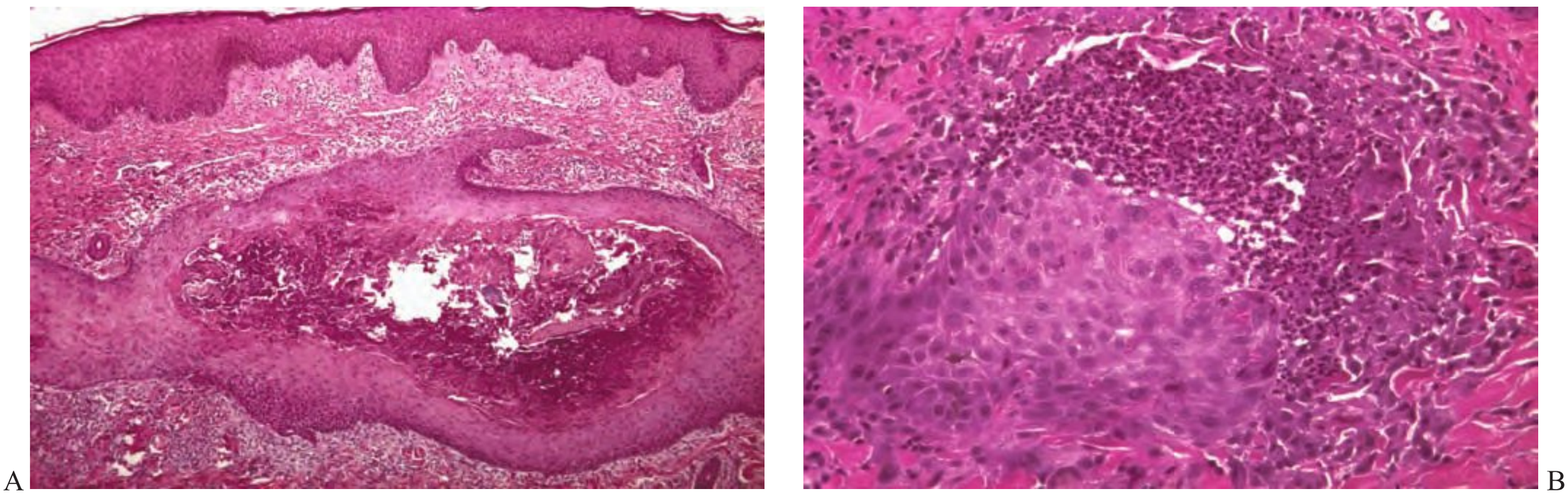


FIGURE 15-4. Perforating folliculitis. A: A widely dilated follicular unit contains a mixture of keratin, basophilic debris, inflammatory cells, and degenerated collagen fibers. B: An area of disrupted follicular epithelium with adjacent associated perifollicular inflammation and alteration of collagen and elastic fibers.

papules are typically 2 to 5 mm in diameter. These papules are arranged in arcuate or serpiginous groups and may coalesce.

Of particular importance is the association of EPS with systemic diseases. The important associations include Down's syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, PXE, and Marfan's syndrome. In addition, on rare occasions, EPS is observed in association with Rothmund-Thompson syndrome or other connective tissue disorders and as a secondary complication of penicillamine administration.

Histopathology. The essential findings include a narrow transepidermal channel that may be straight, wavy, or of corkscrew shape and thick, coarse elastic fibers in the channel admixed with granular basophilic staining debris (Fig. 15-5A, B). A mixed

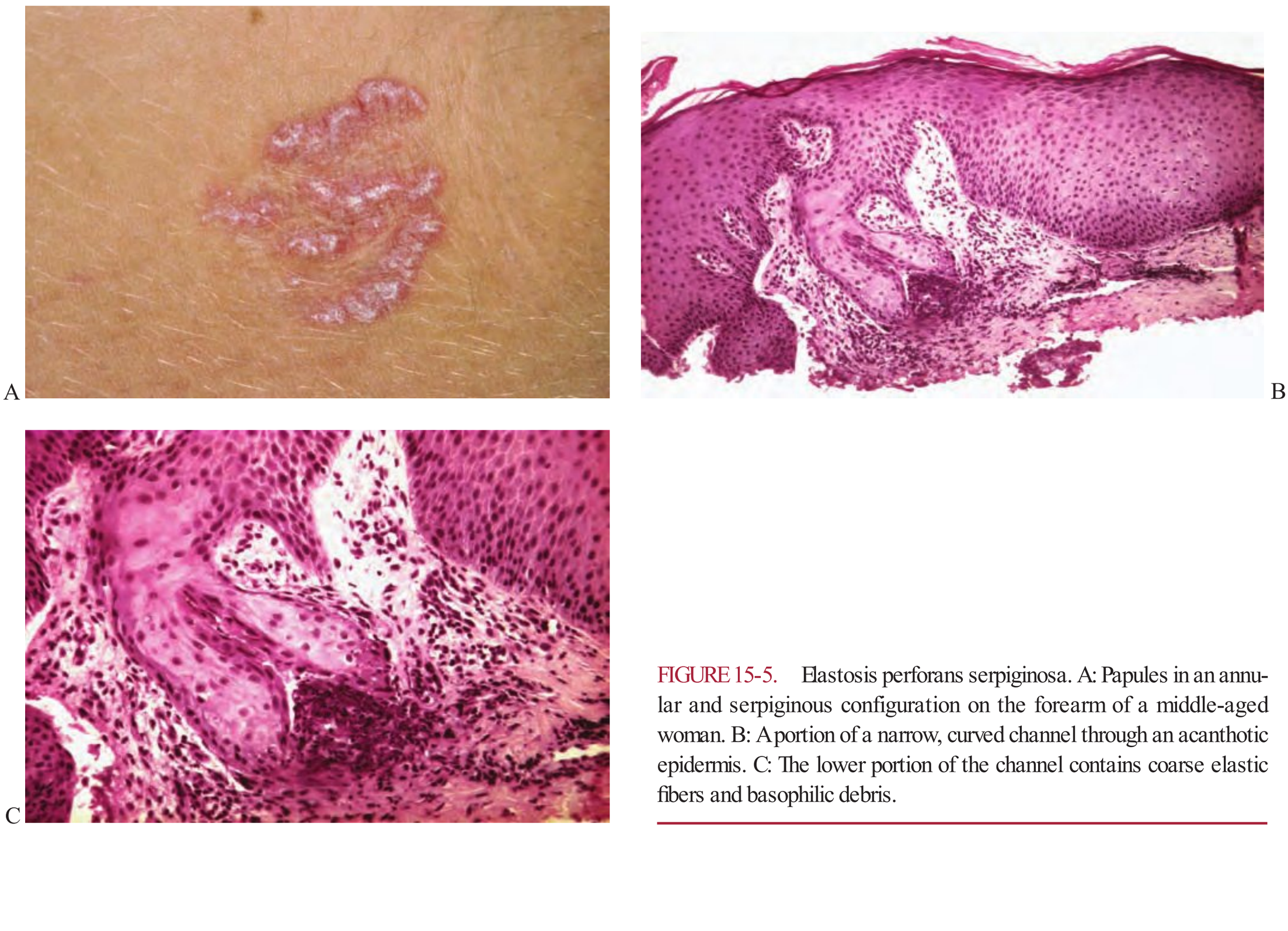


FIGURE 15-5. Elastosis perforans serpiginosa. A: Papules in an annular and serpiginous configuration on the forearm of a middle-aged woman. B: A portion of a narrow, curved channel through an acanthotic epidermis. C: The lower portion of the channel contains coarse elastic fibers and basophilic debris.

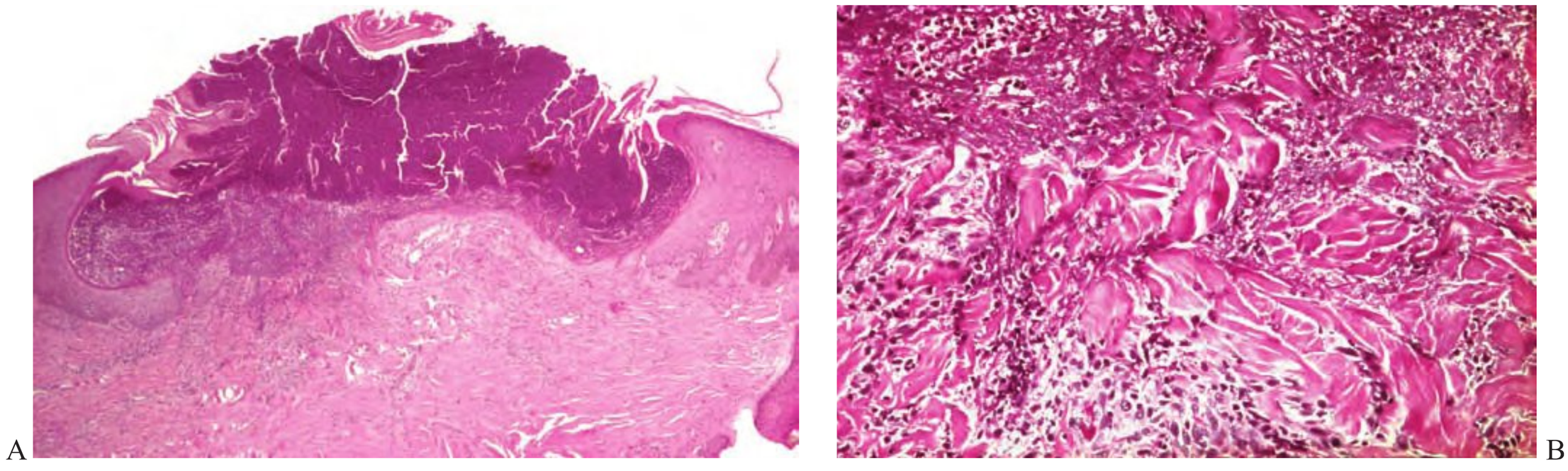


FIGURE 15-6. Reactive perforating collagenosis. A: A shallow, cup-shaped invagination of the dermis containing a mixture of basophilic material and degenerated collagen bundles. The adjacent epidermis displays acanthosis. B: Vertically oriented perforating bundles of collagen are present at the base of the invagination.

inflammatory cell infiltrate accompanies the fibers in the channel. Also observed are abnormal elastic fibers in the upper dermis in the vicinity of the channel. In this zone, the elastic fibers are increased in size and number. As these fibers enter the lower portion of the channel, they maintain their normal staining characteristics, but as they approach the epidermal surface, they may not stain as expected with elastic stains (53).

Histogenesis. The cause of EPS is not known. Because the elastic fibers show no obvious abnormality within the dermis except hyperplasia, it is conceivable that the thickened elastic fibers act as mechanical irritants or "foreign bodies" and provoke an epidermal response in the form of hyperplasia. The epidermis then envelops the irritating material and eliminates it through transepidermal channels. The degeneration of the elastic fibers within the channels probably is caused by proteolytic enzymes set free by degenerating inflammatory cells (53). The channel is formed as a reactive phenomenon through which the foreign bodies are extruded. Because copper metabolism is essential to the formation of elastin (54) and because the administration of penicillamine, a copper chelating agent, has been found to induce EPS (55), it may be suggested that the primary abnormality begins with a defect in the metabolism of this essential element.

Differential Diagnosis (Table 15-1). As in EPS, both Kyrle's disease and perforating folliculitis have a central keratotic plug and a perforation through which degenerated material is eliminated. In addition, perforating folliculitis, like EPS, shows the elimination of degenerated eosinophilic elastic fibers. However, neither of the two diseases shows the great increase in elastic tissue that is observed in EPS in the uppermost dermis and particularly in the dermal papillae on staining with elastic tissue stains.

Reactive Perforating Collagenosis

RPC is a rare perforating disorder in which altered collagen is extruded by means of TEE. True, classic RPC is a genodermatosis that is inherited as an autosomal dominant or recessive trait (56,57). The lesions are precipitated by trauma, arthropod assaults, folliculitis, and even exposure to cold. RPC occurs early in life, and both genders are equally affected.

The primary clinical lesion is a small papule that enlarges to the size of 5 to 10 mm with a hyperkeratotic central umbilication. Often, the lesion appears eroded. These lesions spontaneously regress, leaving superficial scars with postinflammatory pigmentary alteration. Koebnerization is common.

An adult, acquired type of RPC has been described in association with diabetes mellitus and chronic renal failure (58–64) and may be best interpreted as an expression of APD (see text following).

Histopathology. The classic lesion shows a vertically oriented, shallow, cup-shaped invagination of the epidermis, forming a short channel (Fig. 15-6A). The channel is lined by acanthotic epithelium along the sides. At the base of the invagination, there is an attenuated layer of keratinocytes that in some foci appear eroded. Within the channel, there is densely packed degenerated basophilic staining material and basophilically altered collagen bundles. Vertically oriented perforating bundles of collagen are present interposed between the keratinocytes of the attenuated bases of the invagination (Fig. 15-6B). It is important that a Masson trichrome stain be done to confirm that the fibers are collagen.

Histogenesis. The basic process in RPC consists of the TEE of histochemically altered collagen. Nevertheless, as delineated by electron microscopy, the collagen fibrils appear intact, with regular periodicity (61).

Differential Diagnosis. See Table 15-1.

Acquired Perforating Dermatosis

The term *acquired perforating dermatosis* was suggested by Rapini et al. to describe a pathologic process encompassing the various forms of TEE seen in patients with renal disease and/or

diabetes mellitus (65). Differences in clinical and histologic features, such as the presence of koebnerization, or histologic evidence of follicular involvement with or without collagen fibers in the epidermis have variably led to diagnoses of Kyrle's disease, "acquired" RPC, or perforating folliculitis (66–68). Other terms that have been used include *perforating disorder secondary to chronic renal failure and/or diabetes mellitus*, *perforating folliculitis of hemodialysis*, *Kyrle-like lesions*, and *uremic follicular hyperkeratosis* (69–72). Clinically, lesions are frequently pruritic and range from hyperkeratotic papules and nodules resembling Kyrle's disease to RPC-like umbilicated papules, nodules, and plaques to erythematous, follicular papules and nodules mimicking perforating folliculitis (62,65,72). Annular plaques and erythematous pustules have also been described, with histologic features of RPC and perforating folliculitis, respectively (72). The most common location is the extensor surfaces of the extremities, especially lower, but the trunk and head can also be involved (65,72). APD has also been described in renal disease secondary to chronic nephritis, obstructive uropathy, anuria, and hypertension-related nephrosclerosis (62). Cases of APD have also been reported in patients with lymphoma, AIDS, hypothyroidism, hyperparathyroidism and has been associated with pruritis secondary to liver disease, neurodermatitis, "atopic dermatitis," and malignant neoplasia (65,66).

Histopathology. As mentioned, the histologic features of APD are variable, even within different lesions from the same patient. When vertically oriented, Masson trichrome–positive collagen bundles are present within a perforation, the findings are suggestive of RPC. When perforation is associated with a follicle, the findings resemble perforating folliculitis. However, chronic rubbing can lead to superimposed features of prurigo nodularis, thus distorting the follicle and making it unrecognizable. TEE in the absence of follicular involvement, without demonstrable collagen or elastin, is reminiscent of Kyrle's disease. Perforation associated with elastic van Gieson (EVG)-positive elastic fibers within a transepidermal canal, as seen in EPS, has also been described (64,72). Patterson et al. (63) reported a patient who had multiple lesions biopsied, which variably showed histologic features of RPC, perforating folliculitis, and Kyrle's disease. Combined TEE of both elastic and collagen fibers has been observed in four patients with renal disease (65), a finding that has only rarely been described in Kyrle's disease or RPC (68).

Histogenesis. RPC, EPS, and perforating folliculitis exist as distinct perforating disorders when not associated with renal disease and diabetes. At least in the setting of APD, however, the presence of various histologic patterns suggests the possibility of a common underlying mechanism (65). A nearly ubiquitous clinical feature of APD is pruritis. Certainly, lesions are often distributed in areas accessible to scratching, and reducing pruritis can lead to clearance (66). Poor blood supply secondary to diabetic microangiopathy combined with trauma may lead to dermal necrosis, alteration of connective tissue, and TEE (66–68). Others have suggested that a consequence of dialysis is the underlying cause of APD (72). Possible etiologies include disruption of metabolism of vitamins A and/or D (73) or the accumulation of a poorly dialyzable substance in the dermis (70,71). Fibronectin, a glycoprotein of the extracellular matrix, accumulates in the serum of uremic and diabetic patients. It has been suggested that transcriptional induction of fibronectin, possibly by transforming growth factor beta or platelet-derived growth factor, increases epithelial migration and proliferation and leads to TEE (73). APD has been reported in 5% to 11% of patients with chronic renal failure who are undergoing hemodialysis (62,70), and clearance of APD following renal transplant has been reported. However, it has also occurred following transplant in patients with normal renal function (72). In addition, some cases have occurred prior to the start of hemodialysis or in patients who never underwent dialysis (62). Patterson (68) suggests that TEE may represent a "final common pathway" of a variety of dermal and epithelial processes acting alone or in concert.

Differential Diagnosis. See Table 15-1.

PERFORATING CALCIFIC ELASTOSIS (PERIUMBILICAL PERFORATING PSEUDOXANTHOMA ELASTICUM)

In perforating calcific elastosis, also referred to as *periumbilical perforating pseudoxanthoma elasticum*, a gradually enlarging, well-demarcated, hyperpigmented patch or plaque is usually seen in the periumbilical region in middle-aged, obese, multiparous women with hypertension (74). Most patients described have been black (75). The patch or plaque is in some instances atrophic with discrete keratotic papules at the periphery (76); in other instances, it has a verrucous border (77); in still others, it has a fissured, verrucous surface throughout (78). Lesions occurring on the breast have also been described (79,80). Perforating calcific elastosis was initially regarded as cases of EPS coexisting with PXE (81–85). The disorder was later shown to be distinct from EPS (77).

Four patients with perforating calcific elastosis associated with renal failure have been described (75,80,86,87). One patient demonstrated regression of the lesions with hemodialysis (75).

Histopathology. Numerous altered elastic fibers are observed in the reticular dermis. They are short, thick, and curled and are encrusted with calcium salts, as shown by a positive von Kossa stain. They are thus indistinguishable from the elastic fibers seen in PXE (74). As in PXE, the elastic fibers are visible even in sections stained with hematoxylin-eosin, owing to their basophilia (76). The altered elastic fibers in perforating calcific elastosis are extruded to the surface either through the epidermis in a wide channel (77) or through a tunnel in the hyperplastic epidermis that ends in a keratin-filled crater (76) (Fig. 15-7).

Histogenesis. Electron microscopic examination reveals electron-dense deposits of calcium primarily in the central core of

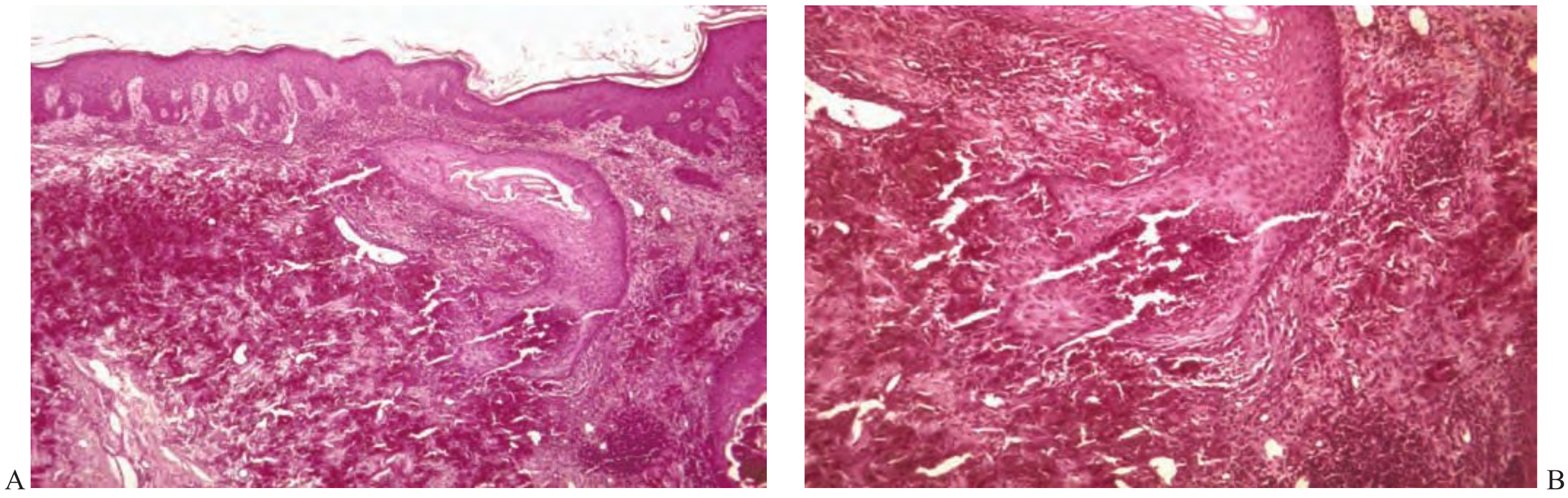


FIGURE 15-7. Perforating calcific elastosis. A: Degenerating elastic fibers encrusted with calcium salts in the reticular dermis surround a distorted transepidermal channel. B: The calcified fibers are in the process of being extruded through the base of the channel.

elastic fibers. Calcification of collagen bundles is also seen (79). The etiologic nature of perforating calcific elastosis has been debated. Some hypothesize that it is an acquired lesion developing as a consequence of local cutaneous trauma from such factors as obesity, multiple pregnancies, ascites, or multiple abdominal surgeries (74,76,79). They cite the characteristic clinical presentation, lack of systemic manifestations, and absence of familial predisposition in most cases. The occurrence of perforating calcific elastosis in patients with renal failure may suggest that conditions resulting in an abnormal calcium phosphate product may produce abnormal calcification of elastic fibers. The occurrence of PXE-like eruptions in patients exposed to saltpeter (calcium-ammonium-nitrate salts) (88) and in one patient with chronic idiopathic hyperphosphatasia (89) supports this concept. Others have argued that perforating calcific elastosis may represent a localized cutaneous expression of hereditary PXE (78). Arguments for the latter theory include a history of hypertension in three quarters of reported patients and angioid streaks in one third of examined patients (75). The presence of perforation is also not distinctive, as the finding has also been noted to occur in lesions of classic hereditary PXE. The disorder may represent a spectrum ranging from a purely acquired form with no systemic manifestations to an inherited form with limited systemic expression.

LATE-ONSET FOCAL DERMAL ELASTOSIS

Late-onset focal dermal elastosis has been described in a small number of elderly patients with lesions clinically resembling PXE (90,91).

Histopathology. Focal elastosis along with an increased accumulation of normal-appearing elastic fibers in the mid and deep dermis are seen (90). No pathologic changes of PXE are present.

Histogenesis. There is an increase in elastin and collagen contents in tested patients as compared with controls. An increase in elastin type I and III collagen messenger RNAs (mRNAs) from patients' fibroblasts has been observed. No change in excreted elastin peptides is noted in affected patients. An overexpression of elastin has been postulated (92).

HYPERKERATOSIS LENTICULARIS PERSTANS (FLEGEL'S DISEASE)

A rare dermatosis first described in 1958, hyperkeratosis lenticularis perstans consists of asymptomatic, flat, hyperkeratotic papules from 1 to 5 mm in diameter, located predominantly on the dorsa of the feet and on the lower legs (93). Removal of the adherent, horny scale causes slight bleeding. In addition to the central horny scale, larger papules often have a peripherally attached collarette of fine scaling. In two reported instances, extensive papular lesions were present on the oral mucosa (94). Other reported sites include the thighs, upper extremities, and ears (95,96).

The disorder starts in late life and persists indefinitely. An autosomal dominant transmission has been noted in several instances (97–99). Unilateral involvement may represent postzygotic mosaicism (100).

Histopathology. In some instances, the histologic picture is nonspecific, showing hyperkeratosis with occasional areas of parakeratosis, irregular acanthosis intermingled with areas of flattening of the stratum malpighii, and vascular dilation with a moderate amount of perivascular lymphocytic inflammation (101). However, it seems that if the specimen is obtained from a well-developed, markedly hyperkeratotic lesion, a characteristic, although not necessarily diagnostic, histologic picture may be revealed. The lesion shows a greatly thickened, compact, strongly eosinophilic horny layer standing out in sharp contrast to the less heavily stained basket-weave keratin of the

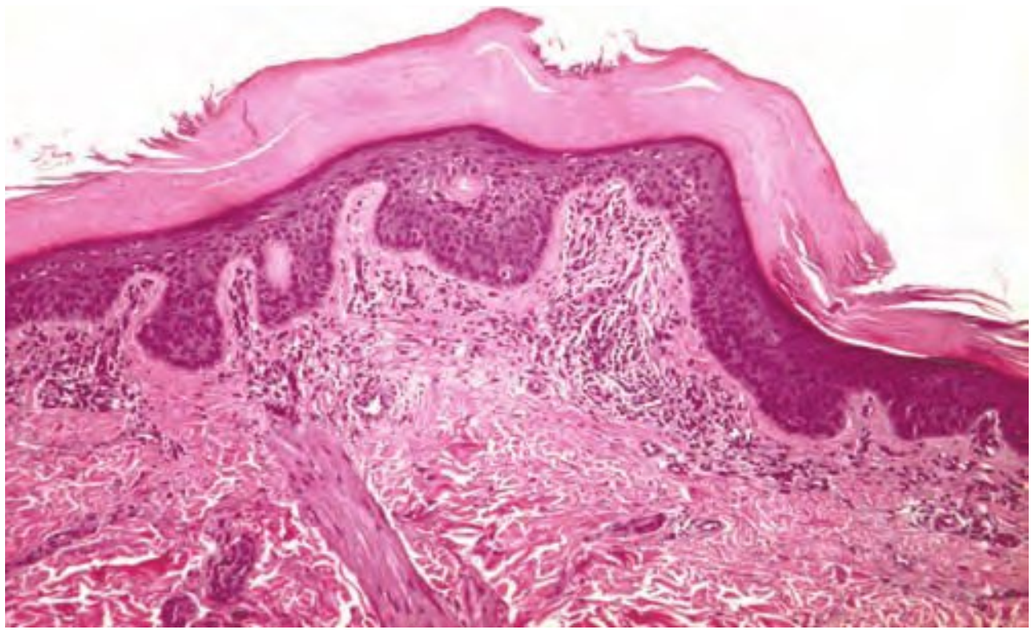


FIGURE 15-8. Hyperkeratosis lenticularis perstans. Dense compact orthokeratosis surmounts an epidermis with focal flattening of the stratum malpighii. A lymphocytic infiltrate is present in the upper dermis.

uninvolved epidermis (95). The underlying stratum malpighii appears flattened, with thinning or even absence of the granular layer (Fig. 15-8).

Acanthosis is observed at the periphery. In some instances, bordering on the central depression, the epidermis at the periphery forms a papillomatous elevation resembling a church spire (93,102,103). Vacuolar alteration and apoptotic cells in the basal layer have been seen in some cases (95,104,105). The dermal infiltrate is composed largely of lymphoid cells and is located as a narrow band fairly close to the epidermis with a rather sharp demarcation at its lower border. Immunohistochemical studies have shown the infiltrate to be predominantly T cells (106–108).

Histogenesis. Under electron microscopic examination, the absence of membrane-coating granules was noted in some cases and regarded as the primary lesion of hyperkeratosis lenticularis perstans (94,99).

A defect in the membrane-coating granules seems likely to play a role in Flegel's disease, because in other cases in which membrane-coating granules were present, the granules lacked a lamellar internal structure and appeared vesicular (109,110). In one case, both lamellar and vesicular bodies were observed, with lamellar bodies greatly predominating in uninvolved epidermis and vesicular bodies in lesional epidermis (111). However, one study of lesional skin from four patients found no such abnormalities in lamellar bodies (112).

Other ultrastructural findings in Flegel's disease that have been described in some cases include Sezary cell-like lymphocytes (113), rodlike intracytoplasmic inclusions (114), and wormlike bodies in histiocytes (111). The significance and role of these findings in the etiology of Flegel's disease is unknown.

STRIAE DISTENSAE

Striae distensae occur most commonly on the abdomen, on the thighs, and in the inguinal region. They consist of bands of thin, wrinkled skin that at first are red, then purple, and finally white.

Histopathology. The epidermis is thin and flattened. There is a decrease in the thickness of the dermis. The upper portion of the dermis shows straight, thin collagen bundles arranged parallel to the skin surface and transverse to the direction of the striae. The elastic fibers are arranged similarly. Fine elastic fibers predominate in early lesions, whereas in older lesions they are thick (115). Within the striae, nuclei are scarce and sweat glands and hair follicles are absent (116).

Histogenesis. The histologic findings support the view that striae distensae are scars. They occur in conditions associated with increased production of glucocorticoids by the adrenal glands. Among these conditions are pregnancy, obesity, adolescence, and especially Cushing's disease (117). In obesity, the increased adrenocortical activity is a consequence of the obesity, and the production of glucocorticoids returns to normal when the body weight is reduced (118). Similarly, the occurrence of striae in nonobese adolescents, as noted in 35% of the girls and 15% of the boys examined, is associated with an increase in 17-kerosteroid excretion (119). Striae may also form in response to prolonged intake of corticosteroids or following the prolonged local application of corticosteroid creams to the skin. The action of the glucocorticoids consists of an antianabolic effect suppressing both fibroblastic and epidermal activity, as tissue culture studies have shown (120).

LINEAR FOCAL ELASTOSIS (ELASTOTIC STRIAE)

Linear focal elastosis (elastotic striae) is an uncommon, but more likely underdiagnosed or underreported, disorder presenting as palpable striae-like yellow linear bands. The disorder was initially described in the lumbosacral region of elderly males (121). Lesions on the thigh and legs have also been reported (122,123). Occasionally, the lesions arise in association with striae distensae (124–127). A number of cases have occurred in individuals younger than age 30 years (128–130).

Histopathology. Abundant fragmented, clumped, and wavy elastic fibers are present between hypertrophic collagen bundles in the mid reticular dermis (11,127). Elongated elastic fibers with split ends resembling a "paintbrush" can be seen (131). A decrease in papillary dermal elastic fibers has been demonstrated in the elastotic striae from one patient with coexistent pseudoxanthoma-like papillary dermal elastolysis (123). Unlike striae distensae, there is no decrease in thickness of the dermis or atrophy of the overlying epidermis.

Histogenesis. Electron microscopic examination reveals fragmented elastic tissue throughout the dermis (121). Widespread elastic fiber microfibrils, some occurring in continuity with intracytoplasmic filaments of fibroblasts, along with sequential maturation of elastic fibers have been observed suggesting an elastogenic process (132). An increased number of elastic fibers

in lesional skin has also been documented (131). It has been postulated that elastotic striae may represent a regenerative process of striae distensae (124,127). This view is supported by the presence of contiguous striae distensae and elastotic striae in several patients. Accumulations of thin elastic fibers have been observed in late stages of striae distensae (133–135). Thus, linear focal elastosis may represent an excessive "keloidal" repair process occurring in striae distensae (127).

PSEUDOXANTHOMA ELASTICUM–LIKE PAPILLARY DERMAL ELASTOLYSIS

Papillary dermal elastolysis, first described in 1992, is a rare, acquired condition consisting of soft coalescent yellow-white papules mainly on the lateral neck and supraclavicular regions of elderly women (123,136–143). The clinical appearance of the skin lesions closely resembles those of PXE. However, no other systemic features of PXE are seen. A similar and possibly related disorder, *white fibrous papulosis of the neck*, is characterized by paler, more discrete and firm papules (144–150). The term *fibroelastolytic papulosis of the neck* has been suggested to encompass the spectrum of the two disorders (150).

Histopathology. There is a marked decrease to an absence of elastic fibers in the papillary dermis (136). Focal elastotic changes in the subpapillary and mid-dermis have also been demonstrated (151). No calcification or fragmentation of elastic fibers is seen. A slight decrease in elastic fibers along with the presence of thickened collagen bundles in the papillary dermis are differentiating features in *white fibrous papulosis of the neck* (146,150).

Histogenesis. Electron microscopic examination confirms the absence of elastic fibers in the papillary dermis along with the presence of immature elastic fibers in the upper reticular dermis. Fibroblasts with prominent rough endoplasmic reticulum with numerous dilatations and elongated dendritic processes are present (136,142). In one patient, formation of loose component fibrils of elastic fibers and elastophagocytosis were seen ultrastructurally (140). Papillary dermal elastolysis has been suggested to be a disorder of intrinsic skin aging due to its histologic similarity (136). However, immunohistochemical studies have shown a decrease in both fibrillin-1 and elastin in affected areas, whereas aged normal-appearing skin demonstrates only a decrease in fibrillin-1. A defect in elastogenesis may contribute to the pathogenesis of the disorder (136,143). The female predominance and the report of a familial occurrence may suggest possible genetic factors (142).

MID-DERMAL ELASTOLYSIS

Mid-dermal elastolysis is a rare disorder, first described in 1977, occurring predominantly on the arms and trunk of middle-aged women (152). Clinically, two patterns are seen. The type-1 pattern consists of widespread, large areas of fine wrinkling along skin cleavage lines. The type-2 pattern consists of small, soft, papular lesions with tiny perifollicular protrusions, leaving the hair follicle itself as an indented center (153,154). These two patterns may coexist in the same patient. Persistent reticulate erythema is a recently described presentation (155). Urticaria (152), erythematous patches (156), or granuloma annulare (157) may precede some of the lesions. These postinflammatory forms of mid-dermal elastolysis have some similarity to a disorder first described in young South African girls termed *postinflammatory elastolysis and cutis laxa* (158–160). In the latter disorder, widespread wrinkling followed an acute phase of firm, erythematous, infiltrated lesions. An overlap with another disorder described as *disseminated nevus anelasticus* is also likely (161).

Histopathology. In this condition, there is a selective absence of elastic tissue strictly limited to the mid-dermis of involved areas (152). The perifollicular protrusions around indented hair follicles result from preservation of a thin layer of elastic tissue in the immediate vicinity of the follicles. This causes the hair follicles to appear retracted while the perifollicular skin protrudes (153). A mild perivascular inflammatory infiltrate of mononuclear cells with occasional interstitial multinucleated giant cells exhibiting elastophagocytosis may be seen (162–164). Electron microscopic examination also reveals fragments of normal-appearing elastic fibers within macrophages (162,165).

Histogenesis. The disorder likely represents a postinflammatory process, although in some cases this may be subclinical or remote. Immunohistochemical evidence of immune activation has been observed in lesional T lymphocytes and endothelial cells (166). The cytokines and elastases produced by inflammatory cells along with elastophagocytosis by macrophages may contribute to the loss of elastic fibers (162). A possible autoimmune mechanism has been hypothesized based on its associations with rheumatoid arthritis (167), silicone mammoplasty, elevated autoantibodies, false-positive Lyme titers (168), lupus erythematosus (169), and Hashimoto's thyroiditis (170). Culture studies performed with dermal fibroblasts from lesional skin showed an 80-fold increase in elastin mRNA and a 2-fold increase in elastolysis compared with normal skin (173). An idiosyncratic reaction to ultraviolet light has also been proposed as an etiologic or exacerbating factor (171,172). Recent studies suggest that ultraviolet exposure may lead to increased expression, by fibroblast-like cells, of elastin-degrading matrix metalloproteinase MMP-9 (174).

MACULAR ATROPHY (ANETODERMA)

Atrophic patches located mainly on the upper trunk characterize macular atrophy, or anetoderma. The skin of the patches is thin and blue-white and bulges slightly. The lesions may give the palpating finger the same sensation as a hernial orifice. Two types of macular atrophy are generally distinguished: the Jadassohn-Pellizzari type, in which the atrophic lesions initially appear red and on histologic examination show an inflammatory infiltrate;

and the Schweninger-Buzzi type, which clinically is noninflammatory from the beginning. However, not every case can be clearly assigned to one or the other of these two types; many clinically noninflammatory cases show an inflammatory infiltrate when examined histologically (175). The justification for distinguishing between the inflammatory and noninflammatory types has therefore been questioned (176). In many patients, new lesions continue to appear over a period of several years. Rare congenital and familial cases have been reported (177–181).

The so-called secondary form of macular atrophy occurs in the courses of various diseases, such as syphilis, lupus erythematosus, tuberculosis, sarcoidosis, and leprosy (182–185). The macular atrophy then represents the atrophic stage of the preceding disease (186). Other cases of secondary anetoderma have occurred in association with porphyria (187), urticaria pigmentosa (188,189), pilomatricomas (190,191), Down's syndrome (192,193), acrodermatitis chronica atrophicans (194), Takayasu's arteritis (195), Grave's disease (196), Addison's disease (196), autoimmune hemolysis (196), systemic scleroderma (196), varicella (197), anticardiolipin and antiphospholipid antibodies (198–204), HIV (205), Sjogren's syndrome (206,207), alpha-1 antitrypsin deficiency (201), B-cell lymphoma (206,208), plasmacytoma (209,210), cutaneous lymphoid hyperplasia (209), angular cheilitis (211), juvenile xanthogranuloma (212,213), and generalized granuloma annulare (214). Macular atrophy has also been observed after iatrogenic procedures such as leech application (215), monitoring electrode placement in premature infants (216,217) hepatitis B vaccination (218), and after prolonged treatment with penicillamine (219).

Histopathology. Early, erythematous lesions usually show a moderately pronounced perivascular infiltrate of mononuclear cells (220–225). In a few instances, however, the early inflammatory lesions show a perivascular infiltrate in which neutrophils and eosinophils predominate and nuclear dust is present, resulting in a histologic picture of leukocytoclastic vasculitis (221,222). Microthrombosis has also been noted in patients with anetoderma and associated antiphospholipid antibodies (209–212).

The elastic tissue may still appear normal in the early stage of an erythematous lesion (223). Usually, however, it is already decreased or even absent within the lesion. In cases in which there is a decrease in the amount of elastic tissue, mononuclear cells may be seen adhering to elastic fibers (220). Elastophagocytosis within macrophages and giant cells may be seen (224).

Long-standing, noninflammatory lesions generally show a more or less complete loss of elastic tissue, either in the papillary and upper reticular dermis or in the upper reticular dermis only (Fig. 15-9). A perivascular and periadnexal lymphocytic infiltrate of varying intensity is invariably present; thus, a distinction of an inflammatory and a noninflammatory type is not justified. In some instances, the involved areas show small, normal elastic fibers, which are probably the result of resynthesis, or abnormal, irregular, granular, twisted, fine fibers (175). Immunofluorescence studies of primary anetoderma have revealed immune deposits in a pattern indistinguishable from that of lupus erythematosus (225,226).

Histogenesis. Electron microscopic examination of lesions reveals a few thin, irregular elastic fibers, with more or less complete loss of the amorphous substance elastin but with relative conservation of the microfibrils. Macrophages, lymphocytes, and some plasma cells are observed. It appears possible that partial destruction by elastases originating in the macrophages occurs, because it is known that the elastases preferentially destroy the amorphous substance of the elastic

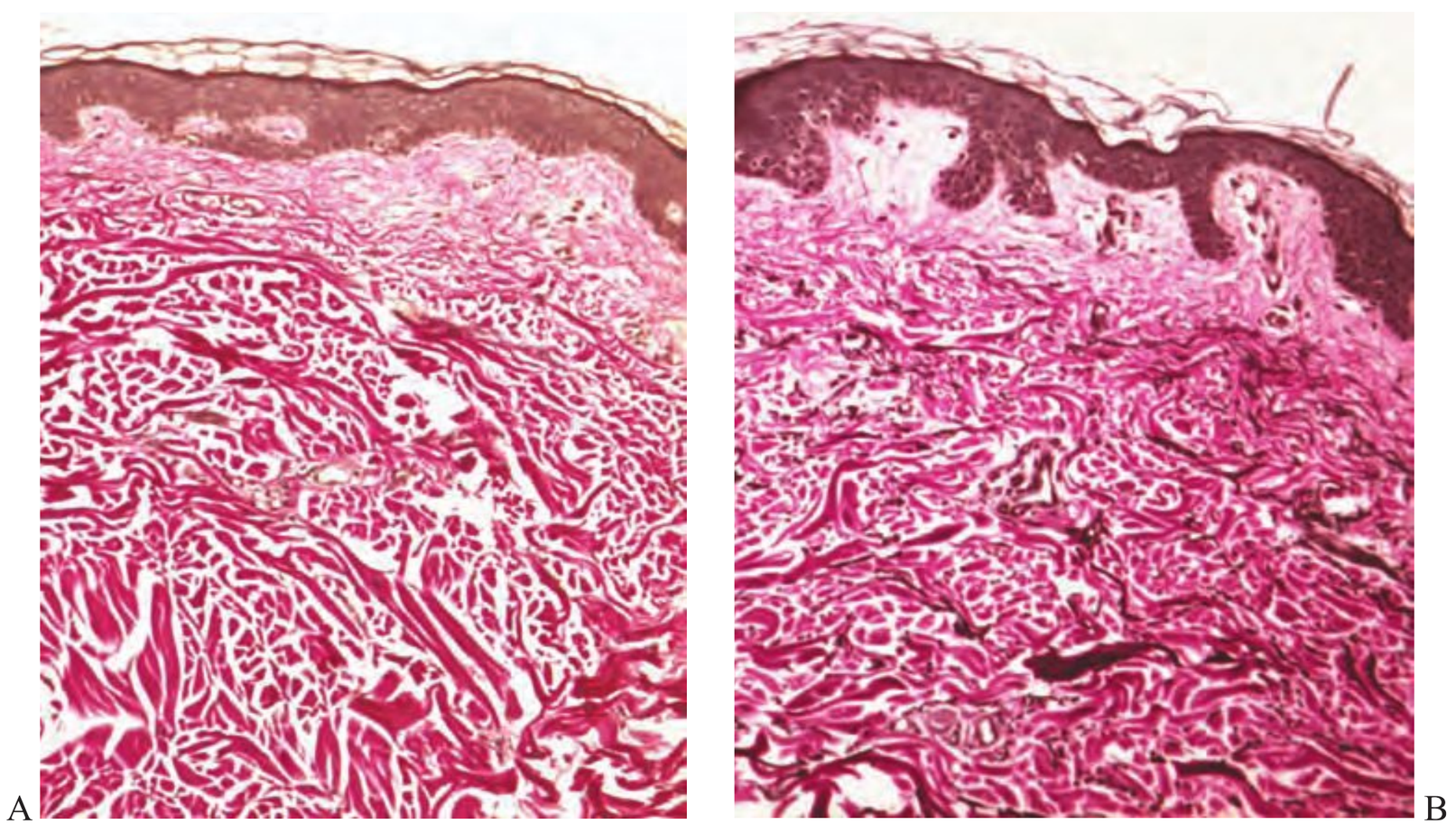


FIGURE 15-9. Anetoderma. Decreased to absent elastic fibers in a case of anetoderma (A) as compared with a normal control (B).

fibers (226). Two elastase-type proteinases, gelatinase A (metalloproteinase-2) and B (MMP-9), have been shown to have increased expression in skin explants from patients with anetoderma (227). Morphometric analysis has demonstrated decreases in the diameter of oxytalan and dermal elastic fibers as well as the volume fractions of pre-elastic and dermal elastic fibers (228). This analysis has been used to differentiate anetoderma from other disorders of elastic tissue such as cutis laxa.

There is increasing evidence for an immunologic basis for anetoderma. In support of this hypothesis is the association of numerous autoimmune disorders and the findings of immune deposits at both the dermal–epidermal junction and dermal blood vessels (196,225). In particular, the association of antiphospholipid antibodies with anetoderma is intriguing. The exact mechanism by which these antibodies may induce lesions remains to be elucidated. Some authors have postulated that microthrombosis produced by antiphospholipid antibodies with resultant ischemia of dermal tissues may induce elastic fiber degeneration (200,203). Others have hypothesized that the antibodies may alter the inhibitors of elastolytic enzymes, thus allowing the destruction of elastic fibers (229).

PERIFOLLICULAR ELASTOLYSIS

Perifollicular elastolysis is a relatively common condition consisting of small, hypopigmented, follicular papules on the face and upper trunk. The papules may protrude or herniate (230–233). There is a strong association with acne vulgaris, and some have suggested the term *papular acne scars* for the disorder (233).

Histopathology. There is an absence of elastic fibers localized to the regions around pilosebaceous units (230).

Histogenesis. Perifollicular elastolysis most likely represents a form of anetoderma related to acne scarring (233). Elastase-producing strains of *Staphylococcus epidermidis* have been found in lesional hair follicles and have been proposed as the causative factor (230,232).

ACRO-OSTEOLYSIS

The term *acro-osteolysis* refers to destructive lytic changes on the distal phalanges. Three types are recognized: familial; idiopathic, nonfamilial; and occupational, which is associated with exposure to vinyl chloride gas. In addition, acro-osteolysis may be a feature of genetic syndromes such as Haim-Munk syndrome, pycnodystosis, Hutchinson-Gilford syndrome, and Hajdu-Cheney syndrome (234–237).

The *familial type* affects mainly the phalanges of the feet and is associated with recurrent ulcers on the soles (238).

The *idiopathic type* affects the hands more severely than the feet. Involvement of the distal phalanges of the fingers causes shortening of the fingers. This variant may be associated with Raynaud's phenomenon. Only one case has been described, with cutaneous lesions consisting of numerous yellow papules 2 to 4 mm in diameter and showing a linear distribution and coalescence into plaques, mainly on the arms (238).

Occupational acro-osteolysis, like the idiopathic type, causes shortening of the fingers due to osteolysis. This variant is often associated with Raynaud's phenomenon and progressive thickening of the skin of the hands and forearms simulating scleroderma. There may be erythema of the hands, and the thickening may consist of papules and plaques (239). The skin of the face may show diffuse induration (240). In addition, there may be thrombocytopenia, portal fibrosis, and impaired hepatic and pulmonary function (241). A variant of occupational acro-osteolysis has been described in guitar players and is believed to be secondary to mechanical stress (243).

Histopathology. The histologic changes in the papules and plaques of idiopathic and occupational acro-osteolysis consist of thickening of the dermis, with swelling and homogenization of the collagen bundles, indistinguishable from scleroderma. Staining for elastic tissue shows disorganization of the elastic fibers, which appear thin and fragmented (238–240).

Histogenesis. Vinyl chloride disease is an immune-complex disorder associated with hyperimmunoglobulinemia, cryoglobulinemia, and evidence of *in vivo* activation of complement (241). The immunologic nature of the disease explains why it is developed by <3% of the workers exposed to vinyl chloride gas (239).

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CHAPTER 16

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Cutaneous Manifestations of Nutritional Deficiency States and Gastrointestinal Disease

DEFICIENCIES OF VITAMINS, OTHER AMINO ACIDS, AND MINERALS

Scurvy

The manifestations of scurvy, which is due to vitamin C (ascorbic acid) deficiency, have been known for 3,000 years. In 1753, Sir James Lind demonstrated the efficacy of citrus fruits in the prevention of this condition (1,2), which is characterized by follicular purpuric macules with or without follicular hyperkeratosis and corkscrew hairs, ecchymoses, particularly in the pretibial areas, and conjunctival and gingival hemorrhages, the latter associated with gingival hyperplasia (3). Subcutaneous hemorrhage with woody edema of the lower extremities and hemarthrosis may occur (4). Nonspecific aches and pains and impaired wound healing are frequent. Anemia, possibly related to decreased amounts of active folate and blood loss, is present in approximately 75% of individuals (4,5). For humans, the principal source of vitamin C, a substance that cannot be synthesized from glucose derivatives, is fruits and vegetables. Scurvy occurs in individuals such as autistic patients who selectively avoid these foods (6), the elderly, chronic alcoholics, renal dialysis patients, and malnourished displaced refugee populations (7), who also suffer other micronutrient deficiencies when dependent on food aid (8,9).

Histopathology. Follicular hyperkeratosis and perifollicular erythrocyte extravasation without an accompanying vasculopathy are characteristic. Extensive extravasations are usually associated with deposits of hemosiderin within and outside of macrophages. A coiled hair may emanate from the dilated follicular orifice (10).

Differential Diagnosis. Other pauci-inflammatory hyperkeratotic dermatoses that should be considered in the differential diagnosis include keratosis pilaris, vitamin A deficiency, pityriasis rubra pilaris, ichthyosis vulgaris, and a resolving lichenoid follicular hyperkeratotic process such as lichen planopilaris, lichen spinulosus, or lupus erythematosus. Pilotropic T-cell dyscrasia including alopecia mucinosa and frank pilotropic mycosis fungoides can demonstrate prominent follicular hyperkeratosis. Coiled or "corkscrew" hairs are not pathognomonic of scurvy and may be seen in certain ectodermal dysplasia syndromes (11).

Pathogenesis. Most manifestations of scurvy can be attributed to defective collagen synthesis. Lysine and proline hydroxylase enzymes require vitamin C to reduce Fe^{3+} during the reaction. In vitamin C deficiency, the end product, hydroxyproline, which stabilizes the collagenous domain of procollagen, is deficient (3). Individuals with the Hp 2-2 genetic polymorphism of haptoglobin, a hemoglobin-binding antioxidant, have markedly lower levels of vitamin C despite an adequate nutritional supply, establishing a basis for a potential genetic influence (12). Because of the impaired antioxidant ability of Hp 2-2 haptoglobin, there is a higher rate of vitamin C oxidation, which significantly reduces the stability of L-ascorbic acid (13) and decreases its availability to hydroxylase enzymes. Ultrastructurally, the dermal fibroblasts appear shrunken and show a decreased amount of rough endoplasmic reticulum (14). Around these fibroblasts, one observes increased amounts of extracellular filamentous or amorphous material that has failed to polymerize into normal collagen fibrils. The extravasation of red cells is caused by vacuolar degeneration and junctional separation of adjoining endothelial cells and their detachment from the basement membrane in capillaries and small venules (14).

Vitamin A Deficiency (Phrynoderma)

Seen mainly in Asia and Africa, vitamin A deficiency is rare in the United States but may occur after intestinal bypass surgery for obesity (15) or visceral myopathy (16). One reported case in France attributed the phrynoderma to severe combined endogenous deficiencies of vitamins A and C secondary to intestinal malabsorption caused by chronic intestinal parasitic infection by *Giardia intestinalis* (17). Dryness and roughness of the skin along with conical follicular keratotic plugs characterize the cutaneous changes. Night blindness, xerophthalmia, and keratomalacia also occur.

Histopathology. The skin shows moderate hyperkeratosis with distension of the upper part of the follicle by large, horny plugs (15). Sebaceous glands are greatly reduced in size and may

exhibit epithelial atrophy (18). In severe cases both eccrine and sebaceous glands may exhibit squamous metaplasia (19).

Differential Diagnosis. The other causes of a pauci-inflammatory interfollicular and follicular hyperkeratosis are mentioned in the prior discussion of scurvy. Striking orthohyperkeratosis with only minimal parakeratosis, hyperplasia of the epidermis, acantholysis, and a superficial dermal lymphocytic infiltrate with basilar vacuolar change are additional histologic features that distinguish pityriasis rubra pilaris from phrynoderma (20). Superficial dermal fibroplasia with melanophage accumulation is the hallmark of resolved lichen planopilaris, lupus erythematosus, and graft-versus-host disease. Sebaceous gland atrophy has been described in pellagra. Squamous metaplasia of the eccrine apparatus has been seen with methotrexate therapy and graft-versus-host disease. Lymphocyte satellitosis around eccrine ductular cells is an additional helpful clue pointing toward a diagnosis of graft-versus-host disease.

Acquired Vitamin B_3 Deficiency (Pellagra)

The word "pellagra" is derived from two Italian words, "*pelle*," meaning "skin," and "*agra*," meaning "sharp burning" or "rough." Although primarily ascribed to niacin (vitamin B_3) deficiency, other vitamin deficiencies or protein malnutrition (21) appear integral to the development of the pellagra symptom complex. Presenting as cutaneous lesions, gastrointestinal symptoms, and mental changes, pellagra has been ascribed the acronym of the three Ds: dermatitis, diarrhea, and dementia. In the United States, the enrichment of whole-wheat flour with niacin has almost eliminated pellagra, but it is still prevalent in countries such as Mexico and some African nations where cornmeal is the main constituent of the diet, as well as in displaced populations (8,9). Pellagra in the United States and Europe is seen mainly in chronic alcoholics (22) and in patients with anorexia nervosa, malignant gastrointestinal tumors, and intestinal parasitosis (21). Its appearance in carcinoid syndrome is believed to reflect a depression of endogenous niacin production by tumor cell diversion of tryptophan toward serotonin (23). Pellagra has also been reported in patients receiving isoniazid, pyrazinamide, ethionamide, azathioprine, chloramphenicol, and anticonvulsants (24). Isoniazid, a structural analogue of niacin, can cause suppression of endogenous niacin production.

Three basic skin eruptions occur in pellagrins (25,26). The first is a photo-induced eruption that is intensely erythematous and subsequently exfoliates to yield a hyperpigmented residuum. The second eruption comprises painful erythematous erosions in genital and perineal areas possibly induced by pressure, heat, and trauma (21). The increased skin fragility may reflect aberrations in the collagen and elastic fiber content of the skin. Pellagrins may develop a seborrheic dermatitis–like rash involving the face, scalp, and neck. Oral manifestations include beefy, red, cracked lips and a fissured or smooth, red, sore tongue (27). Among the neurologic symptoms are dementia, psychosis, anxiety, defective memory, burning sensations, sudden attacks of falling, dizziness, and headaches. A cause of sudden death is central pontine myelinolysis (21).

Histopathology. Psoriasiform epidermal hyperplasia with hyperkeratosis, parakeratosis, and a lymphocytic perivascular inflammatory cell infiltrate characterize initial lesions. Additional features include scattered necrotic keratinocytes, granular cell layer loss, and architectural disarray with dysmaturation of the epidermis. Depigmentation of the basal layer with accumulation of fat droplets is described, as is vacuolation of cells within the granular and spinous layers (28). Epidermal atrophy, hypermelanosis, vascular ectasia, and sebaceous atrophy characterize end-stage lesions (28). Seborrheic dermatitis–like lesions may show sebaceous gland hyperplasia with follicular dilation. Fragmentation, swelling, and thickening of elastic fibers, swelling of collagen fibers, and merging of elastic tissue with collagen have been described. A morphology indistinguishable from that of necrolytic migratory erythema and acrodermatitis enteropathica has been reported, comprising intracellular edema with vacuolar change of the upper stratum malpighii and keratinocyte necrosis, sometimes accompanied by neutrophilic infiltration of the upper spinous layers, subcorneal pustulation localized to or in isolation from these areas, and folliculitis (21).

Pathogenesis. A deficiency in urocanic acid caused by a reduction in histidine and histidase activity has been postulated as a possible mechanism of photosensitivity in pellagra; urocanic acid protects the skin from ultraviolet (UV) wavelengths by absorbing light in the UVB range (21). Kynurenic acid, a metabolic byproduct of the tryptophan-kynurenine-nicotinic pathway, accumulates in pellagra as a result of a deficiency of nicotinamide, which blocks the formation of kynurenic acid. Kynurenic acid induces a phytotoxic reaction in skin subjected to long-wave UV radiation ranging from 350 to 380 mm (21). Some of the gastrointestinal symptoms may relate to degenerative changes of the dorsal vagal nuclei. The neurologic symptoms may be due to chromatolysis of various cortical and brainstem nuclei (21).

Differential Diagnosis. The histopathology is similar to that of the nutritional dermatoses acrodermatitis enteropathica and necrolytic migratory erythema. In addition, those dermatitides associated with hyperkeratosis, a maturation disarray, and/or scattered degenerating keratinocytes need to be considered, as discussed in the differential diagnosis section of necrolytic migratory erythema.

Congenital Vitamin B_3 Deficiency (Hartnup's Disease)

Named after the family in which it was first described in 1956, Hartnup's disease is a distinctive autosomal recessive syndrome comprising pellagrinous skin (29,30), neurologic abnormalities including mental deterioration and cerebellar ataxia, and abnormal aminoaciduria (31). The intermittent skin eruption is seen primarily in the summer at times of maximal sun exposure and

at times resembles either poikiloderma vasculare atrophicans (32) or, when vesicles are prominent, hydroa vacciniforme (33). Hartnup's disease, in contrast to pellagra, does not respond to treatment with niacin (33).

Histopathology. The histopathology usually resembles that of pellagra. Poikilodermatous lesions manifest flattening of the epidermis and prominent dermal melanophage accumulation (32).

Pathogenesis. An intestinal and renal tubular defect of tryptophan absorption leads to a deficiency in endogenous niacin, accounting for the pellagra-like symptomatology. The genetic abnormality involves a mutation in the gene for SCL6A19 (34,35), a transporter for monoamino-monocarboxylic acids located mainly in the kidney and intestine, which maps to chromosome 5p15 (36). Chromatographic studies of urine show persistent aminoaciduria, particularly of tryptophan and of indolic substances derived from tryptophan (30,32).

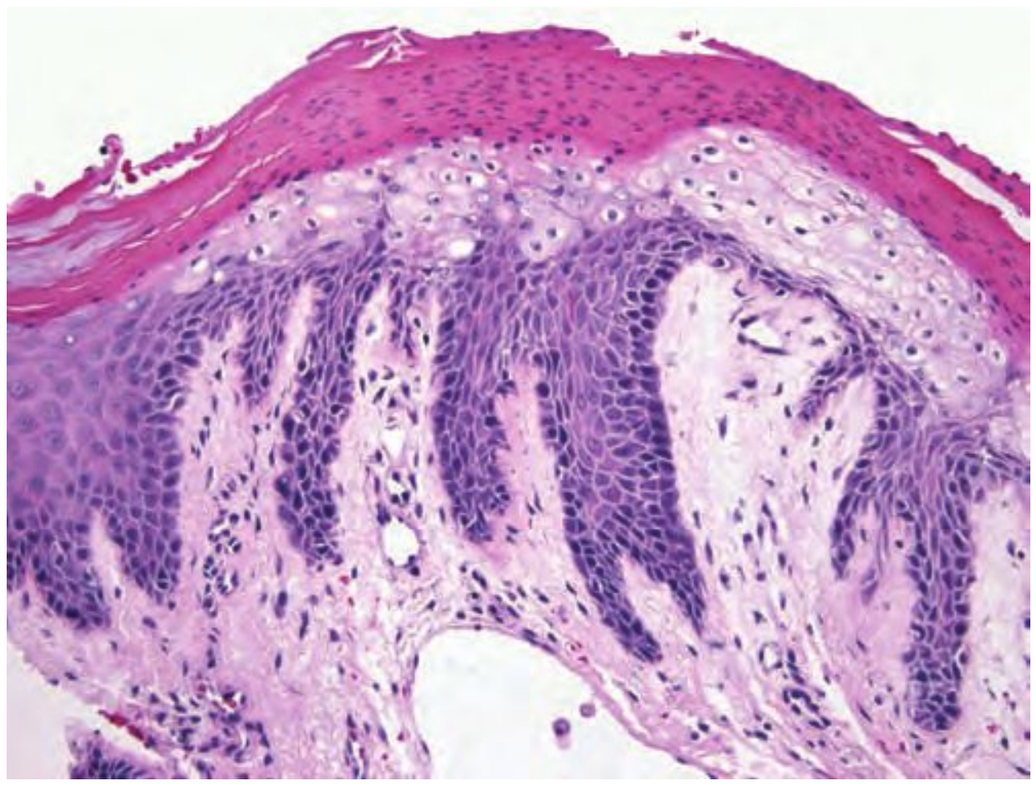


FIGURE 16-1. Necrolytic migratory erythema (glucagonoma syndrome). The lower portion of the stratum malpighii appears viable, whereas the upper portion shows necrolysis or "sudden death." The necrolytic portion manifests cytoplasmic eosinophilic homogenization with pyknotic nuclei.

OTHER FORMS OF NUTRITIONAL DERMATOSES

Necrolytic Migratory Erythema (Glucagonoma Syndrome)

First described in 1942 in a patient with a pancreatic islet cell carcinoma (36), this distinctive dermatosis, which can precede all other symptoms of pancreatic carcinoma by several years (37), is most commonly seen in association with a glucagon-secreting alpha cell tumor of the pancreas. Surgical extirpation of the neoplasm may result in resolution of the eruption, as may amino acid and fatty acid infusion (38,39).

The manifestations of glucagonoma syndrome include cutaneous and mucosal lesions, weight loss, anemia, adult-onset diabetes, glucose intolerance, elevation of serum glucagon levels, and thromboembolism (40). Skin lesions are seen mainly on the face in perioral and perinasal distribution, the perineum, genitals, shins, ankles, and feet and include erythema, erosions, and flaccid vesicular-pustular lesions that rupture easily and often have a circinate appearance due to peripheral spreading. Rapid healing and the continuous development of new lesions result in daily fluctuations of the eruption. Cheilitis, glossitis, brittle nails, and dyspareunia due to mucosal lesions are also reported (41).

Histopathology. The characteristic acute lesion shows abrupt necrosis of the upper layers of the stratum spinosum, which may detach from the subjacent viable epidermis. Keratinocyte degeneration varies from marked hydropic swelling to cytoplasmic eosinophilia and nuclear pyknosis. Neutrophilic chemotaxis to the necrotic epithelium may eventuate in a subcorneal pustule. Chronic lesions have as their hallmark a psoriasiform dermatitis. In both acute and chronic lesions there is architectural disarray, reflecting a maturation defect; it manifests as basal layer hyperplasia, vacuolar change, and a deficient granular layer. The epidermis is surmounted by a broad parakeratotic scale (Fig. 16-1). *Candida* may be noted (42,43).

Pathogenesis. Patients with glucagonoma have sustained gluconeogenesis resulting in a negative nitrogen balance, with protein amino acid degradation, even of epidermal proteins (44). In addition to glucagonoma, necrolytic migratory erythema has been reported with hepatic cirrhosis (45), jejunal adenocarcinoma with hepatic dysfunction, hepatitis B (46), malabsorption with villous atrophy (47), opiate dependency (48,49), and myelodysplastic syndrome (50). Glucagon levels may be normal. A comparable syndrome in dogs develops in the setting of diabetes mellitus and hepatic cirrhosis (43). In all of these conditions, malabsorption and diarrhea lead to isolated deficiencies of certain essential fatty acids, zinc, and amino acids. The pathophysiology may reflect in part a phospholipid fatty acid abnormality in cells due to defective delta-6-desaturase enzyme, which is known to be inhibited by zinc deficiency and excess alcohol intake. In patients with unresectable glucagonoma who manifest necrolytic migratory erythema, infusion of amino acids has resulted in rapid clearing of the cutaneous lesions (51). There is an interesting subgroup of patients with necrolytic erythema in whom the lesions are primarily confined to the dorsum of the feet. These cases are associated with hepatitis C and fall under the designation of necrolytic acral erythema (52). The dermatitis responds to a combination of antiviral therapy and zinc.

Differential Diagnosis. The histopathology is similar to that of other nutritional dermatoses, namely acrodermatitis enteropathica and pellagra. Those dermatitides associated with hyperkeratosis, a maturation disarray, and/or scattered degenerating keratinocytes such as graft-versus-host disease, subacute cutaneous lupus erythematosus, dermatomyositis, pityriasis rubra pilaris, and toxic drug eruptions, particularly those that are photo-induced, should also be considered.

Acrodermatitis Enteropathica

Acrodermatitis enteropathica, first described in 1942 (53), is transmitted as an autosomal recessive trait. Caused by defective intestinal absorption of zinc (54), it usually manifests in the first 4 to 10 weeks of life in bottle-fed infants as an acral and periorificial eruption with intractable diarrhea and diffuse partial alopecia. The skin exhibits areas of moist erythema, occasionally associated with vesiculobullous and/or pustular lesions (55). Untreated cases eventuate in death from malnutrition and infection because of immunologic defects reflecting zinc deficiency, the latter including decreased natural killer cell activity, impaired delayed-type hypersensitivity, and thymic atrophy (56). Paronychia, stomatitis, photophobia, blepharitis, conjunctivitis, corneal opacities, and hoarseness are additional manifestations. An acquired form occurs in patients receiving intravenous hyperalimentation with low zinc content (57), in infants who are fed breast milk low in zinc (58), in patients with Crohn's disease, in patients with ornithine transcarbamylase deficiency (59), in patients with status post pancreaticouodenectomy (60), and in the setting of AIDS nephropathy when proteinuria eventuates in excessive loss of protein-bound zinc (56).

Histopathology. The upper part of the epidermis shows pallor due to intracellular edema and is surmounted by a confluent, thick, parakeratotic scale that may contain neutrophils. There is granular cell layer diminution and focal dyskeratosis. As with necrolytic migratory erythema, there may be architectural disarray and dismaturation. Subcorneal vesicles may be present. The epidermis manifests variable psoriasiform hyperplasia and atrophy and, in a few instances, acantholysis (55,58). Superinfection with *Candida* may occur (Fig. 16-2).

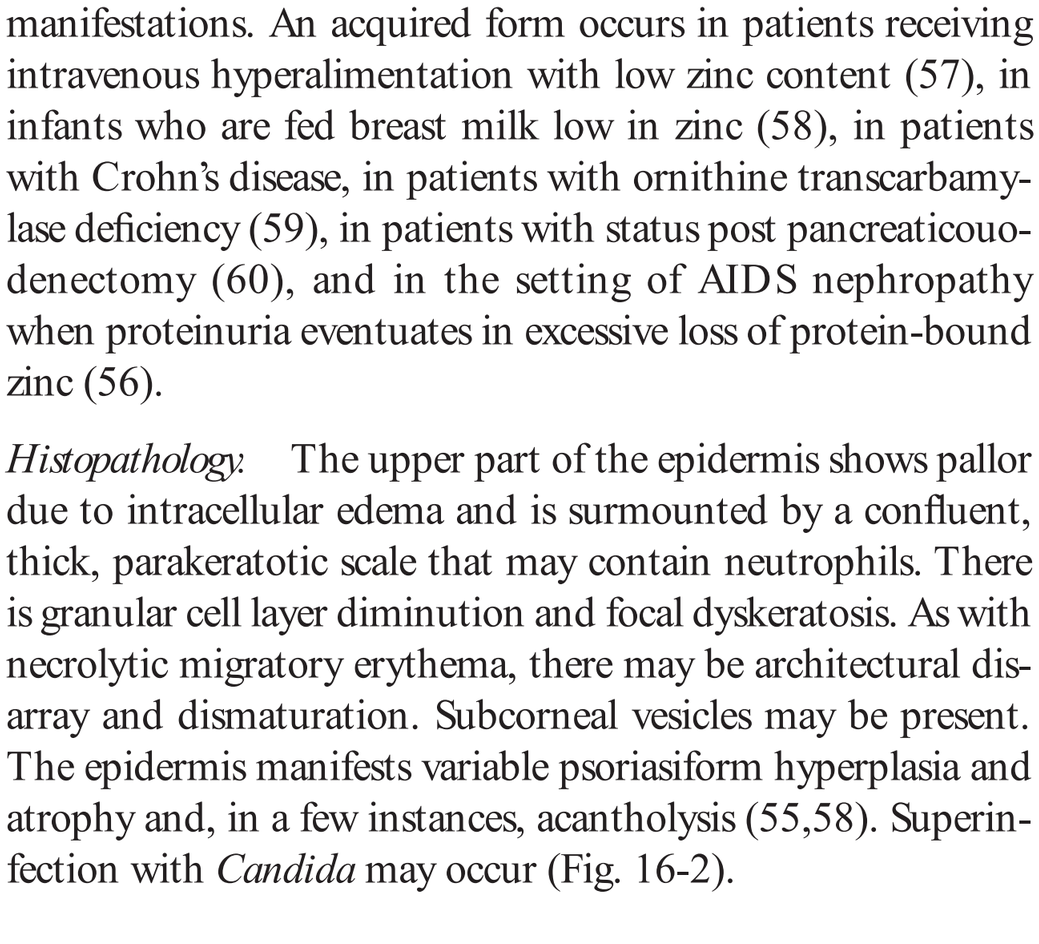


FIGURE 16-2. Acrodermatitis enteropathica. The epidermis demonstrates psoriasiform hyperplasia, dysmaturation, granular cell layer diminution, and vacuolar change. The epidermis is surmounted by a compact parakeratotic scale. Vascular ectasia is also present.

Pathogenesis. Defective intestinal absorption of zinc has been demonstrated in children with acrodermatitis enteropathica (61), resulting in plasma zinc levels well below the normal range of 68 to 112 μg/dL. Oral administration of zinc sulfate results in rapid and complete resolution of the disease. Electron microscopy shows abnormal keratinization with decreased keratohyalin granules and increased number of keratinosome-derived lamellae within intercellular spaces. Keratinosomes contain several zinc-dependent enzyme systems, the metabolism of which may be affected (62).

Congenital zinc deficiency leading to acrodermatitis enteropathica shortly after birth has been linked to a novel mutation in the SLC39A4 gene, localized to chromosome region 8q24.3 (63). The SLC39A4 gene is expressed in tissues involved in zinc absorption, including the stomach, small intestine, colon, and kidney; a mutation alters the protein's function of zinc absorption, causing zinc deficiency (64).

Differential Diagnosis. Pellagra, necrolytic migratory erythema, and acrodermatitis enteropathica share a constellation of histologic features that should suggest a diagnosis of nutritional dermatosis, namely, confluent parakeratosis, granular layer diminution, epidermal pallor and focal dyskeratosis, psoriasiform hyperplasia, and architectural disarray and dismaturation. Such cases can be misdiagnosed as eczema and psoriasis.

Kwashiorkor

Kwashiorkor is a form of protein malnutrition coupled to carbohydrate excess resulting in reduction of a patient's weight by 20% to 40%. Primary manifestations include generalized hypopigmentation that begins circumorally and in the pretibial regions. With disease progression, hyperpigmented plaques with a waxy texture develop over the elbows and ankles and in the intertriginous areas. Dryness, desquamation, and decreased skin elasticity occur. "Crazy pavement" or "flaky-paint dermatosis" describes the extensive desquamation with erosions and fissuring, vesicles, and bullae that may be seen in severe cases (65). Prominent edema can mask the underlying muscle and subcutaneous tissue atrophy (66). Hair abnormalities include a diffuse alopecia, alternating bands of normal and hypopigmented hair referred to as the "flag" sign, and an unusual reddish-brown discoloration called hypochromotrichia (65). Extracutaneous manifestations include cerebral atrophy secondary to loss of myelin lipid (67), diarrhea, hepatic steatosis, and mucosal abnormalities such as a smooth tongue, angular stomatitis, and perianal and nasal erosions.

Histopathology. The histologic picture of skin lesions is not diagnostic but is said to resemble that of pellagra (68). The changes include psoriasiform hyperplasia with hyperkeratosis and increased pigmentation throughout the epidermis or atrophy with irregular shortening and flattening of the rete (68).

Pathogenesis. The etiology of the edema includes reduced capillary blood flow, hypoalbuminemia, and increased peripheral vasoconstriction (69).

CUTANEOUS MANIFESTATIONS OF GASTROINTESTINAL DISEASE

Pyoderma Gangrenosum

First described in 1930 (70), pyoderma gangrenosum was once considered pathognomonic of idiopathic ulcerative colitis but has since been described in association with a wide variety of disorders, including roughly 5% of patients with Crohn's disease. Beginning as folliculocentric pustules or fluctuant nodules, the lesions ulcerate and have sharply circumscribed violaceous, raised edges in which necrotic pustules may be seen. The disease most commonly occurs on the lower extremities and trunk in adults who are 30 to 50 years old. Occasionally it occurs in childhood, affecting the buttocks, perineal region, and head and neck area (71,72). Koebnerization occurs at sites of trauma, including intravenous puncture sites, surgical wounds, and peristomal sites (73). Roughly 70% of cases are associated with inflammatory bowel disease, hematologic disorders including acute lymphoid and myeloid leukemias and myeloma, rheumatologic conditions including rheumatoid arthritis and lupus erythematosus, and hepatopathies (74,75), including chronic active hepatitis, primary biliary cirrhosis, and sclerosing cholangitis (72,76). Both a superficial granulomatous variant (77) and a vesiculopustular variant comprising disseminated vesicles and necrotizing pustules, some follicular based, have been observed without accompanying systemic disease. The vesiculopustular variant has also been seen in association with ulcerative colitis and/or underlying liver disease (76,78). Pyoderma gangrenosum has been associated with the administration of drugs including interferon (IFN)-α in the setting of chronic granulocytic leukemia, the antipsychotic agent sulpride (79), granulocyte colony-stimulating factor (80), the epidermal growth factor-tyrosine kinase inhibitor gefitinib (Iressa) (81), the retinoid isotretinoin (82), and the thionamide propylthiouracil (83).

Histopathology. Pyoderma gangrenosum exhibits a dichotomous tissue reaction, showing central necrotizing suppurative inflammation, usually with ulceration, and a peripheral lymphocytic vascular reaction comprising perivascular and intramural lymphocytic infiltrates, usually without fibrin deposition or mural necrosis (Figs. 16-3 and 16-4). Transitional areas show neutrophils in a loose cuff around the angiocentric lymphocytic infiltrates, defining a mixed lymphocytic and neutrophilic vascular reaction termed a *Sweet's-like vascular reaction* (84,85). Bullous lesions may also demonstrate a Sweet's-like vascular reaction with perivascular disintegrating neutrophilic infiltrates and hemorrhage without mural necrosis or luminal fibrin deposition. At variance with Sweet's syndrome is destruction of the connective tissue framework with resultant tissue pathergy (86,87). Although a leukocytoclastic vasculitis may be observed in areas of maximal tissue pathology, pyoderma gangrenosum does not reflect a primary vasculitis (72). In some cases a necrotizing pustular follicular reaction may be the central nidus of the lesion, particularly in the vesicular pustular variant associated with ulcerative colitis or

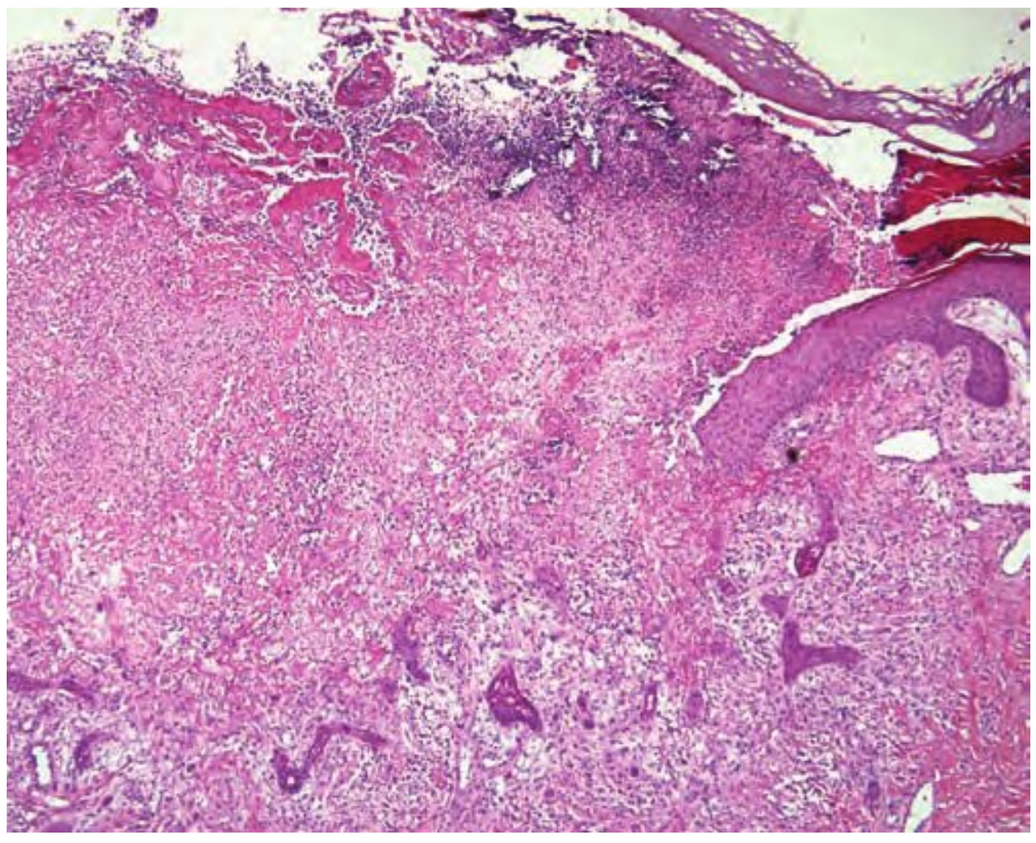


FIGURE 16-3. Pyoderma gangrenosum. The center of the lesion shows a neutrophilic infiltrate with leukocytoclasia and dermolysis. This biopsy is from a patient with Crohn's disease, as evidenced by the presence of multinucleated histiocytes within the infiltrate.

hepatobiliary disease. In the superficial granulomatous variant, florid pseudoepitheliomatous hyperplasia may be observed along with the intraepithelial and superficial dermal suppurative granulomatous inflammation with admixed plasma cells and eosinophils (77). Cases of pyoderma gangrenosum associated with Crohn's disease may have areas of granulomatous inflammation (88).

Differential Diagnosis. Tissue neutrophilia with epithelial undermining and ulceration in the absence of leukocytoclastic vasculitis, fungal, bacterial, or mycobacterial organisms (which, if indicated, may be demonstrable with culture and special stains, e.g., periodic acid–Schiff, Gomori methanamine

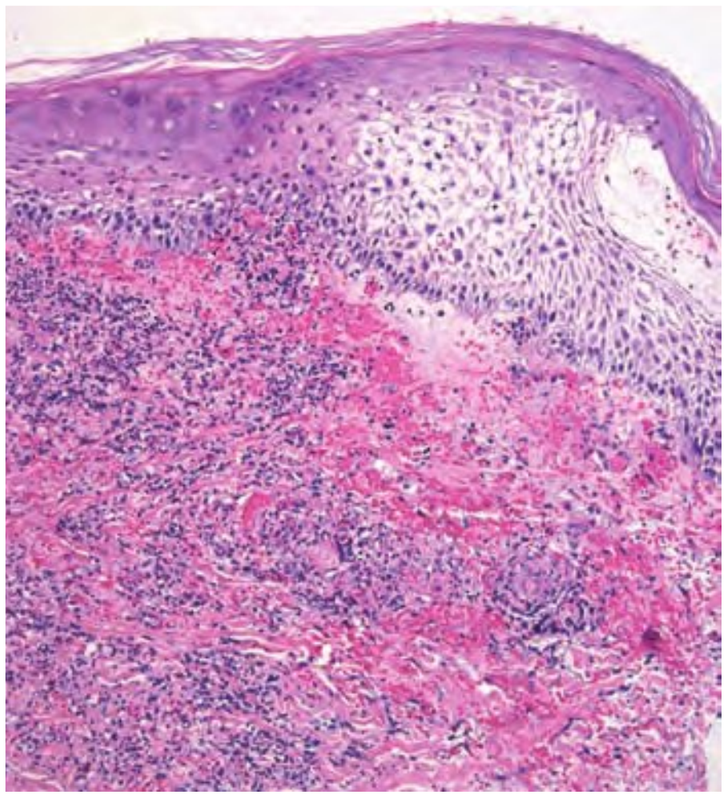


FIGURE 16-4. Pyoderma gangrenosum. The undermined epidermis often shows spongiosis or pustulation.

silver, Brown and Brenn, Gram's, Ziehl-Neelson, and auramine-rhodamine preparations), strongly implicates pyoderma gangrenosum when seen in the appropriate clinical setting (72). An incipient lesion of pyoderma gangrenosum, however, may be indistinguishable from Sweet's syndrome, although the latter is rarely folliculocentric and does not show lysis of dermal collagen or vessel wall necrosis in areas of maximum dermal neutrophilia. In addition, clinical features usually make the distinction possible. Because of prominent follicular involvement, the differential diagnosis should also include other causes of necrotizing pustular follicular reactions with an accompanying vasculopathy, such as mixed cryoglobulinemia, Behçet's disease, rheumatoid vasculitis, herpetic folliculitis, acute pustular bacterid, and pustular drug reactions (89). These other conditions frequently have a necrotizing mononuclear cell or neutrophil predominant vasculitis in contrast to the nonnecrotizing vascular reaction of pyoderma gangrenosum. Other causes of a Sweet's-like vascular reaction include the bowel arthritis dermatosis syndrome, Behçet's disease, idiopathic pustular vasculitis, rheumatoid arthritis, acute pustular bacterid, and Sweet's syndrome (84,85).

Pathogenesis. Direct immunofluorescence testing supports a vasculopathy by virtue of perivascular deposition of immunoreactants, mainly immunoglobulin (Ig) M and C3 (90), in more than half of patients. This change occurs in nonspecific vessel injury and does not support a humoral-based pathogenesis. Defective cell-mediated immunity without humoral abnormalities has been implicated in some patients (91). Immunoelectrophoresis has revealed a monoclonal gammopathy, most commonly of the IgA type, in 10% of patients with pyoderma gangrenosum (92). A recent polymerase chain reaction analysis demonstrated that patients with pyoderma gangrenosum have clonal expansions of T cells in the peripheral blood and skin. These clonal expansions are shared between both sites, suggesting that T cells are trafficking to the skin under the influence of an antigenic stimulus (93). In further support of a potential antigenic stimulus, patients with pyoderma gangrenosum have elevated levels of interleukin-8 (IL-8), a powerful neutrophilic chemoattractant, in both the serum and fibroblasts of affected skin (94).

Bowel-Associated Dermatosis–Arthritis Syndrome (Bowel Bypass Syndrome)

After intestinal bypass surgery for morbid obesity or after extensive small bowel resection, some patients develop an intermittent eruption, mainly on the extremities, comprising purpuric macules and papules that may evolve into necrotizing vesiculopustular lesions. Polyarthritis, malaise, and fever are often associated with and may precede the eruption (95). Although originally called the bowel bypass syndrome, it now bears the more appropriate appellation *bowel arthritis dermatosis syndrome* because a similar picture may develop in patients with diverticulosis, peptic ulcer disease, and idiopathic inflammatory bowel disease (96–99).

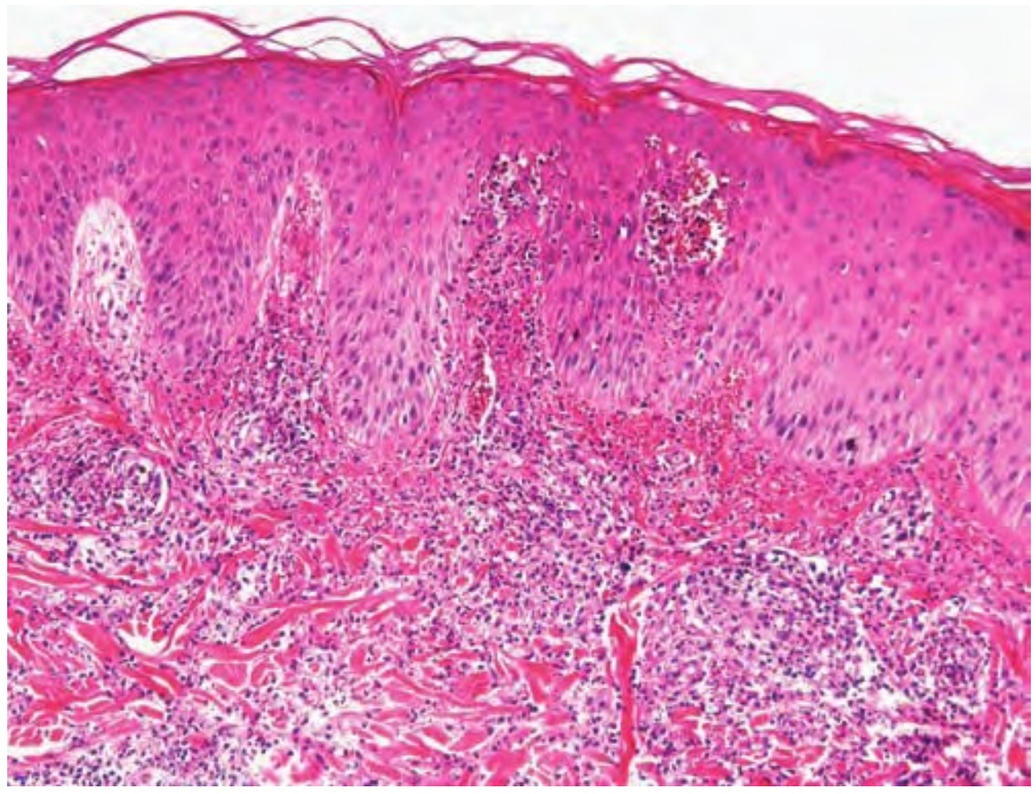


FIGURE 16-5. Bowel arthritis dermatosis syndrome. Pustular vasculitis characterized by dermal papillae microabscess formation along with a leukocytoclastic vasculitis.

Histopathology. Characteristically, there is a perivascular lymphocytic infiltrate with a peripheral cuff of disintegrating neutrophils, erythrocyte extravasation, and absent or minimal fibrin deposition consistent with a Sweet's-like vascular reaction; a leukocytoclastic vasculitis occurs less often (99). Papillary dermal edema may be striking and may lead to subepidermal vesiculation (95). Epidermal pustulation, variable epithelial necrosis, and massive superficial dermal neutrophilia complete the picture (Fig. 16-5) and define pustular vasculitis (95,100).

Pathogenesis. Circulating immune complexes, including those containing cryoproteins, are demonstrable in most patients. The antigenic trigger may be peptidoglycans from intestinal bacteria (96), which are structurally and antigenically similar to the peptidoglycan of *Streptococcus*. The latter exacerbate symptoms in patients with this condition and produce a similar syndrome in animals (96). Direct immunofluorescence testing has shown linear and granular deposits of immunoglobulins and complement along the dermal–epidermal junction and within vessels (96). One study showed *Escherichia coli* antigens in a granular array along the dermal–epidermal junction. Via an indirect methodology, a pemphigus-like pattern of intercellular staining has been reported (96), the significance of which is unclear.

Differential Diagnosis. The differential diagnosis of bowel arthritis dermatosis syndrome includes Sweet's syndrome, incipient pyoderma gangrenosum, and certain of the pustular vasculitides, such as acute pustular bacterid related to antecedent streptococcal infection, such as Henoch-Schönlein purpura (100), septic vasculitis due to *Meningococcus* and *Gonococcus*, Behçet's syndrome, leukocytoclastic vasculitis in patients with a pustular psoriasiform diathesis (101), idiopathic pustular vasculitis, and acute generalized exanthemous pustulosis (85,101). The distinction may be impossible in those conditions that manifest a

Sweet's-like vascular reaction—namely, Behçet's disease, Sweet's syndrome, pyoderma gangrenosum, acute pustular bacterid, and idiopathic pustular vasculitis (85).

SPECIFIC DISEASES

Aphthosis (Behçet's Disease)

Behçet's disease is a symptom complex of oral and genital ulceration and iritis that has a worldwide distribution but is most common in the Pacific rim and eastern Mediterranean (102,103). The presence of oral ulceration plus any two signs of genital ulceration, skin lesions (e.g., pustules or nodules), or eye lesions (e.g., uveitis or retinal vasculitis) is diagnostic.

The cutaneous lesions include erythema nodosum–like nodules, vesicles, pustules, pyoderma gangrenosum, Sweet's syndrome, a pustular reaction to needle trauma, superficial migratory thrombophlebitis, ulceration, infiltrative erythema, acral purpuric papulonodular lesions, and acneiform folliculitis (104,105).

The extracutaneous manifestations are categorized as oral and/or genital aphthae; vasculo-, ocular-, entero-, or neuro-Behçet's disease; renal disease; and arthritis. Oral apthosis recurring at least three times over a 12-month period is essential to the diagnosis (103). In vasculo-Behçet's disease, aneurysms and occlusive venous and arterial main vessel lesions occur. The ocular manifestations include uveitis, hypopyon iritis, optic neuritis, and choroiditis. Entero-Behçet's disease manifests as diarrhea, constipation, abdominal pain, vomiting, and melena. Neuro-Behçet's disease presents as brainstem dysfunction, meningoencephalitis, organic psychiatric symptoms, and mononeuritis multiplex (104). Asymptomatic microhematuria and/or proteinuria are among the renal manifestations. An oligoarthritis may involve the wrist, elbow, knee, or ankle joints. Morbidity and mortality in one large series of Turkish patients were greatest in young males; both the onset and the severity of ocular disease were greatest early in the course of disease, suggesting that the "disease burden" in Behçet's disease is greatest early and that it tends to "burn out" over time (106). However, neurologic and major vessel disease can occur at any time and can have late onset 5 to 10 years into the course of illness (106).

Histopathology. The cutaneous lesions can be categorized histopathologically into two main groups: vascular and extravascular with or without vasculopathy including acneiform.

The pathologic spectrum of the cutaneous vasculopathy encompasses a mononuclear cell vasculitis with variable mural and luminal fibrin deposition; a paucicellular thrombogenic vasculopathy (Fig. 16-6); and a neutrophilic vascular reaction involving capillaries and veins of all calibers. The mononuclear cell reaction may be frankly granulomatous or it may be lymphocytic predominant to define a lymphocytic vasculitis. The neutrophilic vascular reaction may resemble that of Sweet's syndrome (Fig. 16-7) (107) or a leukocytoclastic vasculitis. Diffuse extravascular mononuclear cell– and/or neutrophil–

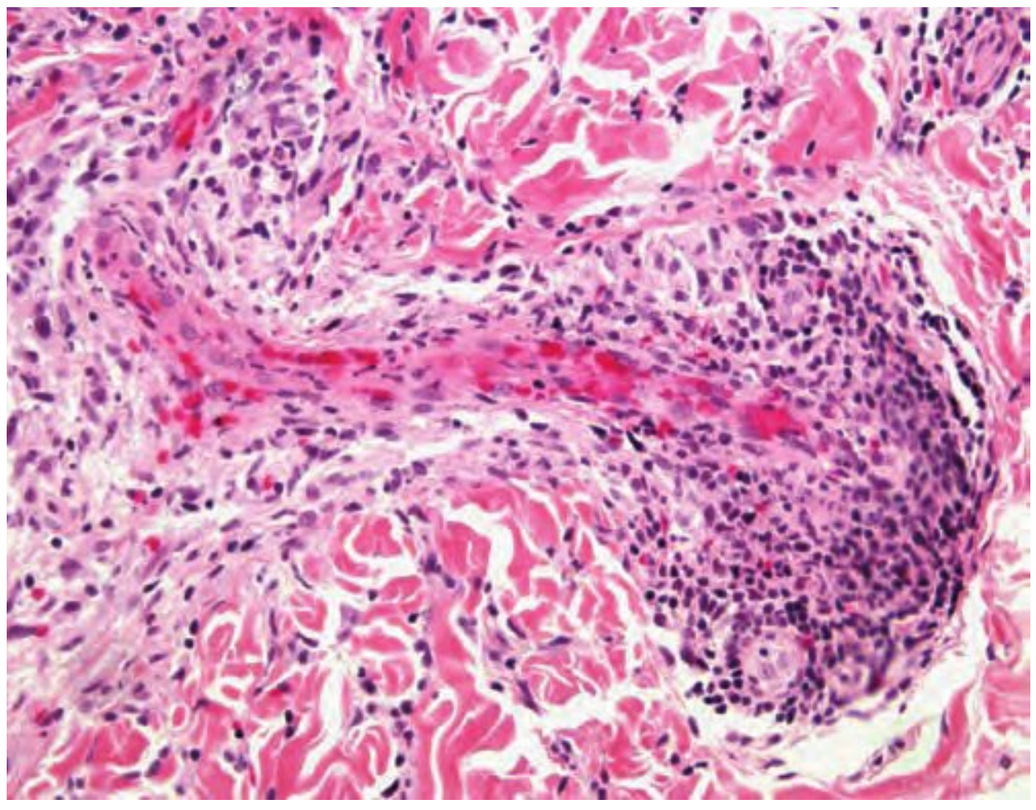


FIGURE 16-6. Behçet's disease. A characteristic vascular reaction pattern is a lymphocytic thrombogenic vasculopathy.

predominant inflammation of the dermis and/or panniculus may occur with or without the aforementioned vascular changes. The histiocytes infiltrating the panniculus may manifest phagocytosis of cellular debris. Suppurative or mixed suppurative and granulomatous folliculitis with or without vasculitis characterizes the acneiform lesions. Acral purpuric papulonodular lesions show a lymphocytic interface dermatitis with lymphocytic exocytosis, dyskeratosis, and a perivascular lymphocytic infiltrate, recapitulating the mucosal histopathology (105).

Extracutaneous lesions histologically mirror the skin changes. Oral aphthous ulcers demonstrate a central diffuse

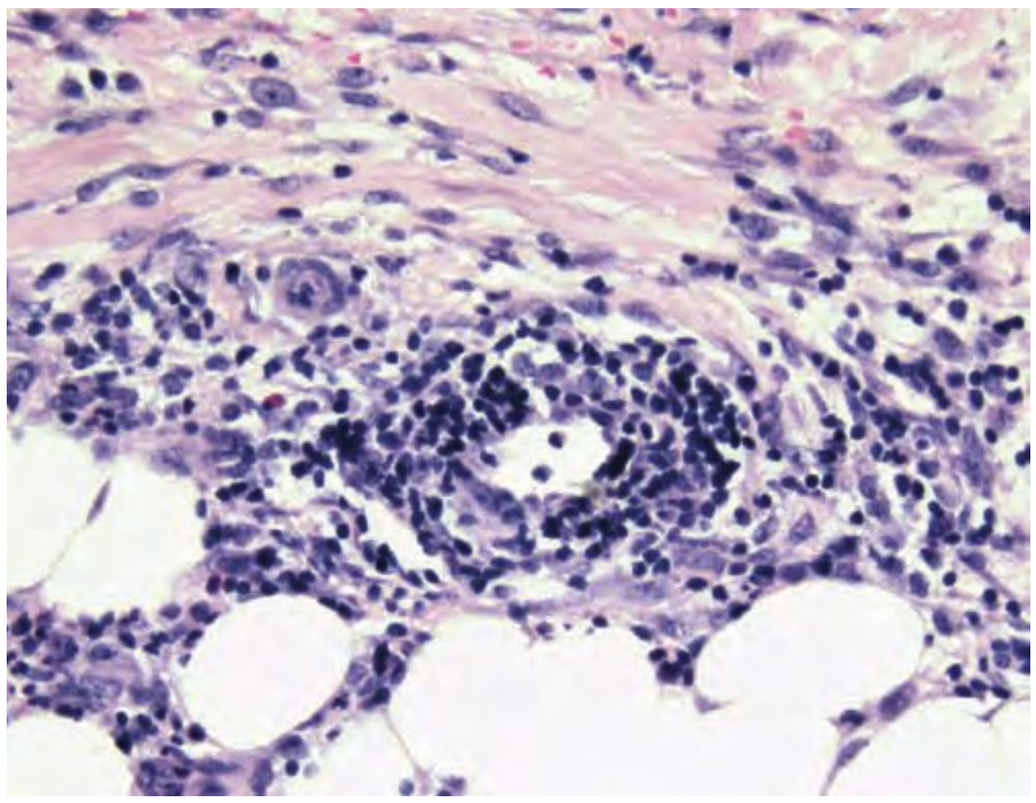


FIGURE 16-7. Behçet's disease. There is a Sweet's-like vascular reaction manifested by angiocentric mononuclear cell and neutrophilic infiltrates with erythrocyte extravasation and leukocytoclasia but without accompanying mural and intraluminal fibrin deposition.

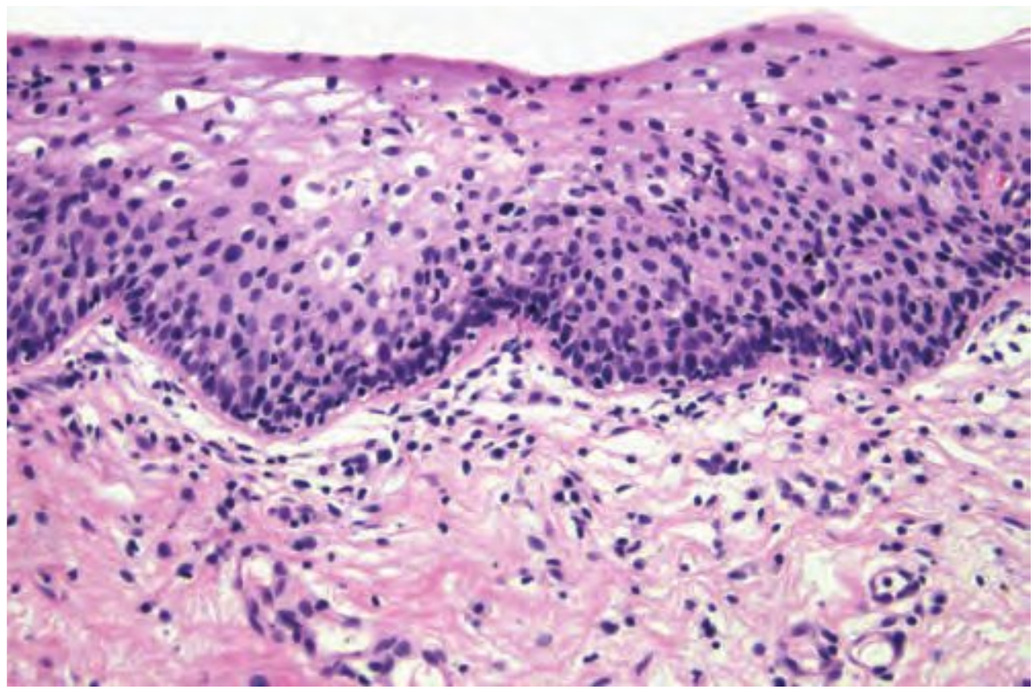


FIGURE 16-8. Behçet's disease. Although the center of an oral or vulvar aphthous ulcer is predominated by a neutrophilic response, biopsies of the periphery typically show a lymphocyte predominate infiltrate both in an extravascular and angiocentric disposition with variable lymphocytic exocytosis.

neutrophilic infiltrate with necrosis of the epithelium and connective tissue pathergy of the submucosa and peripherally a border showing dense lymphocytic infiltration with lymphocytic exocytosis and degenerative epithelial changes. Genital aphthae have the same appearance (Fig. 16-8) (104). The large-vessel arteriopathy represents an ischemic sequelum of a mononuclear cell vasculitis of the vasa vasorum (108), whereas venous thrombosis may be due in part to an underlying hypercoagulable state. A lymphocytic vascular reaction with or without mural and intraluminal fibrin deposition is the histopathology of neuro-, entero-, ocular-, and arthritic Behçet's disease, with other organ changes such as demyelination and intestinal ulceration reflecting resultant ischemia (104). The renal histopathology includes IgA nephropathy, focal and diffuse proliferative glomerulonephritis, and amyloidosis (109).

Differential Diagnosis. The lymphocytic vasculitis observed in Behçet's disease may mimic that seen in association with systemic lupus erythematosus, rheumatoid arthritis (110,111), Sjögren's syndrome, relapsing polychondritis, Degos' disease, and paraneoplastic vasculitis in the setting of lymphoproliferative disease. Granulomatous vasculitis may also be observed in Wegener's granulomatosis, allergic granulomatosis of Churg-Strauss, Crohn's disease, sarcoidosis, acquired hypogammaglobulinemia, a postherpetic eruption (112), paraneoplastic syndrome (related to underlying hematologic malignancy), rheumatoid arthritis, hypersensitivity reactions to certain infections including syphilis and tuberculosis (113), scleroderma, and late-stage lesions of microscopic polyarteritis nodosa (85,100,111). Other causes of a Sweet's-like vasculopathy include Sweet's syndrome, bowel arthritis dermatosis, pyoderma gangrenosum, and idiopathic pustular vasculitis (84). Conditions that combine a vasculitis with a folliculitis include pyoderma gangrenosum, mixed cryoglobulinemia, rheumatoid vasculitis, and bacterid (89).

Pathogenesis. An immunogenetic basis is likely in view of the association with certain HLA types, namely HLA-B5, HLA-B12, HLA-B27, and HLA-B51 (114). A recurring association in patients of Japanese, Turkish, Korean, and Iranian ethnicities is with HLA-B51 (115,116), genetic polymorphisms in the promoter region of tumor necrosis factor-α (TNFα) (117–120), and microsatellite instabilities between these two genes (116,121). Polymorphisms of other cytokines have been identified, including IL-1 (122) and IL-18 (123). Behçet's disease patients have elevated levels of Th1 cytokines IL-12, IFNγ, and TNFα (124); increased Th1-associated chemokine receptors CCR5 and CXCR3 (125), and a lower percentage of plasmacytoid dendritic cells in peripheral blood (126), supporting the proposed Th1-mediated pathogenesis of the disease. Patients have shown a heightened immune response to antigenic components of certain streptococcal species (127,128), *Mycobacterium tuberculosis* (129), herpes simplex (130,131), Epstein-Barr virus, and human immunodeficiency virus (HIV) (132). Underlying abnormalities in T-lymphocyte function may be integral to an aberrant response related to the synthesis by microorganisms and mammalian tissue of a family of polypeptides termed heat shock proteins (HSPs) (133,134) produced by cells exposed to stresses such as increased temperature. Sensitized T cells and T-cell clones specific to the 65-kD mycobacterial HSP have been reported in rheumatoid arthritis (135). T lymphocytes from patients with Behçet's disease in one study exhibit a greater stimulation by this HSP compared to normal controls or patients with unrelated disease (136). The γδ T-cell subset has been shown to be the principal populace that responds to the mycobacterial 65-kD HSP, an observation that may account for the increase in circulating γδ T cells in patients with antecedent streptococcal or mycobacterial infections (137) and in those with active Behçet's disease, in whom an exaggerated response to microbial products in mucosal ulcers is postulated (138). The lymphocytes themselves show resistance to Fas-mediated apoptosis, a finding that may promote lymphocyte-mediated tissue destruction in these patients (139).

Tissue neutrophilia may relate to the presence of HLA-B51, which has been associated with neutrophil hyperreactivity (140). Neutrophil functions are also increased in Behçet's disease (141), which may be due to alteration in expression of Toll-like receptors, regulators of innate and adaptive immunity, on both granulocytes and monocytes (142).

Vascular thrombosis has been attributed to antibody-mediated endothelial injury (143), protein C or S deficiency (144), factor XII deficiency, inhibition of plasminogen activator, and circulating lupus anticoagulant (145–147). A prothrombin gene mutation has recently been described (148). Further evidence of a genetic predisposition to thrombosis is the linkage of HLA-B51 expression and the absence of HLA-B35 as risk factors for venous thrombosis in Turkish patients (115); there is also a statistical linkage between superficial and deep venous thrombosis (149). Elevated serum levels of matrix metalloproteinases MMP-2 and MMP-9 are associated with vasculo-Behçet's disease, particularly thrombotic and aneurysmatic involvement, respectively (150).

The role of nitric oxide (NO) is unclear. Some researchers have shown that patients with active Behçet's disease have significantly higher serum levels of NO than patients with recurrent aphthous stomatitis (151), patients with inactive Behçet's disease, and healthy controls (152), whereas others maintain that there is no difference in NO levels among these groups (153,154), and still others contend that levels of NO are lower in Behçet's patients (155,156). Specific genetic polymorphisms have been identified in the manganese superoxide dismutase gene in Japanese Behçet's patients (157) and the Glu298Asp polymorphism in the endothelial nitric oxide synthase (eNOS) gene in Turkish (158,159), Italian (160), and Korean (161) Behçet's patients. One study did not identify the eNOS polymorphism in Turkish Behçet's patients (162). Others propose that the significantly higher levels of IL-2, IL-6, TNFα, and NO are related to the pathogenesis of Behçet's disease (163).

INFLAMMATORY BOWEL DISEASE

Crohn's Disease (Regional Enteritis)

First described in 1932, Crohn's disease is an idiopathic disorder of the gastrointestinal tract. The diagnosis is based on a constellation of radiologic, pathologic, and endoscopic data, namely deep mucosal fissures, fistula formation, transmural inflammation, discontinuous colonic and small bowel disease with preferential right-sided involvement, and sarcoidal granulomatous and fibrosing inflammation of the mucosa and submucosa (164). Extraintestinal manifestations include fever, anemia, lupus anticoagulant, ophthalmic disease such as uveitis and episcleritis, monoarticular large-joint arthritis, polyarthritis, spondylitis, amyloidosis (165), renal lithiasis with resultant hydronephrosis (166), cerebral vascular occlusions, and a spectrum of cutaneous eruptions.

Skin manifestations, principally restricted to patients with colonic disease, occur in 14% to 44% of patients with Crohn's disease, depending on whether perianal disease is considered a cutaneous manifestation (164). Ulcers, fissures, sinus tracts, abscesses, and vegetant plaques may extend in continuity from sites of intraabdominal involvement to the perineum, buttocks, or abdominal wall, ostomy sites, or incisional scars. When sterile granulomatous skin lesions arise at sites discontinuous from the gastrointestinal tract, the appellation "metastatic Crohn's disease" is applied (167). Clinically, metastatic Crohn's disease presents as solitary or multiple nodules, plaques, ulcers, lichenoid lesions, or violaceous perifollicular papules involving extremities, intertriginous areas, abdominal skin folds, or genitalia (168). Erythema nodosum (169)—the most common cutaneous manifestation of Crohn's disease (164)—and pyoderma gangrenosum develop in 15% and 1.5% of patients, respectively. Palmar erythema, a pustular response to trauma (169), erythema multiforme usually with mucosal involvement (169,170), epidermolysis bullosa acquisita, hidradenitis suppurative, rosacea, secondary cutaneous oxalosis, malabsorption-related acrodermatitis enteropathica (169), vasculitic lesions including benign cutaneous polyarteritis nodosa, and digitate hyperkeratosis reminiscent of punctate porokeratosis are described (171). Cutaneous necrosis as a complication of circulating lupus anticoagulant may also occur.

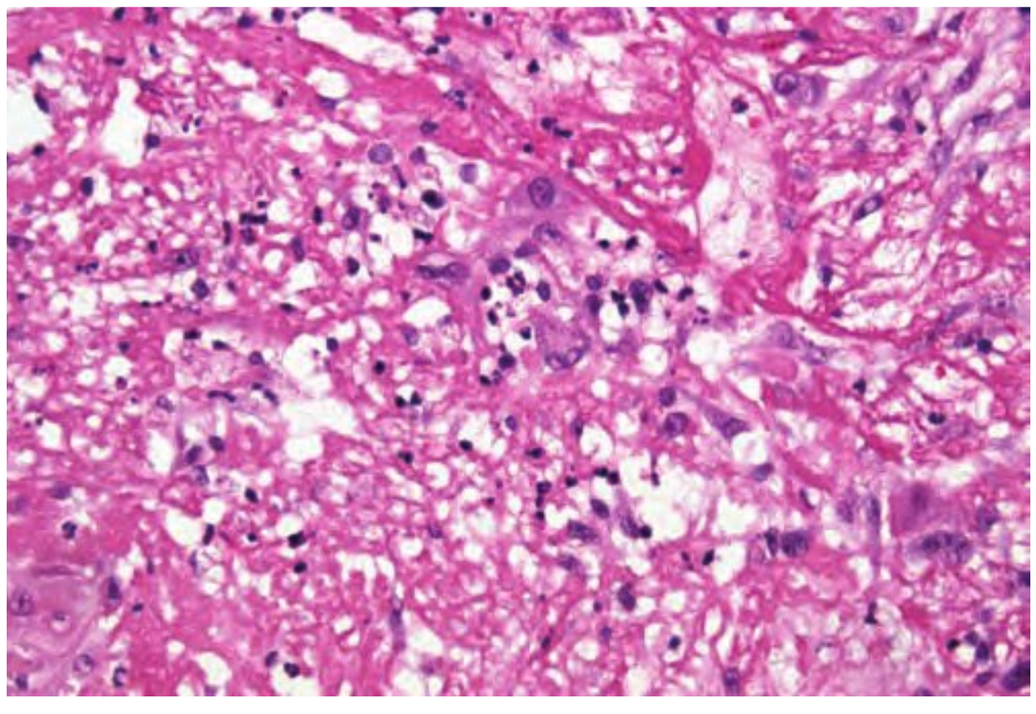


FIGURE 16-9. Crohn's disease: pyoderma gangrenosum. This biopsy shows suppurative granulomatous inflammation with a binucleate histiocyte in the center of the field and a mononuclear cell–predominant vasculopathic reaction patterns; biopsies of metastatic Crohn's disease may show a necrotizing leukocytoclastic and granulomatous vasculitis indistinguishable from cutaneous Wegener's granulomatosis and reminiscent of pyostomatitis vegetans, a prototypic oral lesion of Crohn's disease can be seen.

Oral lesions, manifesting as "cobblestone" lesions, aphthous ulcers, lip swelling, and pyostomatitis vegetans, occur in roughly 5% of patients with Crohn's disease (169).

Histopathology. The perianal mucosal lesions and oral lesions of pyostomatitis vegetans show pseudoepitheliomatous hyperplasia in conjunction with suppurative granulomatous inflammation within the epithelium and subjacent corium (Fig. 16-9). The most frequent histologic patterns seen in metastatic Crohn's disease are nonsuppurative granulomata, which may assume a sarcoidal or diffuse pattern, the latter often in close apposition to the epidermis in the fashion of a lichenoid and granulomatous dermatitis (172) and granulomatous vasculitis. Histologic examination of the erythema nodosum–like lesion may show one of four patterns: (a) septal panniculitis consistent with classic erythema nodosum, (b) dermal-based sarcoidal granulomata (173), (c) a dermal-based small-vessel granulomatous (174) or leukocytoclastic vasculitis, or (d) benign cutaneous polyarteritis nodosa. The latter shows mural infiltration by histiocytes and neutrophils with variable mural fibrinoid necrosis confined to the muscular arteries of the subcutaneous fat (see Fig. 16-12); occasional vessel involvement of the peripheral nerves and skeletal muscle of the affected extremity produce mononeuritis and myositis, respectively (132). A pauci-inflammatory thrombogenic vasculopathy characterizes the cutaneous infarcts associated with lupus anticoagulant. Necrobiosis lipoidica–like or granuloma annulare–like foci (176) may also be seen defined by areas of collagen necrobiosis with concomitant mucin or fibrin deposition and a palisading histiocytic infiltrate. Unlike idiopathic granuloma annulare or necrobiosis lipoidica, there usually

is an accompanying leukocytoclastic vasculitis, thrombogenic or granulomatous vasculopathy, and foci of extravascular neutrophilia (176). Dense neutrophilic infiltration of the dermis accompanied by scattered giant cells has been reported (88,177). We have also seen this pattern of suppurative granulomatous inflammation in concert with the aforementioned necrobiosis lipoidica or granuloma annulare tissue reaction. Cases of lip swelling show nonnecrotizing granulomatous inflammation (169). The histology of pyoderma gangrenosum has been previously discussed. A suppurative panniculitis may also be seen (178).

Differential Diagnosis. The differential diagnosis of sarcoidal granulomatous inflammation in the skin includes sarcoidosis, id reactions to antecedent streptococcal or mycobacterial infections (113), acquired hypogammaglobulinemia, rosacea, paraneoplastic histiocytopathies such as those associated with low-grade lymphoproliferative disease, rheumatoid arthritis, and granulomatous inflammatory reactions to ingested or inoculated inorganic compounds such as silica, zirconium, and beryllium. The lesions resembling benign cutaneous polyarteritis nodosa differ from systemic polyarteritis nodosa by virtue of confinement of the vasculitis to the subcutaneous fat without dermal involvement (175). The changes of pyostomatitis vegetans also should raise the possibility of Wegener's granulomatosis, mycobacterial infection, blastomycosis, and histoplasmosis. The histopathology of the lip swelling may mimic that of Melkersson-Rosenthal syndrome (169). Lichenoid and granulomatous dermatitis calls into consideration the idiopathic lichenoid disorders such as lichen nitidus, certain microbial id reaction states, and also drug reactions such as those to antibiotic, antihypertensive, lipid-lowering, and antihistaminic preparations (172).

Pathogenesis. In the development of Crohn's disease, there is a complex interplay between genetic, immunologic, and environmental factors, which is not completely understood. At least 10 genes have been proposed to play a role; the best studied is *CARD15*/*NOD2*, a gene involved in bacterial recognition by cells involved in innate immunity (179). Three *CARD15*/*NOD2* mutations are associated with Crohn's disease susceptibility, with approximately a 2- to 4-fold risk in heterozygotes and 17- to 40-fold risk in homozygotes (179–181). This dose effect suggests a loss-of-function model and is supported by *in vitro* studies. Speculations claim that the loss of function in innate immunity allows bacterial proliferation and a potential cytokine imbalance allows an inflammatory response from the adaptive immunity, and ultimately causes tissue damage. *In vivo* studies have failed to confirm these speculations and have even generated other hypotheses, including a gain-of-function model (179). Even less is understood about the pathogenesis of skin lesions in Crohn's disease. There is a common morphology shared by the intestinal and cutaneous disease of sarcoidal granulomatous inflammation, suggesting a pathogenetic role for cell-mediated immunity. Circulating immune complexes have been detected in some patients (169) and may play a role in the generation of necrotizing vasculitis; a subset of patients with Crohn's disease has antineutrophil cytoplasmic antibodies. Based on the use of *in situ* polymerase chain reaction methods with a probe seeking bacterial 16rsRNA common to a variety of microbial pathogens implicated in Crohn's disease, bacterial RNA has been shown in the vasculature of the gut in active but not in quiescent cases; the skin lesions are uniformly negative. It would seem, therefore, that the skin manifestations of Crohn's disease are not a bacterial id reaction but rather reflect an autoimmune phenomenon, perhaps involving cross-reacting antibodies between gut- and skin-based antigens (178).

Ulcerative Colitis

Ulcerative colitis is an idiopathic inflammatory bowel disease involving the large intestine, with rectal involvement being almost ubiquitous. It is characterized by glandular destruction and inflammation of variable intensity. Glandular dysplasia eventuating in carcinoma complicates the clinical course, particularly in patients with disease of pediatric onset. Extramucosal associations include chronic active hepatitis, primary sclerosing cholangitis, pulmonary vasculitis (182), chronic fibrosing alveolitis, limited Wegener's granulomatosis of the lung (183), pulmonary apical fibrosis, large-joint monoarticular arthritis, polyarthritis, and ankylosing spondylitis. Cutaneous manifestations may occur, the spectrum of which encompasses vasculitis, erythema nodosum, pyoderma gangrenosum, superficial migratory thrombophlebitis, and cutaneous thrombosis with resultant gangrene (184); the two last-named manifestations are possibly related to underlying lupus anticoagulant or cryofibrinogenemia (185). Pyoderma gangrenosum is more frequently associated with ulcerative colitis than with Crohn's disease and erythema nodosum more frequently with Crohn's disease (Fig 16-10). The

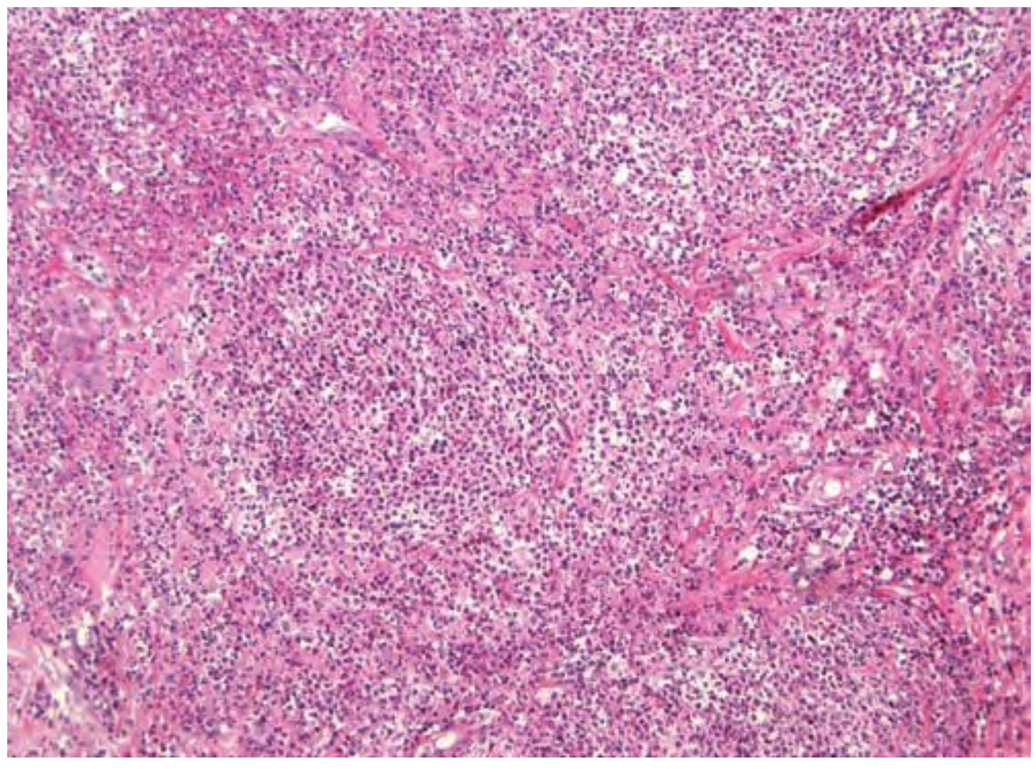


FIGURE 16-10. Ulcerative colitis: pyoderma gangrenosum. There is pronounced neutrophilic dermolysis.

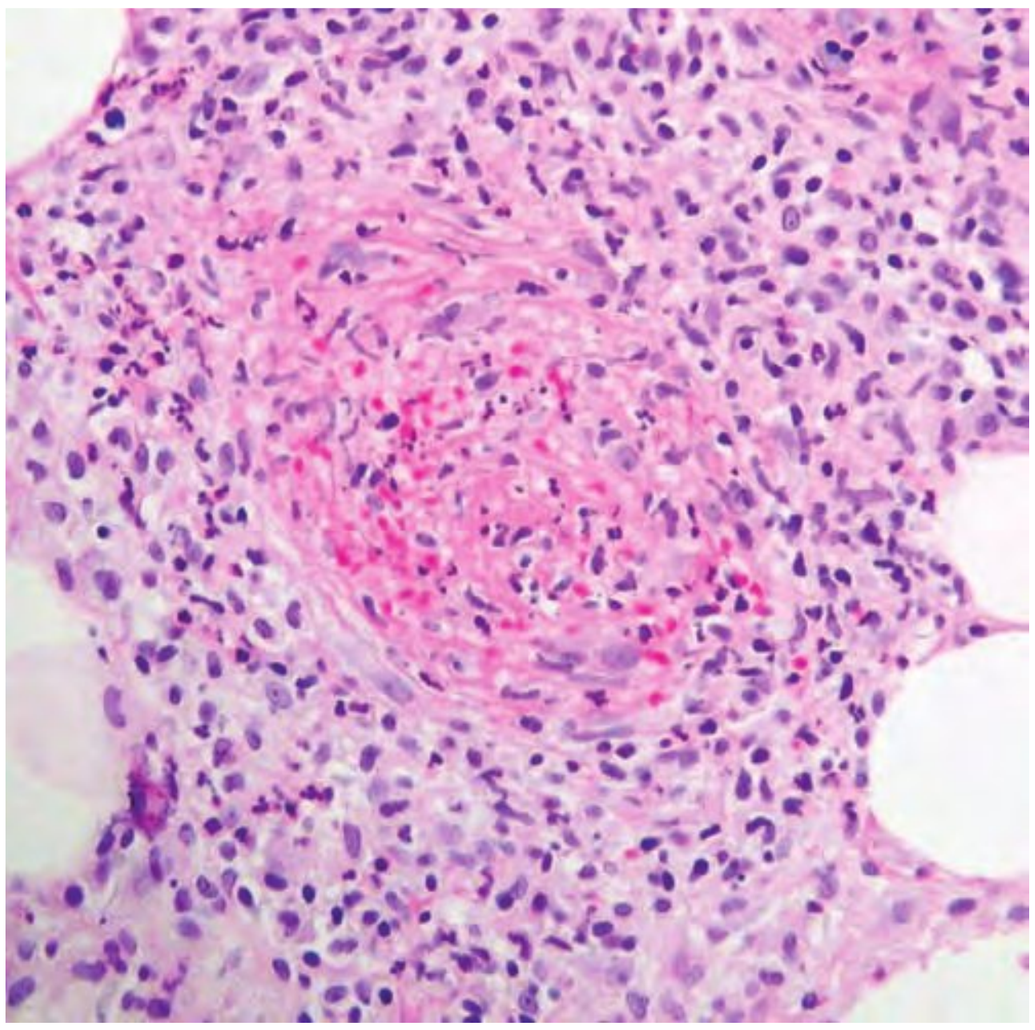


FIGURE 16-11. Polyarteritis nodosa in a patient with ulcerative colitis. Within the subcutaneous fat, the wall of a subcutaneous artery demonstrates striking fibrinoid necrosis and is surrounded and permeated by disintegrating neutrophilic infiltrates unaccompanied by small-vessel involvement. The findings are typical for benign cutaneous polyarteritis nodosa.

lesions of pyoderma gangrenosum also include an unusual disseminated vesiculopustular variant (186).

Histopathology. The histology of pyoderma gangrenosum and erythema nodosum is discussed elsewhere. Cutaneous vasculitis in association with ulcerative colitis includes IgA-associated leukocytoclastic vasculitis (100,187) and benign cutaneous polyarteritis nodosa (Fig. 16-11). A pauci-inflammatory thrombogenic vasculopathy involving vessels throughout the dermis and subcutis characterizes the histomorphology of associated lupus anticoagulant and/or cryofibrinogenemia (185).

Celiac Disease

Celiac disease is a malabsorption syndrome with a prevalence of up to 1% of the adult population of Western countries (188) and is associated with HLA-DQ2 (DQA1*/DQB1*2) in greater than 90% of celiac disease patients (189). It reflects small-intestinal mucosal injury caused by a humoral immune response to ingested gluten and is associated with dermatitis herpetiformis in roughly 25% of cases (188,190,191). A leukocytoclastic vasculitis has also been described in patients with celiac disease (192). A comprehensive review article by Abenavoli et al. illustrates the occurrences of other skin manifestations of celiac disease, including chronic urticaria, hereditary angioneurotic edema, erythema nodosum, necrolytic migratory erythema, psoriasis, and dermatomyositis, among others (189). The presence of IgA or IgG anti–tissue transglutaminase and antiendomysial antibodies is seen in 80% to 90% of patients with active gut mucosal inflammation and has a high specificity for the diagnosis (193). A significant concern with serologic confirmation of the diagnosis is the presence in a minority of celiac disease patients of a selective IgA deficiency; in such patients, however, IgG antitransglutaminase and antiendomysial antibodies are still positive. Underlying mixed cryoglobulinemia may occur, as may mesangial nephritis, the latter a sequela of circulating immune complexes (191,194). Antibodies to transglutaminase may be of pathogenetic significance. Immunofluorescence studies have demonstrated IgA and epidermal transglutaminase (TG3) deposition in the papillary dermis and blood vessel walls of patients with celiac disease. Those patients with concomitant dermatitis herpetiformis showed a stronger intensity of both IgA and TG3 deposition than those without skin lesions (195).

HEPATOBILIARY DISEASE

Sclerosing Cholangitis and Primary Biliary Cirrhosis

Pyoderma gangrenosum, particularly a disseminated superficial vesiculopustular variant (196), and dermatitis herpetiformis have been described in association with sclerosing cholangitis (176). In addition, diffuse superficial pyoderma gangrenosum has been described in patients with ulcerative colitis, an associated finding in 70% of patients with sclerosing cholangitis. Isolated case reports of elastosis perforans serpiginosa with coexisting Down's syndrome (197) and disseminated warts along with primary combined immune deficiency and progressive multifocal leukoencephalopathy have been described in association with sclerosing cholangitis. Lichen planus of the nail (198) and disseminated Langerhans cell histiocytosis (199) have been reported in patients with sclerosing cholangitis. Cutaneous manifestations seen with primary biliary cirrhosis include lichen planus (200), CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), sarcoidal granulomata (201), and vitiligo (202). There are reports that describe cutaneous amyloidosis (203), pustular vasculitis (204), and cutaneous fungal infections (205) in patients with primary biliary cirrhosis.

Histopathology. Vesiculopustular pyoderma gangrenosum is characterized by a necrolytic subepithelial blister in which massive papillary edema is accompanied by sheets of neutrophils within the blister cavity and prominent leukocytoclasia often centered around follicles. Peripheral to the areas of neutrophilia, angiocentric mononuclear-cell infiltrates with minimal accompanying vascular injury are observed (Fig. 16-12).

Pathogenesis. Although of unclear pathogenetic significance, antineutrophil cytoplasmic antibodies (ANCAs) in a perinuclear (p) pattern have been detected in 72% of patients with primary sclerosing cholangitis and ulcerative colitis (206,207). An atypical pANCA, termed xANCA, with a specificity for a

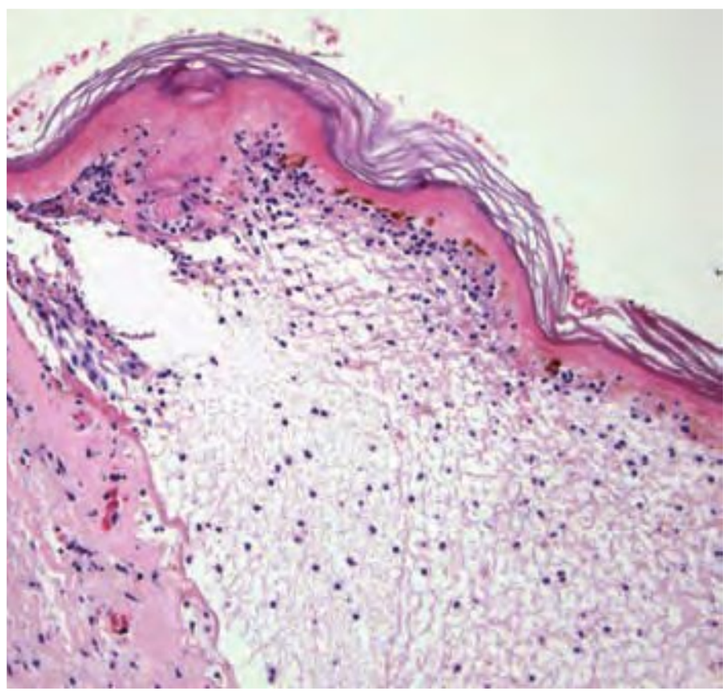


FIGURE 16-12. Vesicular pustular pyoderma gangrenosum. A biopsy of the lesion demonstrated marked subepidermal edema and a subjacent intense neutrophilic and lymphocytic infiltrate with tissue pathergy confined to the superficial dermis.

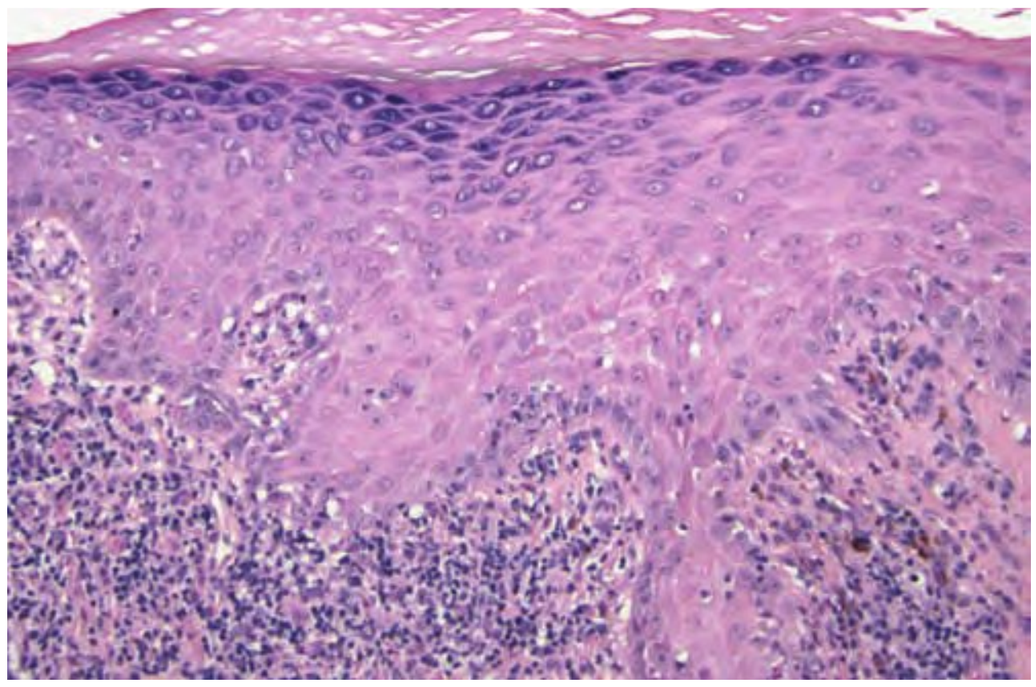


FIGURE 16-13. Lichenoid tissue reaction in the setting of hepatitis C infection. This patient with hepatitis C developed an eruption that was clinically compatible with lichen planus. The histomorphology confirmed the diagnosis by virtue of a dense, bandlike lymphocytic infiltrate in apposition to an epidermis showing colloid body formation.

50-kD myeloid envelope protein is seen in patients with inflammatory bowel disease, autoimmune hepatitis, and primary sclerosing cholangitis (208,209). ANCAs have also been described in Wegener's granulomatosis, microscopic polyarteritis nodosa, and idiopathic crescentic glomerulonephritis. Patients with primary sclerosing cholangitis and concomitant ulcerative colitis (210) have circulating antibodies to colonic epithelial cells (211). An immunogenic basis has also been proposed for primary sclerosing cholangitis in view of the association with HLA-B8 and/or HLA-DR3 antigens.

Hepatitis

Hepatitis can be broadly categorized into infectious and noninfectious causes. Most of the former are viral and are mediated by hepatitis A, B, C, and delta agent, cytomegalovirus, Epstein-Barr virus, and, rarely, varicella, measles, and herpes simplex virus. Chronic active hepatitis of autoimmune etiology is a necroinflammatory disorder of unknown etiology with a predilection for young women (212). Both the clinical presentation and liver chemistry profile may resemble those of infectious hepatitis. Hepatitis C antibodies have been demonstrated in patients with classic autoimmune hepatitis, a finding reputed to represent a nonspecific response that disappears during remission. Conversely, an autoantibody profile mimicking chronic active hepatitis may be seen in hepatitis C (212). Other laboratory abnormalities include anemia, hypergammaglobulinemia, positive lupus erythematosus cell preparations, and positive antibodies to non–organ-specific antibodies, such as antinuclear antibodies, ANCAs, and antibodies to smooth muscle and liver/kidney microsomes (212).

The principal cutaneous manifestations of viral and autoimmune hepatitis are lichen planus, leukocytoclastic vasculitis (213), porphyria cutanea tarda (214), erythema multiforme (215), pyoderma gangrenosum (216), and Gianotti-Crosti syndrome (217). Lichen planus has been reported in patients with hepatitis C, chronic active hepatitis of unknown etiology, and primary biliary cirrhosis (Fig. 16-13) (218). The clinical spectrum of skin lesions in patients infected with hepatitis C comprises photodistributed eruptions, palpable purpura, folliculitis, chilblains-like acral lesions, ulcers, nodules, and urticaria (219). The vasculitis may be on the basis of mixed cryoglobulinemia in the setting of hepatitis C infection (213). Porphyria and erythema multiforme–like eruptions also occur in association with hepatitis C.

Papular acrodermatitis (217) (Gianotti-Crosti syndrome) reflects a primary infection with hepatitis B virus, acquired through the skin or mucous membranes, and comprises a nonpruritic, erythematous, papular eruption on the face, extremities, and buttocks. The eruption usually lasts about 3 weeks and is associated with lymphadenopathy and an acute, usually anicteric hepatitis of at least 2 months' duration that only rarely progresses to chronic liver disease. Hepatitis B surface antigenemia is present (217). A similar eruption may be produced by several other viruses, such as Epstein-Barr virus, coxsackie B virus, and cytomegalovirus (220), in which case there is often no hepatitis or lymphadenopathy. Gianotti-Crosti syndrome has also been reported in children after immunizations with inactivated vaccines for hepatitis A (221), hepatitis B (222), and Japanese encephalitis (223), diphtheria/tetanus/acellular pertussis, and *Haemophilus influenzae* B (224) and after live attenuated oral polio (225) and measles/mumps/rubella vaccines (226). It was reported after inactivated influenza vaccine in an adult (227).

Histopathology. The histologic appearance of the papules in Gianotti-Crosti syndrome includes a moderately dense infiltrate of lymphocytes and histiocytes in the upper and middermis that are found mainly around capillaries that exhibit endothelial swelling, accompanied by erythrocyte extravasation (220). Focal spongiosis, parakeratosis with mild acanthosis, and a focal

interface dermatitis complete the picture (220). The histopathology of lichenoid tissue reactions (Fig. 16-13), pyoderma gangrenosum, erythema multiforme, leukocytoclastic vasculitis, and porphyria cutanea tarda is described in other sections of this book. In our hands, the skin lesions of hepatitis C can be classified by the dominant reaction pattern, the most common being vasculopathies of neutrophilic and lymphocytic vasculitis and pauci-inflammatory subtypes; palisading granulomatous inflammation; sterile neutrophilic folliculitis; neutrophilic lobular panniculitis; benign cutaneous polyarteritis nodosa; neutrophilic dermatoses including neutrophilic urticaria and pyoderma gangrenosum; and interface dermatitis (219). Some patients develop a low-grade lymphoproliferative disease of B-cell lineage cognate to marginal zone lymphoma. Endothelial cell swelling is common. Mixed cryoglobulinemia differs from conventional leukocytoclastic vasculitis by the presence of intraluminal eosinophilic deposits that are strongly PAS positive.

Pathogenesis. The sera of all patients with hepatitis B–induced papular acrodermatitis exhibit hepatitis B surface antigens by radioimmunoassay. Antibodies to hepatitis B surface antigens are not detected during the eruptive phase but only 6 to 12 months after the eruption; patients with antibodies become hepatitis B surface antigen–negative, suggesting a role for humoral immunity in their recovery. As regards the skin lesions of hepatitis C infection, reverse transcriptase *in situ* polymerase chain reaction studies show expression of viral DNA in endothelia in some cases (219).

Acrokeratosis Neoplastica (Bazex's Syndrome)

First described in 1965 (228), this rare but clinically distinctive dermatosis was originally associated with either a primary malignant neoplasm of the upper aerodigestive tract—most commonly squamous cell carcinoma—or metastatic cancer to the lymph nodes of the neck. Other associated malignancies have since been described, including poorly differentiated carcinoma, adenocarcinoma, and small-cell carcinoma among others. Greater than 90% of the patients are male, and most are older than 40 years of age (229). Thickening of the periungual and subungual skin and of the palms and soles occurs initially when the neoplasm is silent. Subsequently, the skin of the ears, nose, face, and trunk and extremities becomes involved and shows a violaceous color, peeling, and fissuring (230,231). The palmar lesions may resemble those of Reiter's disease.

Histopathology. Ill-defined perivascular lymphocytic infiltrates containing a few pyknotic neutrophils in the upper dermis along with mild acanthosis, hyperkeratosis, and scattered parakeratotic foci are described. Eosinophilic and vacuolar degeneration of the spinous layer may be noted (231).

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CHAPTER 17

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Metabolic Diseases of the Skin

AMYLOIDOSIS

Amyloid

The term *amyloid* is applied to extracellular proteinaceous deposits that are resistant to proteolytic digestion and have distinctive physical properties. Deposits can be localized to a body site or can be "systemic," involving several organs and tissues.

By light microscopy, amyloid appears amorphous, eosinophilic, and hyaline. Characteristic staining qualities distinguish it from other glassy, pink substances. The Congo red stain results in a brick red staining reaction and apple-green birefringence and amyloid stains metachromatically with crystal violet and methyl violet stains. These staining characteristics result from the cross beta-pleated sheet conformation of the polypeptide backbones of the amyloid fibrils. These fibrils are ultrastructurally 8 to 12 nm in width and of indeterminate length. Deposits are derived from more than 25 different proteins, and it has been recommended that classification of amyloidoses be based on the fibril protein whenever possible (1,2).

Historically, the distinction between AL amyloid (primary systemic amyloidosis resulting from a plasma cell dyscrasia) and AA amyloid (secondary systemic amyloidosis) was made utilizing the latter's sensitivity to permanganate. More recently, immunohistochemistry, immunofluorescence microscopy, immunoelectron microscopy, and Western blotting have been used in the identification of fibril proteins and the development of proteomic techniques holds some promise for the future (2–5).

Cutaneous deposition of amyloid can result from any one of several systemic disease processes. However, cutaneous amyloid deposits can also result from local processes limited to the skin.

Systemic Amyloidoses That Involve the Skin: AL (Immunoglobulin Light Chains)

In its systemic form, this disease is also known as *primary systemic amyloidosis*. This uncommon disease results from a plasma cell dyscrasia with production of monoclonal light chains (3). The heart, smooth and skeletal muscle, and other soft tissues, as well as the kidneys, liver, and spleen, are frequently involved. However, deposits can be localized to the skin (and lungs) (2). When they are restricted to the skin, the terms *amyloidosis cutis nodularis atrophicans* and *nodular amyloidosis* have been applied. Heart failure, gastrointestinal bleeding, and renal failure can be fatal complications of the systemic form (6,7). Among cutaneous lesions, petechiae and ecchymoses are most common (7). They are the result of involvement of cutaneous blood vessels and are observed mainly on the face, especially on the eyelids and in the periorbital region (Fig. 17-1A). Minor trauma may precipitate these lesions, referred to by some as *pinch purpura*. In addition, there may be discrete or coalescing papules or plaques. They usually have a waxy color but may be blue-red as the result of hemorrhage into them (8,9). In rare instances, one observes firm cutaneous or subcutaneous nodules or plaques or areas of induration of the skin resembling morphea (10). Bullae that may be induced by minor trauma and may be hemorrhagic occur occasionally (9,11,12). Among oral lesions, macroglossia is common, occurring in 17% of the patients (6) (Fig. 17-1B).

Histopathology. Examination of cutaneous lesions in the systemic form of the disease reveals faintly eosinophilic amorphous, often fissured masses of amyloid deposited in the dermis and in the subcutaneous tissues. Quite frequently, accumulations of amyloid are deposited close to the epidermis. They may or may not be separated from the overlying epidermis by a narrow zone of collagen (Fig. 17-2).

They are rarely deposited around individual elastic fibers (13). The involvement of the walls of blood vessels is responsible for the frequent presence of extravasated erythrocytes. Inflammatory cells are lacking or scarce (12). Bullous lesions are of uncertain pathogenesis. Several mechanisms have been proposed: (a) the formation of clefts within large dermal amyloid deposits (11,12) or (b) from disruption of basal keratinocytes and the basement membrane zone (14).

In the subcutaneous tissue, there may be large aggregates of amyloid with infiltration of the walls of blood vessels and so-called amyloid rings, which are formed by the deposition of amyloid around individual fat cells (12). The fat cells may then appear as if cemented together by the amyloid.

Even if there are no skin lesions, fine-needle aspirates of the abdominal fat often are of use in documenting the diagnosis (15,16) (Fig. 17-3). Tissue biopsies of normal-appearing skin yield positive results in about 40% of all patients (10,17). These biopsies show small deposits in the walls of small blood



FIGURE 17-1. A: Primary systemic amyloidosis—pinch purpura. Note the papules and ecchymotic appearance in the characteristic periocular location. B: Primary systemic amyloidosis—macroglossia. The patient's tongue is enlarged with prominent indentations from continuous pressure against the teeth.

vessels in the dermis or the subcutaneous tissue but occasionally also around eccrine glands and lipocytes. The forearm is the recommended area for biopsy (17).

When localized to the skin, nodular amyloid deposits are surrounded by a dense plasmacytic infiltrate, and production of the immunoglobulin light chains is thought to occur locally (18).

Relationship with Multiple Myeloma. AL amyloidosis results from the production of monoclonal immunoglobulins and/or free light chains, usually lambda light chains, by an abnormal population of B cells. The vast majority of the patients (90%) have monoclonal protein in urine or serum (Bence-Jones protein) (19). If there is overtly malignant plasma cell neoplasia, it is referred to as *multiple myeloma*. Systemic amyloidosis is found in 5% to 15% of multiple myeloma patients. However, the majority of patients with AL amyloidosis do not have overt multiple myeloma. These patients have an underlying B-cell dyscrasia and, despite having no tumor masses, show an increased plasma cell population on bone marrow examination. It is uncertain whether or not this patient population will inevitably develop multiple myeloma.

Pathogenesis. In the systemic form of AL amyloidosis, the amyloid originates from monoclonal immunoglobulin light chains produced by plasma cells in the bone marrow. In the localized form, the amyloid is thought to be produced by the local plasma cell infiltrate, and as in the systemic form, the amyloid protein has immunocytochemical characteristics of AL amyloid (18).

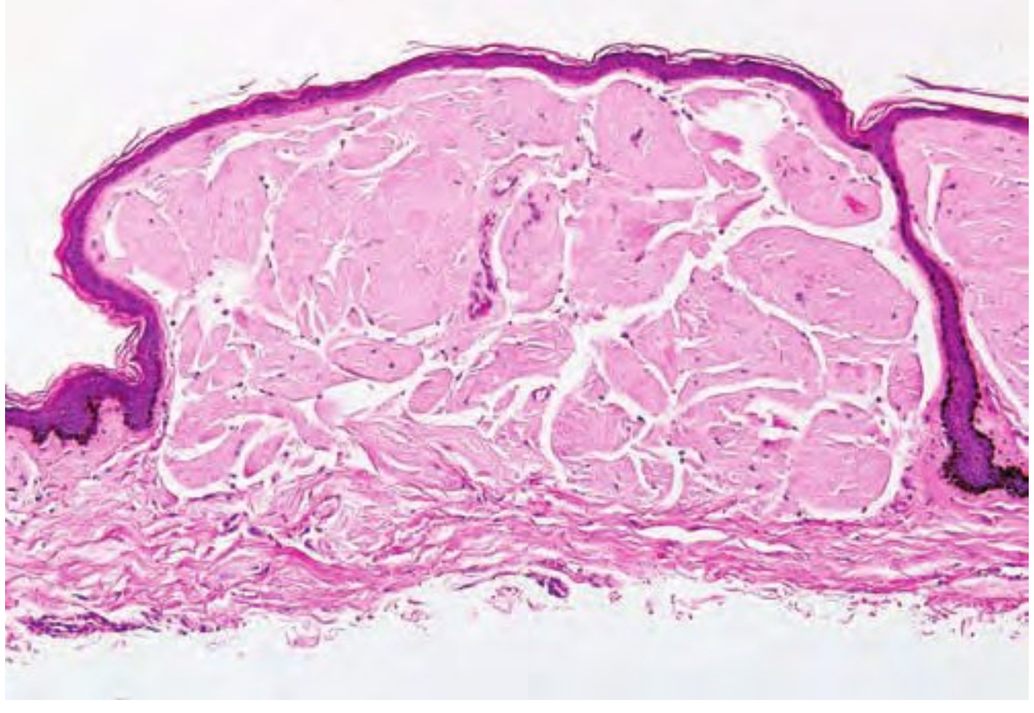


FIGURE 17-2. Primary systemic amyloidosis. There are amorphous, fissured masses of amyloid in the upper dermis. The amyloid material greatly resembles that observed in colloid milium (see Fig. 17-7, page 430).

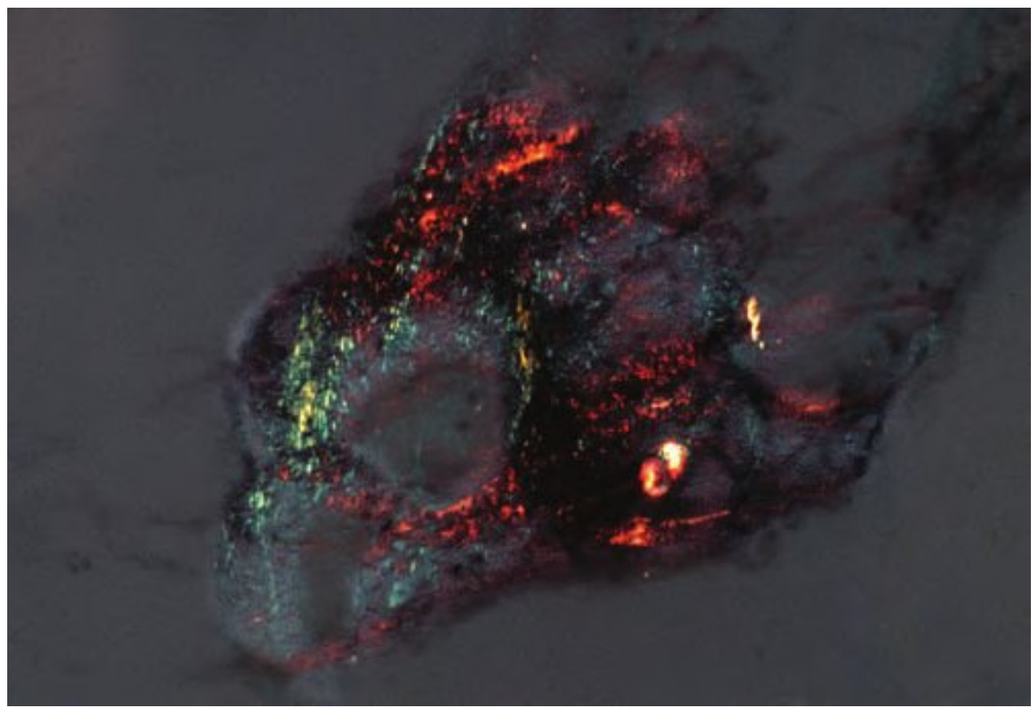


FIGURE 17-3. Primary systemic amyloidosis. Amyloid deposited in subcutaneous fat exhibits green birefringence under polarized light when stained with Congo red in this aspirate from the abdominal fat pad.

Ultrastructurally, amyloid deposits consist of irregularly arranged straight, nonbranching filaments that often appear hollow because their peripheries appear electron dense in comparison with their centers. These filaments are 6 to 7 nm in diameter but are of indeterminate length (20–22).

AA (Serum Amyloid A) Amyloidosis

Also known as *secondary systemic amyloidosis*, AA amyloidosis can result from chronic inflammatory disease or recurring bouts of acute inflammation such as tuberculosis, complications of bronchiectasis, and chronic osteomyelitis. It is now relatively rare in industrialized countries since the development of modern antibiotic therapy, and most cases in the United States and Western Europe are associated with chronic rheumatoid arthritis or related disorders (23). At time of diagnosis, the vast majority of patients have renal insufficiency or the nephrotic syndrome. There are no cutaneous lesions.

Histopathology. AA amyloid is deposited in parenchymatous organs such as the kidneys, liver, spleen, and adrenal. These deposits are found first in the interstitium and blood vessel walls; with progression, the deposits gradually replace the parenchyma. Deposits within the glomeruli and peritubular tissues result in renal failure.

Fine-needle aspiration biopsy of the subcutaneous fat and staining of the aspirated material by the Congo red method is the most sensitive method of diagnosis (15,16,24,25). Tissue biopsy of skin with underlying subcutaneous fat demonstrates deposits of AA amyloid around lipocytes, in blood vessel walls, around eccrine glands, and sometimes free in the dermis (17).

Pathogenesis. AA amyloid is thought to be derived from serum amyloid A (SAA), an acute phase reactant, which is produced in response to inflammation and regulated by cytokines including tumor necrosis factor-alpha (TNF-α) (26). AA protein is then formed when SAA undergoes carboxy terminal cleavage (26–28). This process takes place within lysosomes of macrophages that are receiving antigenic stimulation by a variety of chronic diseases (29). The amyloid is then deposited extracellularly.

Primary Localized Cutaneous Amyloidosis

Lichen Amyloidosis and Macular Amyloidosis

Lichen amyloidosis and macular amyloidosis are best considered as different manifestations of the same disease process. Lichen amyloidosis is characterized by closely set, discrete, brown-red papules that often show some scaling and are most commonly located on the legs, especially the shins, although they may occur elsewhere (Fig. 17-4). Through the coalescence of papules, plaques may form on the legs. These plaques often have verrucous surfaces and then resemble hypertrophic lichen planus or lichen simplex chronicus. Usually, the lesions of lichen amyloidosis itch severely. It is assumed by some authors that the pruritis leads to damage of keratinocytes by scratching and to subsequent production of amyloid (30,31).



FIGURE 17-4. Lichen amyloidosis. There are thin, tan to brown papules coalescing into a larger plaque on the anterior lower leg.

Macular amyloidosis is characterized by pruritic macules showing pigmentation with a reticulated or rippled pattern (Fig. 17-5). Although macular amyloidosis may occur anywhere on the trunk or extremities, the upper back is a fairly common site (32). In Southeast Asia, where macular amyloidosis is common, prolonged friction from a rough nylon towel or a back scratcher is thought to be its cause (33). The eruption



FIGURE 17-5. Macular amyloidosis. Note the rippled appearance of the hyperpigmentation in this close-up photograph of a patient's central upper back, which is a characteristic location.

can be easily passed off as postinflammatory hyperpigmentation by physicians who are unfamiliar with the condition (34).

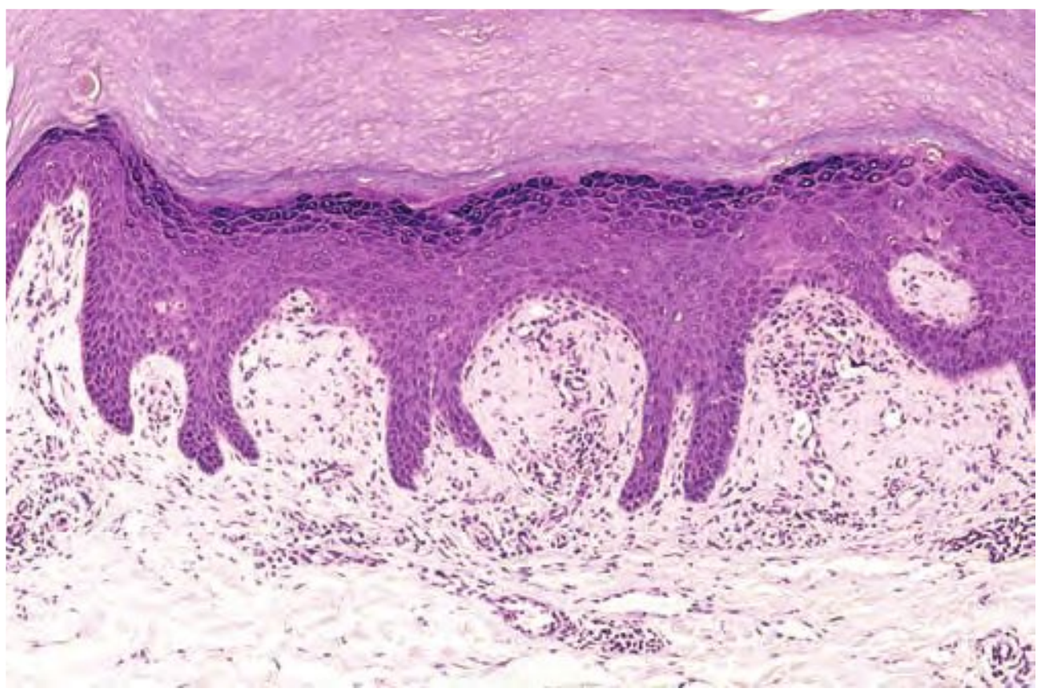
Macular amyloidosis and lichen amyloidosis sometimes occur together in the same patient, and lichen amyloidosis can arise in a setting of macular amyloidosis, presumably due to scratching (35,36). When treated by intralesional injection of steroids, the lichenoid lesions can become macular.

Histopathology. Lichen and macular amyloidosis show deposits of amyloid that are limited to the papillary dermis. Most of the amyloid is situated within the dermal papillae. Although the deposits usually are smaller in macular amyloidosis than in lichen amyloidosis, differentiation of the two on the basis of the amount of amyloid is not possible (34). The two conditions actually differ only in the appearance of the epidermis, which is hyperplastic and hyperkeratotic in lichen amyloidosis. Occasionally, the amount of amyloid in macular amyloidosis is so small that it is missed, even when special stains are used on frozen sections. In such instances, more than one biopsy may be necessary to confirm the diagnosis (37).

In areas in which the entire dermal papilla is filled with amyloid, the amyloid appears homogeneous in both lichen and macular forms. In lesions in which the dermal papillae are only partially filled, as seen more often in macular amyloidosis, the amyloid has a globular appearance and resembles the colloid bodies found in lichen planus (Fig. 17-6). These amyloid bodies in some areas lie in direct contact with the overlying basal cells of the epidermis. Similar colloid bodies are also found in some sections within the epidermis, but in contrast with those located at the dermal–epidermal junction, they do not stain as amyloid. In addition, there often is a striking degree of pigmentary incontinence.

Histogenesis. The light microscopic findings in lichen and macular amyloidosis suggest that degenerating epidermal cells are discharged into the dermis, where they are converted into amyloid. The epidermal origin of the amyloid in lichen and macular amyloidosis is supported by electron microscopy (38,39). Also on electron microscopy, the degenerating epidermal cells resemble the colloid bodies observed in lichen planus. They contain the following components: (a) tonofilaments; (b) degenerated, wavy tonofilaments that are thicker but less electron dense than normal tonofilaments; (c) lysosomes; and (d) typical filaments of amyloid, 6 to 10 nm thick, that are straight and nonbranching (39). It is postulated that the degenerated, wavy tonofilaments are recognized as foreign and are digested


A


B

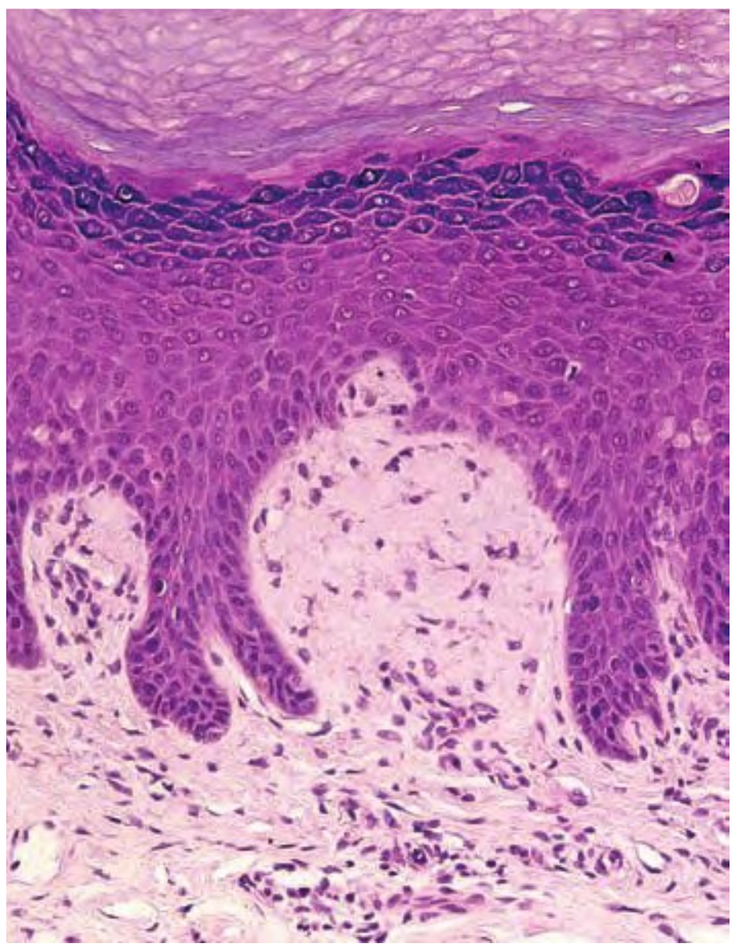

C

FIGURE 17-6. Lichen amyloidosis. There is hyperkeratosis and epidermal hyperplasia. Dermal papillae are rounded and contain globular deposits of amyloid. (A: Hematoxylin and eosin [H&E], original magnification ×40; B: H&E, original magnification ×100; C: H&E, original magnification ×200.)

by the cell's own lysosomes. Such digestion produces amyloid filaments. A conversion of tonofilaments into amyloid filaments requires that the alpha-pleated sheet configuration of the tonofilaments change into the beta configuration of amyloid (40). However, immunohistochemical studies suggest that components of the lamina densa and anchoring fibrils are also associated with amyloid deposits. Further ultrastructural examination shows disruption of the lamina densa overlying these deposits (41).

On direct immunofluorescence, all specimens of lichen or macular amyloidosis fluoresce positively for immunoglobulins or complement, particularly immunoglobulin M (IgM) and the third component of complement (C3). Staining for kappa and lambda light chains is positive. The immunofluorescent pattern is globular and thus is similar to that of lichen planus, except for the absence of fibrin. It suggests that the globular aggregates of lichenoid or macular amyloidosis, like the colloid bodies of lichen planus, act as a filamentous sponge into which immunoglobulins and complement are absorbed (42).

The epidermal derivation of the amyloid in lichen and macular amyloidosis is supported by histochemical and immunologic findings. In contrast to the amyloid of systemic amyloidosis, the amyloid of lichenoid and macular amyloidosis shows fluorescence for disulfide bonds as normally seen in the stratum corneum, suggesting that cross-linking of sulfhydryl groups occurs in amyloidogenesis (43). Furthermore, immunofluorescence studies with an antikeratin antiserum have shown intense staining of the amyloid for the antikeratin antibody (44).

After full agreement apparently had been reached about the keratogenic origin of the amyloid in lichen and macular amyloidosis, some dissenting opinions were expressed. In one study, amyloid stained negatively for keratin determinants and the positive reactions obtained by previous investigators were regarded as nonimmunologic, because amyloid deposits can easily absorb immunoglobulins (45). Degenerating collagen was regarded as the site of formation of amyloid (46). Other authors found direct amyloid fibril formation at the basal surfaces of living basal cells in lichen amyloidosis (47).

The amyloid that may be found in the stroma or in the adjacent connective tissue of basal cell carcinoma and other epithelial tumors has an appearance on electron microscopy and direct immunofluorescence similar to that of lichen and macular amyloidosis, suggesting that it too is derived from tonofilaments (48). This amyloid also shows positive staining with antikeratin antiserum (44).

Nodular Amyloidosis

Nodular amyloidosis is a rare condition in which nodular deposits of AL amyloid are deposited in the skin but in which there is no apparent systemic involvement. One or several nodules are encountered, usually on the legs (49) or face (50) but occasionally elsewhere. The nodules commonly measure from 1 to 3 cm in diameter. In their centers, the skin may appear atrophic (51). In exceptional instances, plaques are observed (52).

Histopathology. Beneath an atrophic epidermis are large masses of amyloid that extend through the entire dermis into the subcutaneous fat. Amyloid deposits are also found within the walls of blood vessels, in the membrana propria of the sweat glands, and around fat cells (52). A lymphoplasmacytic infiltrate is scattered through the masses of amyloid and at the periphery (18,50,51,53). In addition to clusters of plasma cells, Russell bodies and amyloid-containing foreign body giant cells may be seen (54).

Differential Diagnosis. On a histologic basis, differentiation of nodular amyloidosis from primary systemic amyloidosis is not possible.

COLLOID MILIUM AND NODULAR COLLOID DEGENERATION

There are three types of colloid degeneration of the skin: (a) juvenile colloid milium, (b) adult colloid milium, and (c) nodular colloid degeneration. Juvenile colloid milium and nodular colloid degeneration are very rare.

Juvenile colloid milium has its onset before puberty and shows numerous round or angular, brownish, waxy papules located mainly on sun-exposed areas, particularly the face (55,56). There is a family history in nearly half of the reported cases, and the possibility of a hereditary defect has been postulated (56).

Adult colloid milium, which starts in adult life, is clinically indistinguishable from the juvenile type, except that in some instances it involves the dorsa of the hands in addition to the face and neck (57,58). Sun exposure often seems to be a precipitating factor (55).

Nodular colloid degeneration shows either a single large nodule on the face (59) or multiple nodules on the face (60) or the chin and scalp (61). Sun exposure does not seem to play a role, because in some instances, the lesions are limited to the trunk (62).

Histopathology. The histologic findings differ in the three types of colloid degeneration, because the colloid in the juvenile form is of epidermal origin and that in the other two forms is of dermal origin (55,63).

In juvenile colloid milium, fissured colloid masses fill the papillary dermis. The overlying epidermis is flattened, and basal cells show transformation into colloid bodies (64). Ultrastructurally, the colloid material is found within individual basal keratinocytes above an intact basement membrane and in extracellular aggregates in the dermis. These deposits contain remnants of nuclear membrane material, degenerating cell organelles, and desmosomes. The fibrillary structure is similar to that of amyloid ultrastructurally, although staining with Congo red failed to result in birefringence, and other stains for amyloid were negative in the case reported by Handfield-Jones et al (56).

In adult colloid milium, a narrow zone of connective tissue usually separates the homogeneous masses of colloid located in the papillary dermis from the overlying epidermis

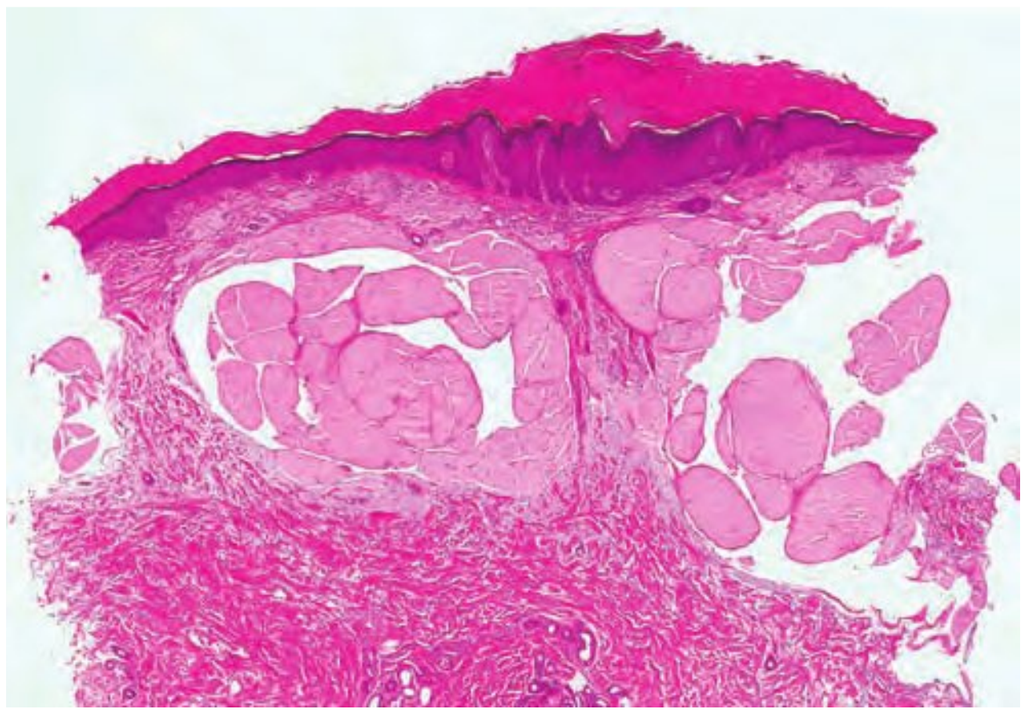


FIGURE 17-7. Colloid milium, adult type. Homogeneous, fissured masses of colloid are present in the uppermost dermis. The colloid material greatly resembles the amyloid material observed in primary systemic amyloidosis (see Fig. 17-2, page 426).

(Fig. 17-7). Elastic tissue staining shows some elastic fibers in this narrow zone of connective tissue (55). In addition, solar elastotic fibers are usually seen at the base of the colloid deposits (65).

In nodular colloid degeneration, the epidermis is flattened. The upper three quarters of the dermis are filled with pale pink, homogeneous material; in some lesions, even the entire dermis is filled with this material (61). Scattered nuclei of fibroblasts are present within the colloid (59). There are scattered clefts or fissures and some dilated capillaries. The hair follicles and sebaceous glands appear well preserved (60).

Pathogenesis. The colloid in all three types shows considerable resemblance to amyloid—not only in its histologic appearance but also in its histochemical reactions (65).

Histochemical staining shows that colloid, like amyloid, is periodic acid-Schiff (PAS) positive and diastase resistant. Staining with Congo red results in green birefringence (sometimes weak), and the colloid fluoresces after staining with thioflavin T (65). However, it does not react with pagoda red and other cotton dyes (66). Serum amyloid P not only is a component of normal and abnormal dermal elastic fibers but reportedly can be stained immunocytochemically in colloid milium (67). Juvenile colloid milium exhibits a positive immunostaining reaction to polyclonal antikeratin antibody. This suggests that the histogenesis of this process may differ from that of the adult form in that the colloid in juvenile colloid milium is more likely derived from keratinocytes (68).

Electron microscopy in a case of juvenile colloid milium has shown that the colloid consists of tightly packed bundles of filaments, 8 to 10 nm thick, in a wavy or whorled arrangement (63). The colloid, which forms by filamentous degeneration of tonofilaments, maintains a cytoid configuration in the dermis and may contain nuclear remnants (68,69).

In adult colloid milium, the colloid masses are seen on electron microscopic examination to consist primarily of a granulofibrillar, amorphous substance. On high magnification, very fine filaments, only 2 nm wide, may be seen embedded in the amorphous substance (55,67). There is rather conclusive evidence that colloid is derived from elastic fibers through sequential degenerative changes. This can be observed at the periphery of the lesion, where colloid is being produced, and within the colloid, where fibrils with a tubular structure and a diameter of 10 nm that are strikingly similar to the microfibrils of elastic fibers can be seen (57). The colloid in adult colloid milium thus represents a final product of severe solar degeneration (67).

The colloid in nodular colloid degeneration, similar to that in adult colloid milium, consists of an amorphous substance and short, wavy, irregularly arranged filaments (61). The diameter of these filaments is 3 to 4 nm (59). These electron microscopic findings exclude nodular amyloidosis as the diagnosis, because in this condition, the filaments have a diameter of about 6 to 7 nm and are long and straight.

LIPOID PROTEINOSIS (HYALINOSIS CUTIS ET MUCOSAE; URBACH-WIETHE DISEASE)

Lipoid proteinosis is a rare disorder that is inherited as an autosomal recessive trait. First described by Siebenmann (70) in 1908, it was established as a distinct clinical and histologic entity by Urbach and Wiethe (71) in 1929. In 1932, Urbach coined the term *lipoid proteinosis* (72).

Clinically, there are papular and nodular lesions on the face. Areas of diffuse infiltration associated with hyperkeratosis are observed on the elbows, knees, hands, and occasionally elsewhere. The papules and nodules on the face cause pitted scars, giving the skin a pigskin-leather appearance. Verrucous plaques can form in areas of friction (73). Beads of small nodules may be present along the free margins of the eyelids. The tongue is firm because of diffuse infiltration. Extension of the infiltration to the frenulum of the tongue restricts normal movement of the tongue, and infiltration of the vocal cords causes hoarseness, which may be present at birth. Convulsive seizures are not uncommon (74,75).

Histopathology. There is extensive cutaneous deposition of amorphous eosinophilic material surrounding capillaries and sweat coils and in the thickened papillary dermis (Fig. 17-8). Focal deposits are found in the deeper dermis. In verrucous lesions, the homogeneous bundles often are oriented perpendicular to the skin surface. This hyaline material is PAS-positive and resistant to diastase digestion. Staining with Alcian blue at pH 2.5 is slightly positive and is sensitive to hyaluronidase digestion (76). The presence of lipids is variable and likely results from adherence of lipids to glycoproteins rather than from abnormal lipid production (77).

Systemic Lesions. Intracranial calcification has been noted quite frequently in x-ray examination of patients with lipoid proteinosis and has been held responsible for convulsive seizures in these patients (74,78). Autopsy findings have established that the calcium is deposited within the walls of capillaries

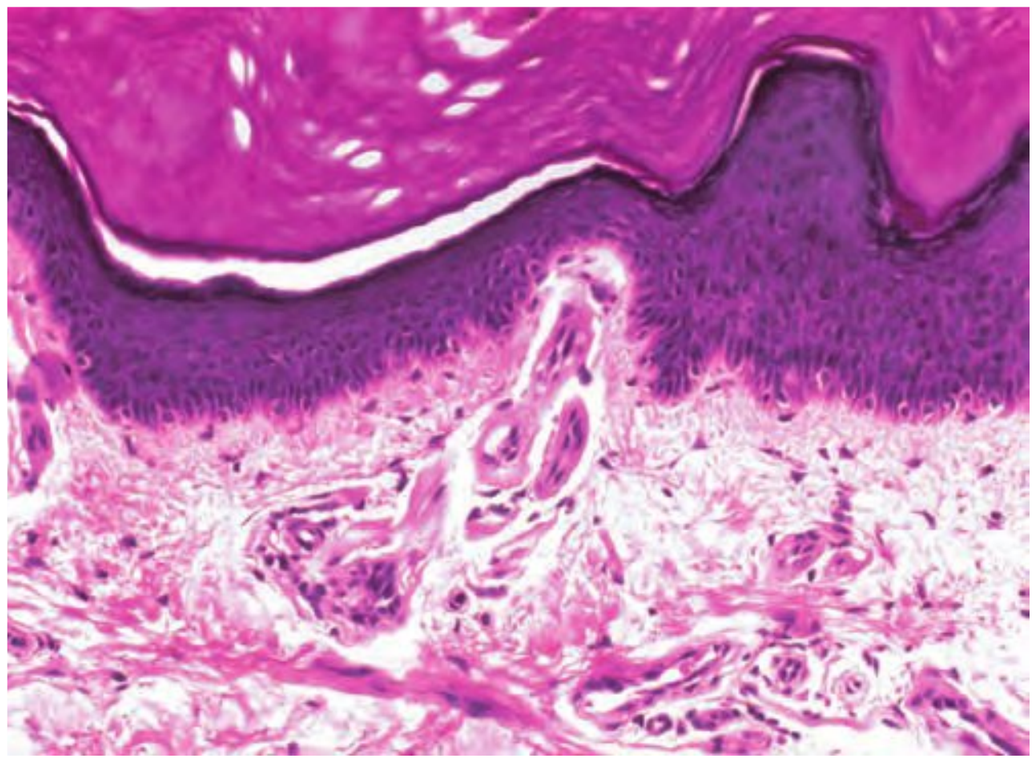


FIGURE 17-8. Lipoid proteinosis. The hyaline material consists of thick mantles surrounding the blood vessels.

located in the hippocampal gyri of the temporal lobes (79). The fact that after decalcification a mantle of PAS-positive material is observed around the endothelium of these vessels indicates that hyalinization precedes calcification of the capillary walls.

The widespread distribution of the pericapillary hyalin deposits has been established by biopsies and autopsies. Deposits have been found in the submucosae of the upper respiratory and digestive tracts and in the submucosae of the stomach, jejunum, rectum, and vagina; in the retina between the vitreous membrane and the pigment epithelium; and in the testes, pancreas, lungs, kidneys, and elsewhere (75,79).

Pathogenesis. Two different substances present in lesions of lipoid proteinosis have the light microscopic appearance of hyalin because they consist of homogeneous eosinophilic material and are PAS positive and diastase resistant (76,80). However, their different appearances and origins become evident on electron microscopy (81,82). One is true hyalin, produced by fibroblasts, and the other represents hyalin-like material consisting of multiplications of basal laminae, produced by a variety of cells.

Lipids are not an essential feature of the disease. They can be removed with lipid solvents without damage to the protein-carbohydrate complex of the true hyalin. This suggests that the lipids are either free or loosely bound to the hyalin (83).

Mutations in the extracellular matrix protein 1 gene (ECM1) have been identified as the cause of lipoid proteinosis (84). The glycoprotein product of this gene is thought to play a functional role in cutaneous physiology and homeostasis. With loss of function of ECM1, there is an accumulation of lipid-like materials in various viscera as well as in the skin as previously described (85).

On electron microscopic examination, three major alterations are noted in the dermis: (a) a considerable thickening of basal laminae; (b) massive depositions of amorphous material (hyalin), predominantly in the upper dermis and around blood vessels (86); and (c) a marked reduction in the number and size of collagen fibrils (82,85). The thickening of the basal laminae in multiple layers is evident around small blood vessels, skin appendages, smooth muscle cells, perineuria, and Schwann cells (87). In contrast, there is almost no multiplication of the basal lamina of the epidermis (87). Around capillaries, basal laminae consist of as many as 20 layers, and occasionally even more, arranged in a concentric "onion-skin" arrangement (86). Interspersed between these layers are fine collagen fibrils in an amorphous matrix. The thickened basement membranes stain intensively for laminin and collagen type IV (82).

A unique feature of hyalinosis cutis et mucosae consists of large depositions of amorphous material in the dermis. The exact chemical nature of this hyaline material is not known, but it is a noncollagenous glycoprotein that contains neither laminin nor fibronectin (82).

The collagen within the areas of hyalin deposits appears as fine but otherwise normal fibrils arranged in bundles or in random fashion. Most fibrils have a diameter $<$50 nm, compared with the usual size of 70 to 140 nm. Involved skin shows a five-fold reduction in collagen type I, the major collagen species of normal skin, and to a lesser extent in collagen type III, as indicated by cell culture studies. As judged by the contents of glycine and hydroxyproline, normal skin contains about 80% collagen, but involved skin in hyalinosis cutis et mucosae contains only 20% collagen as the result of a large accumulation of noncollagenous glycoproteins.

Cultured fibroblasts from lesions of hyalinosis cutis et mucosae have shown an increased synthesis of noncollagenous proteins at the expense of newly synthesized collagens. The hyaline material in hyalinosis cutis et mucosae originates from the overproduction of noncollagenous proteins, most of which are normal constituents of human skin (82).

Differential Diagnosis. Porphyria shows deposits of hyalin-like material around the superficial dermal capillaries that are indistinguishable from the perivascular deposits of hyalin-like material seen in lipoid proteinosis. However, involvement of the membrana propria of the sweat glands is rare, and no true dermal hyalin is present. In addition, the cutaneous lesions in porphyria are limited to sun-exposed areas.

PORPHYRIA

Seven types of porphyria are recognized (Table 17-1). The light sensitivity in the six types with cutaneous lesions is caused by wavelengths that are absorbed by the porphyrin molecule. These wavelengths lie in the 400-nm range, representing long-wave ultraviolet light (UVA) and visible light (88).

In *erythropoietic porphyria*, a very rare disease that typically develops during infancy or childhood, recurrent vesiculobullous eruptions in sun-exposed areas of the skin gradually result in mutilating ulcerations and scarring. It is inherited in an autosomal recessive pattern (89). Hypertrichosis and brown-stained teeth that fluoresce are additional features (90,91).

TABLE 17-1 Classification of the Porphyrias

Porphyrias	Type; heredity; onset	Cutaneous manifestations	Extra-cutaneous manifestations	Urine	Feces	Erythrocytes	Enzymatic defect
Erythropoietic porphyria	Ery; Rec; Infancy	Blisters, severe scarring	Red teeth; hemolytic anemia	Uro I	Copro I	Uro I, stable fluorescence	Uroporphyrinogen cosynthase
Erythropoietic protoporphyria	Ery; Dom; Childhood	Burning, edema, thickening, rarely blisters	Rarely fatal liver disease	Negative	Protoporphyrin continuously	Protoporphyrin, transient fluoresence	Ferrochelatase (Heme synthase)
Acute intermittent porphyria (AIP)	Hep; Dom; Young adulthood	Negative	Abdominal pain, neuropathy, psychoses	ALA, PBG continuously	Negative	Negative	Uroporphyrinogen synthase
Porphyria variegata	Hep; Dom; Young adulthood	Same as PCT	Same as AIP	ALA, PBG during attacks	Protoporphyrin continuously	Negative	Protoporphyrinogin oxidase
Porphyria cutanea tarda (PCT)	Hep; Dom; Middle age	Blisters, scarring, thickening	Decreased liver function, siderosis	Uro III, continuous fluorescence		Negative	Uroporphyrinogen decarboxylase
Hepatoerythrocytic porphyria (homozygous form of PCT)	Ery and Hep; Dom; Childhood	Blisters, severe scarring, thickening	Decreased liver function	Uro I, Uro III	Copro I, Copro III	Protoporphyrin	Uroporphyrinogen decarboxylase
Hereditary coproporphyria	Hep; Dom; Young adulthood	Same as PCT	Same as AIP	Copro, ALA, PBG during attacks	Copro continuously	Negative	Coproporphynnogen oxidase

Ery, erythropoietic; Rec, autosomal recessive; Uro, uroporphyrin; Copro, coproporphyrin; Dom, autosomal dominant; Hep, hepatic; ALA, delta-aminolevulinic acid; PBG, porphobilinogen; PCT, porphyria cutanea tarda; AIP, acute intermittent porphyria.

In *erythropoietic protoporphyria*, the usual reaction to light is erythema and edema followed by thickening and superficial scarring of the skin (92). In rare instances, vesicles are present that may resemble those seen in hydroa vacciniforme (93–95). It is an autosomal dominant disorder that results from a mutation in the gene that codes for ferrochelatase, which is the final enzyme in the heme synthesis chain (96). The protoporphyrin is formed in reticulocytes in the bone marrow and is then carried in circulating erythrocytes and in the plasma. When a smear of blood from a patient is examined under a fluorescence microscope, large numbers of red-fluorescing erythrocytes are observed. The protoporphyrin is cleared from the plasma by the liver and excreted into the bile and feces (97). It is not found in the urine. In rare instances, fatal liver disease develops quite suddenly, usually in persons of middle age (98) but occasionally in patients only in the second decade of life (99,100).

In *porphyria variegata*, different members of the same family may have either cutaneous manifestations identical to those of porphyria cutanea tarda or systemic involvement analogous to acute intermittent porphyria, or both, or the condition may remain latent (95,101). The presence of protoporphyrin in the feces distinguishes porphyria variegata from porphyria cutanea tarda (102) (see Table 17-1). Also, a sharp fluorescence emission peak at 626 nm is specific for the plasma of porphyria variegata (103,104).

Three forms of *porphyria cutanea tarda* can be distinguished: sporadic, familial, and hepatoerythropoietic (105). In the *sporadic form*, only the hepatic activity of uroporphyrinogen decarboxylase is decreased. Almost all patients are adults, and no clinical evidence of porphyria cutanea tarda is found in other members of the patient's family. Although the sporadic form can occur without any precipitating factor, in most instances, in addition to the inherited enzymatic defect, an

acquired damaging factor to liver function is needed. The damaging agent most commonly is ethanol, but iron supplements, estrogen treatment, and hepatitis are also implicated (106,107).

In the *familial form*, a dominantly inherited disorder, in addition to the hepatic activity, the extrahepatic activity of uroporphyrinogen decarboxylase is decreased to about 50% of normal. The enzymatic activity usually is determined on the erythrocytes. The familial form may occur at any age, including childhood, and often, but not always, there is a family history of overt porphyria cutanea tarda. A reliable laboratory method for the diagnosis of the porphyrias is now provided by molecular genetics (106).

In the very rare *hepatoerythropoietic form*, the skin lesions appear in childhood and the activity of uroporphyrinogen decarboxylase in all organs is decreased to <10% of normal. Family studies suggest that these patients are homozygous for the gene that causes porphyria cutanea tarda (105).

Clinically, the sporadic form of porphyria cutanea tarda, by far the most common type of porphyria, shows blisters that arise through a combination of sun exposure and minor trauma, mainly on the dorsa of the hands but sometimes also on the face (Fig. 17-9). Mild scarring may result. The skin of the face and the dorsa of the hands often is thickened and sclerotic. Hypertrichosis of the face is common. Evidence of hepatic cirrhosis with siderosis is regularly present but generally is mild (108). In rare instances, hepatocellular carcinoma or a carcinoma metastatic to the liver induces porphyria cutanea tarda (109). In the familial form of porphyria cutanea tarda, the clinical picture is similar to that of the sporadic form, but the changes are more pronounced. In the hepatoerythropoietic form, the manifestations are even more severe. On clinical grounds, the symptoms of most patients resemble those of erythropoietic porphyria, but when symptoms are milder, they resemble those of erythropoietic protoporphyria (110). Vesicular eruptions lead to ulceration, severe scarring, partial alopecia, and sclerosis (111). Erythrocytes and teeth may show fluorescence (112). Liver damage develops with increasing age (113).



FIGURE 17-9. Porphyria cutanea tarda. There are crusts from healing vesicles scattered over the dorsal hand. Scars and milia are present on the mid-dorsal hand.

In *hereditary coproporphyria*, a very rare disorder, there are episodic attacks of abdominal pain and a variety of neurologic and psychiatric disturbances analogous to those observed in acute intermittent porphyria and porphyria variegata (114). In some cases, there are also cutaneous manifestations indistinguishable from those of porphyria cutanea tarda and porphyria variegata (114,115).

Histopathology. The histologic changes in the skin lesions are the same in all six types of porphyria with cutaneous lesions. Differences are based on the severity rather than on the type of porphyria. Homogeneous, eosinophilic material is regularly observed, and bullae are present in some instances. In addition, sclerosis of the collagen is present in old lesions (116,117).

In mild cases, homogeneous, pale, eosinophilic deposits are limited to the immediate vicinity of the blood vessels in the papillary dermis (117). These deposits are best visualized with a PAS stain, being PAS positive and diastase resistant.

In severely involved areas, which are most common in erythropoietic protoporphyria, the perivascular mantles of homogeneous material are wide enough in the papillary dermis to coalesce with those of adjoining capillaries. In addition, deeper blood vessels may show homogeneous material around them, and similar homogeneous material may be found occasionally around eccrine glands (118). PAS staining demonstrates this material particularly well. In some instances, it also contains acid mucopolysaccharides, shown with Alcian blue or the colloidal iron stain (117), or lipids, demonstrable with Sudan IV or Sudan black B (93,118). In addition, the PAS-positive dermal–epidermal basement membrane zone may be thickened (117).

In areas of sclerosis, which occur especially in porphyria cutanea tarda, the collagen bundles are thickened. In contrast to scleroderma, PAS-positive, diastase-resistant material is often present in the dermis in perivascular locations (117).

The bullae, which are most common in porphyria cutanea tarda and least common in erythropoietic protoporphyria, arise subepidermally (Fig. 17-10). Some blisters are dermolytic and arise beneath the PAS-positive basement membrane zone (119); others form in the lamina lucida and are situated above the PAS-positive basement membrane zone (120) (Fig. 17-11). It has been suggested that the blisters in porphyria cutanea tarda in mild cases arise within the junctional zone but that in severe cases they form beneath the PAS-positive basement membrane zone and thus heal with scarring (121). It is quite characteristic of the bullae of porphyria cutanea tarda that the

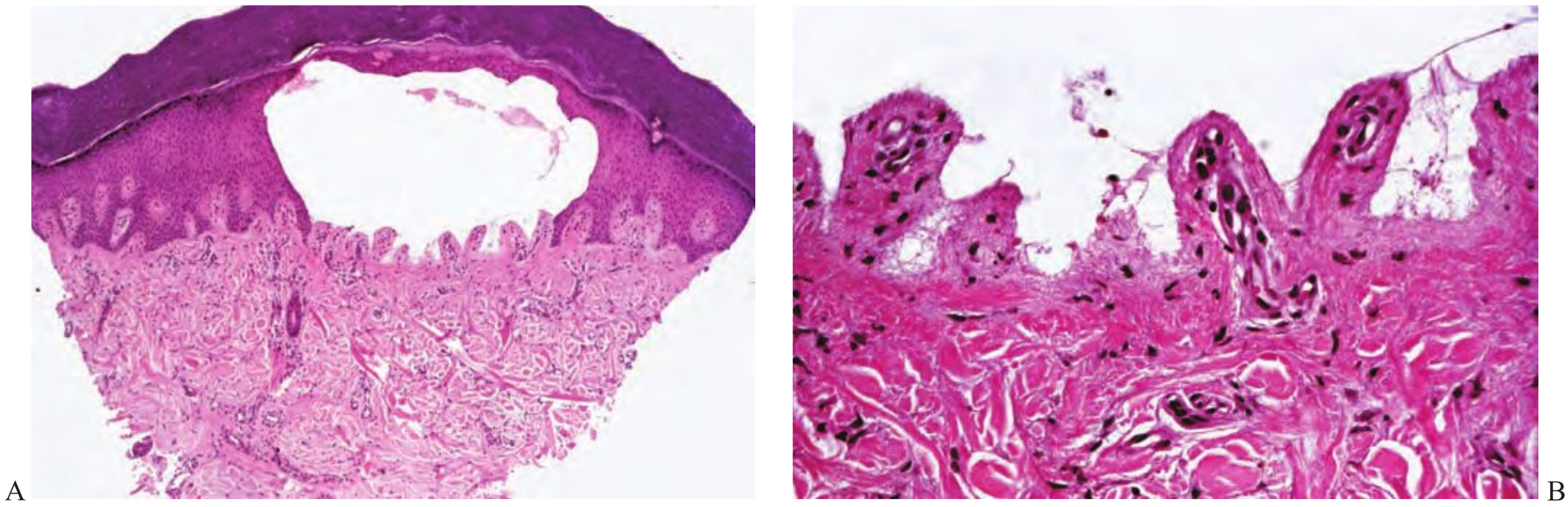


FIGURE 17-10. Porphyria cutanea tarda. A: There is a subepidermal blister. The architecture of the dermal papillae remains intact. The dermis contains no significant inflammatory infiltrate (H&E). B: Vessels within preserved dermal papillae at the blister base are surrounded by PAS-positive, diastase-resistant deposits.

dermal papillae often extend irregularly from the floor of the bulla into the bulla cavity (104,122). This phenomenon, referred to as *festooning*, is explained by the rigidity of the upper dermis induced by the presence of eosinophilic material within and around the capillary walls in the papillae and the papillary dermis.

The epidermis forming the roof of the blister often contains eosinophilic bodies that are elongate and sometimes segmented (123). These "caterpillar bodies" are PAS positive and diastase resistant. Ultrastructurally, they have been found to contain three components: (a) cellular organelles, including melanosomes, desmosomes, and mitochondria; (b) colloid that may be located intracellularly or extracellularly; and (c) electron-dense material thought to be of basement membrane origin (124).

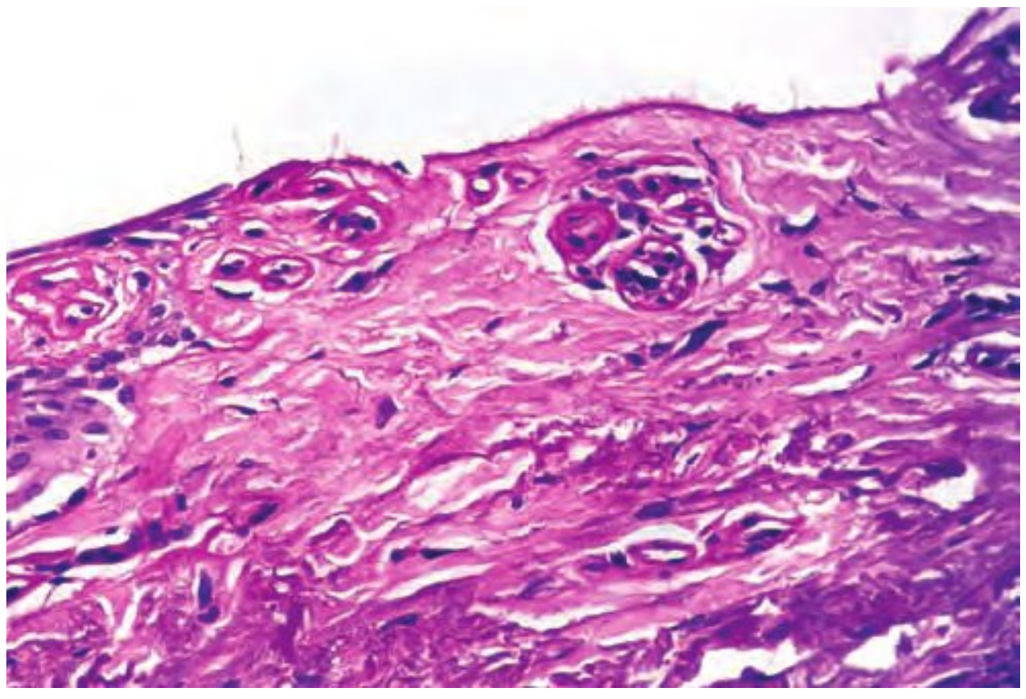


FIGURE 17-11. Porphyria cutanea tarda. On staining with the PAS reaction after diastase digestion, the PAS-positive basement membrane zone is observed at the floor of the blister. PAS-positive hyalin-like material is present in the walls of capillaries in the upper dermis.

Pathogenesis. The substance around dermal vessels has the appearance of hyalin because it consists of homogeneous, eosinophilic material and is PAS positive and diastase resistant. However, just as the perivascular material in lipoid proteinosis, it is only hyalin-like and consists of multiplications of basal laminae (125). True hyalin, which is present in large amounts in the dermis of lipoid proteinosis and produced by fibroblasts as amorphous material, is absent.

On electron microscopic examination, concentric duplications of the basement membrane around the dermal blood vessels are observed. Peripheral to this multilayered basement membrane, one observes a thick mantle of unlayered material with the same filamentous and amorphous composition as that of the basement membrane. Often, a gradual transition from the layered to the unlayered zone can be observed (125,126). Scattered through the thick, unlayered zone are solitary collagen fibrils with an average diameter of only 35 nm, in contrast to the 100 nm of mature collagen (116,125). In cases with severe involvement, intermingled filamentous and amorphous material is seen throughout the upper dermis and even in the mid dermis.

Proof that the perivascular material in porphyria represents excessively synthesized basement membrane material and as such contains type IV collagen is provided by positive immunofluorescence staining with anti–type IV collagen monospecific antibody (127). The presence of small collagen fibrils analogous to reticulum fibrils suggests the presence also of type III collagen.

In the majority of patients, direct immunofluorescence testing has revealed the presence of immunoglobulins, particularly immunoglobulin G (IgG) (117), and occasionally also of complement (128), in the walls of blood vessels and at the dermal–epidermal junction of light-exposed skin. It is unlikely that these deposits indicate an immunologic phenomenon; rather, they are the result of "trapping" of immunoglobulins and complement in the filamentous material.

The *enzymatic defect* that causes each form of porphyria is known (see Table 17-1). Enzyme determinations may be carried out on cultured skin fibroblasts, erythrocytes, or liver tissue.

Liver damage is generally mild and chronic in porphyria cutanea tarda. In erythropoietic protoporphyria, however, liver function tests are usually normal, even though microscopic deposits of protoporphyrin in the liver are found frequently (94). Yet, in rare instances, death occurs from liver failure developing swiftly after the initial detection of hepatic dysfunction (98). Patients with liver failure have very high levels of protoporphyrin in the erythrocytes and at the time of death show extensive deposits of protoporphyrin in a cirrhotic liver. The protoporphyrin in hepatocytes and Kupffer cells appears as dark brown granules (100). This pigment exhibits birefringence on polariscopic examination and in unstained sections viewed with ultraviolet light shows red autofluorescence (98). In patients with normal liver function tests, biopsy of the liver may or may not show portal and periportal fibrosis (99).

Pseudoporphyria Cutanea Tarda

In patients with chronic renal failure who are receiving maintenance hemodialysis, an eruption indistinguishable from that of porphyria cutanea tarda may develop on the dorsa of the hands and fingers during the summer months (129). Rarely, blisters are seen also on the face, and atrophic scarring develops (130). In a series of 180 patients receiving hemodialysis, 28 (16%) showed this type of eruption (131). Normal porphyrin levels in urine, stool, and plasma are the rule in hemodialyzed patients developing clinical signs of porphyria cutanea tarda. However, in a few patients receiving hemodialysis for chronic renal failure, a true porphyria cutanea tarda coexists (132,133). In such patients, if a certain degree of diuresis persists, urinalysis may not be representative of the porphyria metabolism, and the plasma and fecal porphyrins should always be measured (134).

Pseudoporphyria cutanea tarda may also occur following the ingestion of certain drugs, such as furosemide, nalidixic acid, tetracycline hydrochloride, and naproxen (135). Because many patients on hemodialysis for renal failure also are receiving furosemide, withdrawal of the drug can determine whether the dialysis or the medication is the cause of the pseudoporphyria, because in drug-induced cases, withdrawal of the drug is curative (135).

Histopathology. In patients with pseudoporphyria, the histologic picture is indistinguishable from that seen in mild cases of porphyria. The superficial blood vessels show thickened walls, and the PAS-positive basement membrane zone is often thickened as well. Blisters are subepidermal, with festooned dermal papillae. The blisters usually are situated above the PAS-positive basement membrane zone (130–135).

Pathogenesis. Electron microscopic findings are identical to those of porphyria (131). As in porphyria, immunoglobulins are often observed in vessel walls and at the dermal–epidermal junction. Complement is also occasionally present (129,131).

CALCINOSIS CUTIS

There are four forms of calcinosis cutis: metastatic calcinosis cutis, dystrophic calcinosis cutis, idiopathic calcinosis cutis, and subepidermal calcified nodule.

Metastatic Calcinosis Cutis

Metastatic calcification develops as the result of hypercalcemia or hyperphosphatemia. Hypercalcemia may result from (a) primary hyperparathyroidism, (b) excessive intake of vitamin D (136), (c) excessive intake of milk and alkali (137), or (d) extensive destruction of bone through osteomyelitis or metastases of a carcinoma (138). Hyperphosphatemia occurs in chronic renal failure as the result of a decrease in renal clearance of phosphorus and is associated with a compensatory drop in the serum calcium level. The low level of ionized calcium in the serum stimulates parathyroid secretion, leading to secondary hyperparathyroidism and to resorption of calcium and phosphorus from bone. The demineralization of bone causes both osteodystrophy and metastatic calcification (139,140).

Metastatic calcification most commonly affects the media of the arteries and the kidneys. In addition, other visceral organs, such as the myocardium, the stomach, and the lungs (139,141), may be involved.

Metastatic calcification in the subcutaneous tissue is occasionally observed in association with renal hyperparathyroidism (139), in uremia (142), in hypervitaminosis D (136), and as the result of excessive intake of milk and alkali (137) but rarely in primary hyperparathyroidism (138). Palpable, hard nodules, occasionally of considerable size, are located mainly in the vicinity of the large joints (139). With an increase in size, the nodules may become fluctuant (143).

Calciphylaxis is a life-threatening condition in which there is progressive calcification of small- and medium-sized vessels of the subcutis often accompanied by necrosis. It most frequently arises in the setting of hyperparathyroidism associated with chronic renal failure. Calciphylaxis is often, but not always, associated with an elevated serum calcium/phosphate product, with other factors, including several glycoproteins (matrix G1a protein and glycopontin) likely playing a role in the development of vascular calcification (144).

Clinically, the lesions present as a panniculitis or vasculitis. Bullae, ulcerations, or a livedo reticularis–like eruption can be present (145). Potential complications of gangrene, sepsis, pancreatitis, and multisystem organ failure contribute to an overall mortality of >60% (146).

Instances of *cutaneous metastatic calcinosis* are rare. Most reports have concerned patients with renal hyperparathyroidism and osteodystrophy. The cutaneous lesions may consist of firm, white papules (147); papules in a linear arrangement (143); symmetric, nodular plaques (140); or papules and nodules from which a granular, white substance can be expressed (148).

Mural calcification of arteries and arterioles in the deep dermis or subcutaneous tissue occurs rarely in primary

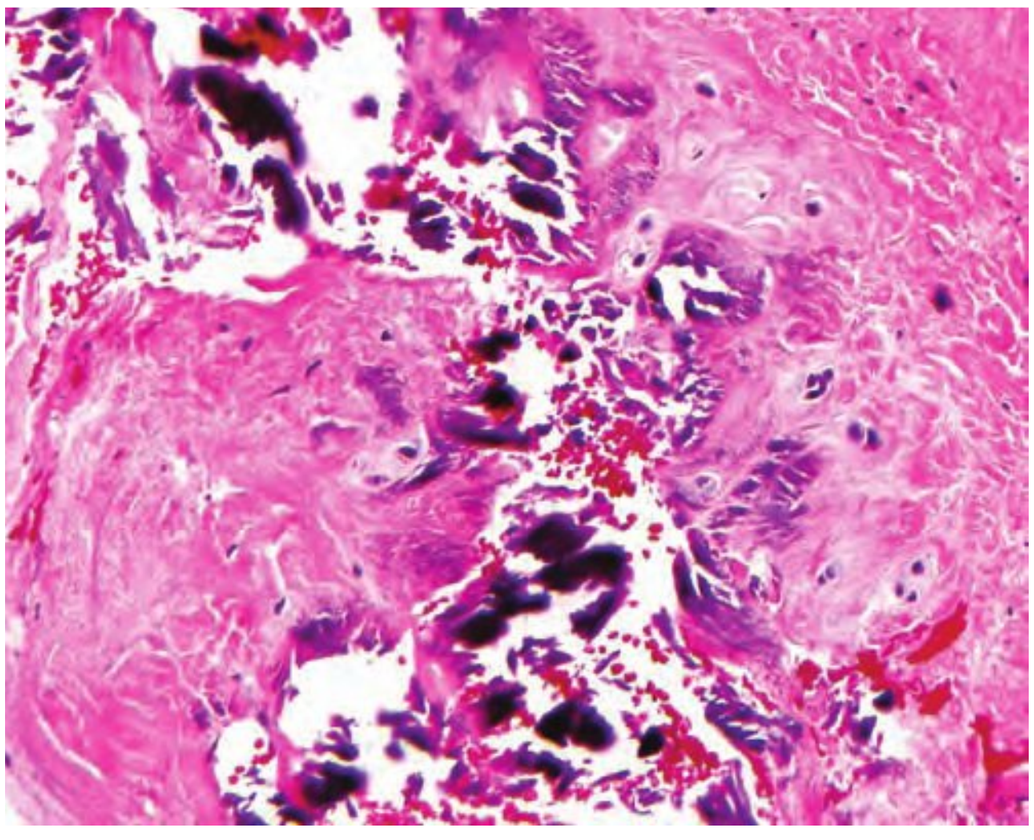


FIGURE 17-12. Metastatic calcinosis cutis. Amorphous deposits of basophilic material are present in the dermis.

hyperparathyroidism (149) but somewhat more frequently in secondary hyperparathyroidism subsequent to renal disease and particularly if subsequent to dialysis for chronic renal disease or to renal allograft (150,151). This may lead to occlusion of these vessels and to infarctive ulcerations, especially on the legs.

Histopathology. Calcium deposits are recognized easily in histologic sections, because they stain deep blue with H&E. They stain black with the von Kossa stain for calcium phosphate. As a rule, the calcium occurs as massive deposits when located in the subcutaneous fat and usually as granules and small deposits when located in the dermis (Fig. 17-12). Large deposits of calcium often evoke a foreign body reaction; thus, giant cells, an inflammatory infiltrate, and fibrosis may be present around them (140).

In areas of infarctive necrosis, as a result of calcification of dermal or subcutaneous arteries or arterioles, the involved vessels show calcification of their walls and intravascular fibrosis with attempts at recanalization of the obstructed lumina (149). Mural calcification often is most pronounced in the internal elastic membranes of arteries or arterioles (150).

The histologic changes in calciphylaxis include calcium deposits in the subcutis, chiefly within the walls of small- and medium-sized vessels (Fig. 17-13). These deposits can be associated with endovascular fibrosis, thrombosis, or global calcific obliteration (152). The fully evolved disease process shows, in addition, areas of necrosis with a clean background or accompanied by neutrophils (146).

It is particularly important that these findings be recognized in order that appropriate therapy, which often includes parathyroidectomy, might be instituted immediately.

Dystrophic Calcinosis Cutis

In dystrophic calcinosis cutis, the calcium is deposited in previously damaged tissue. The values for serum calcium and phosphorus are normal, and the internal organs are spared. There may be numerous large deposits of calcium (calcinosis universalis) or only a few deposits (calcinosis circumscripta).

Calcinosis universalis occurs as a rule in patients with dermatomyositis (Fig. 17-14), but exceptionally it has also been observed in patients with systemic scleroderma (153). Large deposits of calcium are found in the skin and subcutaneous tissue and often in muscles and tendons (154). In dermatomyositis, if the patient survives, the nodules of dystrophic calcinosis gradually resolve.

Calcinosis circumscripta occurs as a rule in patients with systemic scleroderma; rarely, however, it may be observed in patients with widespread morphea (155,156). Generally, in the presence of calcinosis, systemic scleroderma manifests itself as acrosclerosis. The association of acrosclerosis and calcinosis is

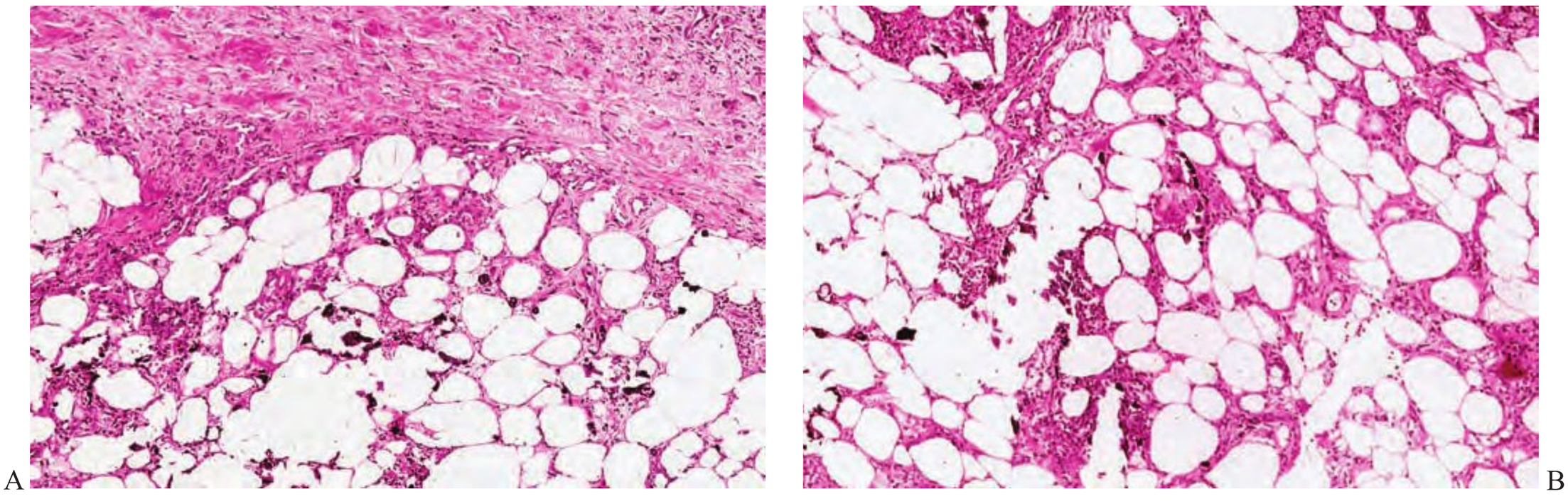


FIGURE 17-13. Calciphylaxis. There is a panniculitis with associated calcification of soft tissues in the walls of small vessels (A: H&E, original magnification ×20; B: H&E, original magnification ×100.)

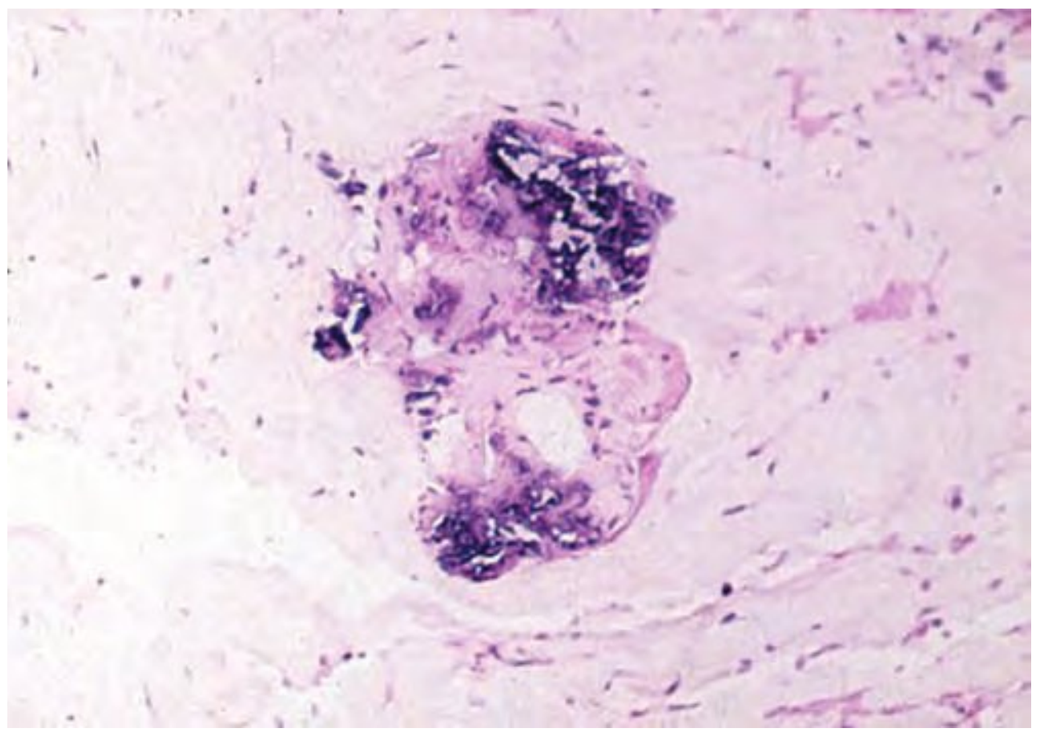


FIGURE 17-14. Dystrophic calcinosis cutis. Granules and globules of calcium are located beneath the epidermis. This biopsy is from the buttock of a child with dermatomyositis who had extensive calcification also of muscles and tendons.

often referred to as the *Thibierge-Weissenbach syndrome* or as the *CREST syndrome*, because the manifestations usually consist of calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia (153,155,157). Patients with this syndrome often have a better prognosis than those with generalized scleroderma or systemic sclerosis. Clinically, calcinosis circumscripta shows successively appearing areas of induration that often break down and extrude white, chalky material.

Lupus erythematosus is only rarely associated with dystrophic calcinosis cutis (158). In addition to occurring in the connective tissue diseases, dystrophic calcinosis is often seen in subcutaneous fat necrosis of the newborn and, rarely, in the subcutaneous nodules occurring in Ehlers-Danlos disease.

Histopathology. As in metastatic calcinosis cutis, the calcium in dystrophic calcinosis cutis usually is present as granules or small deposits in the dermis and as massive deposits in the subcutaneous tissue (156). A foreign-body giant cell reaction is often found around large deposits of calcium (159). The calcium deposits usually are located in areas in which the collagen or fatty tissue appears degenerated as a result of the disease preceding the calcinosis.

Idiopathic Calcinosis Cutis

Even though the underlying connective tissue disease in some instances of dystrophic calcinosis cutis may be mild and can be overlooked unless specifically searched for, there remain cases of idiopathic calcinosis cutis that resemble dystrophic calcinosis cutis but show no underlying disease (160–162).

One entity is regarded as a special manifestation of idiopathic calcinosis cutis: tumoral calcinosis. It consists of numerous large, subcutaneous, calcified masses that may be associated with papular and nodular skin lesions of calcinosis (163,164). The disease usually is familial and is associated with hyperphosphatemia (164,165). Otherwise, the resemblance of tumoral calcinosis to the dystrophic calcinosis universalis observed with dermatomyositis is great.

Histopathology. Tumoral calcinosis shows in the subcutaneous tissue large masses of calcium surrounded by a foreign body reaction (159). Intradermal aggregates are present in some cases. Discharge of calcium may take place through areas of ulceration or by means of transepidermal elimination (164).

Pathogenesis. Two authors have studied lesions of idiopathic calcinosis cutis by electron microscopy (160,161). They agree that the deposits consist of pleomorphic calcium phosphate (apatite) crystals. However, according to one opinion, the earliest deposits of calcium are situated in the ground substance (160), whereas according to the other, the earliest calcium deposits lie within collagen fibrils and subsequently extend into the ground substance as the apatite crystals grow (161).

Idiopathic Calcinosis of the Scrotum

Idiopathic calcinosis of the scrotum consists of multiple asymptomatic nodules of the scrotal skin. The nodules begin to appear in childhood or in early adult life, increase in size and number, and sometimes break down to discharge their chalky contents (166).

Histopathology. At one time, the accepted view was that some of the calcific masses in calcinosis of the scrotum were surrounded by a granulomatous foreign body reaction and others were not (166,167). However, in recent publications in which numerous scrotal nodules were examined, some of the lesions were epidermal cysts, whereas other cystic lesions showed calcification of their keratin contents, and still others showed ruptures of their epithelial walls. The cyst wall was eventually destroyed, leaving only dermal collections of calcium. Thus, according to this view, calcinosis of the scrotum represents the end stage of dystrophic calcification of scrotal epidermal cysts (168,169). Other authors who also had examined either several patients or multiple nodules agreed that the lesions originated from cysts. One author favored eccrine duct milia as the origin because of a positive reaction for carcinoembryonic antigen, which is a marker of eccrine sweat glands (170). Another author found various types of cysts—epidermal, pilar, and indeterminate cysts showing various degrees of calcification (171). It can be assumed that early lesions start out as cysts but, as they age and calcify, lose their cyst walls. It is likely that authors who found no cyst walls were examining old lesions.

Subepidermal Calcified Nodule

In subepidermal calcified nodule, also referred to as *cutaneous calculi*, usually a single small, raised, hard nodule is present. Occasionally, however, there are two or three nodules (172,173), and in some instances, there are numerous (174) or even innumerable (175) nodules. Most patients are children; however, in some patients, a nodule is present at birth (176) or

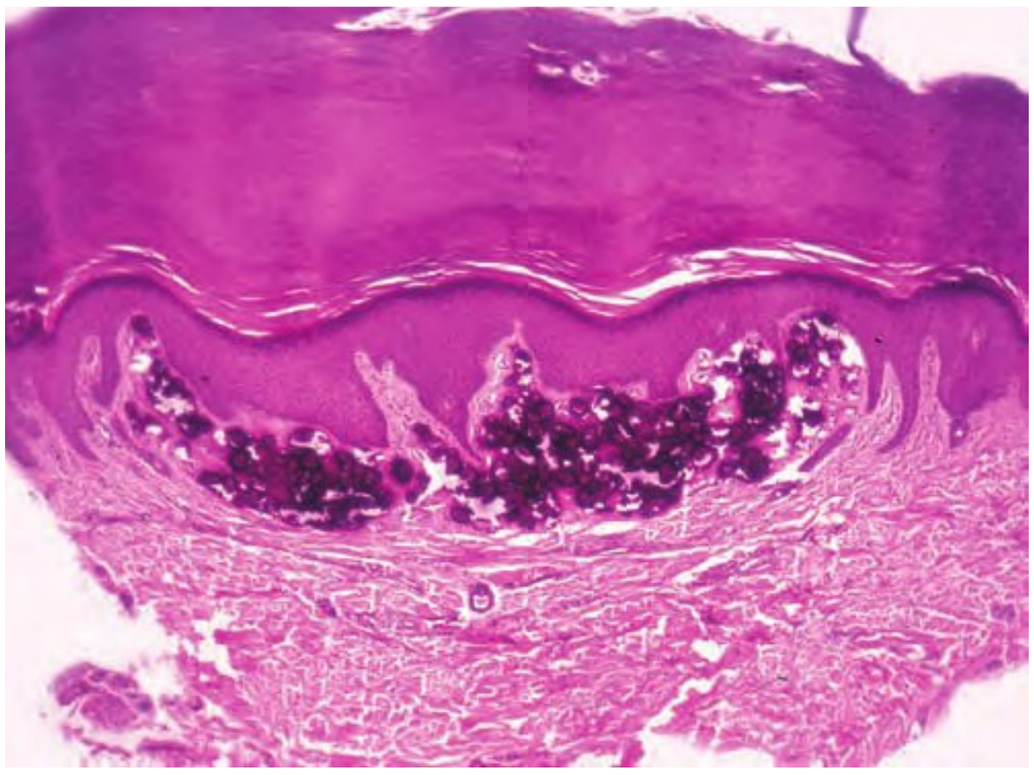


FIGURE 17-15. Subepidermal calcified nodule. A large deposit of calcium in the dermis distorts the overlying epidermis (H&E).



FIGURE 17-16. Gouty tophi. There are yellow-white urate deposits on the elbow.

does not appear until adulthood (177). In most instances, the surface of the nodule is verrucous, but it may be smooth. The most common location of the nodule is the face.

Histopathology. The calcified material is located predominantly in the uppermost dermis, although in large nodules, it may extend into the deep layers of the dermis. The calcium is present largely as closely aggregated globules (Fig. 17-15). In some instances, however, there are also one or several large, homogeneous masses of calcified material (172,173). Both the globules and the homogeneous masses occasionally contain well-preserved nuclei (172). Macrophages and foreign body giant cells may be arranged around the large, homogeneous masses (172). The epidermis is often hypertrophic. Calcium granules may be observed within the epidermis, which is indicative of transepidermal elimination (175,178).

Pathogenesis. The primary event seems to be the formation of large, homogeneous masses that undergo calcification and break up into numerous calcified globules (173). The origin of the homogeneous masses is obscure. It is not likely that they originate from a specific preexisting structure, such as sweat ducts (176) or nevus cells (177), as has been assumed.

GOUT

In the early stage of gout, there usually are irregularly recurring attacks of acute arthritis. In the late stage, deposits of monosodium urate form within and around various joints, leading to chronic arthritis with destruction in the joints and the adjoining bone. During this late stage, urate deposits, called *tophi*, may occur in the dermis and subcutaneous tissue. The incidence of tophaceous lesions in gout has significantly decreased since 1950, from 14% to 3%, even though the incidence of gout has remained unchanged. Improved methods of treatment account for this decrease (179).

Tophi are observed most commonly on the helix of the ears, over the bursae of the elbows, and on the fingers and toes (180) (Fig. 17-16). They may attain a diameter of several centimeters. When large, tophi may discharge a chalky material. In rare instances, gout may present as tophi on the fingertips or as panniculitis on the legs without the coexistence of a gouty arthritis (181–183).

Histopathology. For the histologic examination of tophi, fixation in absolute ethanol or an ethanol-based fixative, such as Carnoy's fluid, is preferable to fixation in formalin; it has been stated that aqueous fixatives such as formalin dissolve the characteristic urate crystals, leaving only amorphous material (184). However, some authors contend that formalin-fixed, paraffin-embedded tissue that is sectioned, floated in alcohol (as opposed to a water bath), and then placed onto a slide without staining will display refractile crystals when examined under polarized light (185). An alternate staining protocol to preserve any urate crystals remaining in formalin-fixed tissue after processing also has been forwarded (186).

On fixation in alcohol, tophi can be seen to consist of variously sized, sharply demarcated aggregates of needle-shaped urate crystals lying closely packed in the form of bundles or sheaves (Fig. 17-17). The crystals often have a brownish color and are doubly refractile on polariscopic examination (Fig. 17-18). If a red compensator is used along with polarizing filters in tissue that has been processed to preserve crystals, the crystals will appear yellow when they are parallel to the direction of the compensator and blue when perpendicular to it (187). The aggregates of urate crystals are often surrounded by a palisaded granulomatous infiltrate containing many foreign body giant cells (Fig. 17-17). The urate crystals appear black and the surrounding tissue yellow when the sections are stained with 20% silver nitrate solution (188).

Even when the specimen has been fixed in formalin, the diagnosis of gout can be made without difficulty because of the

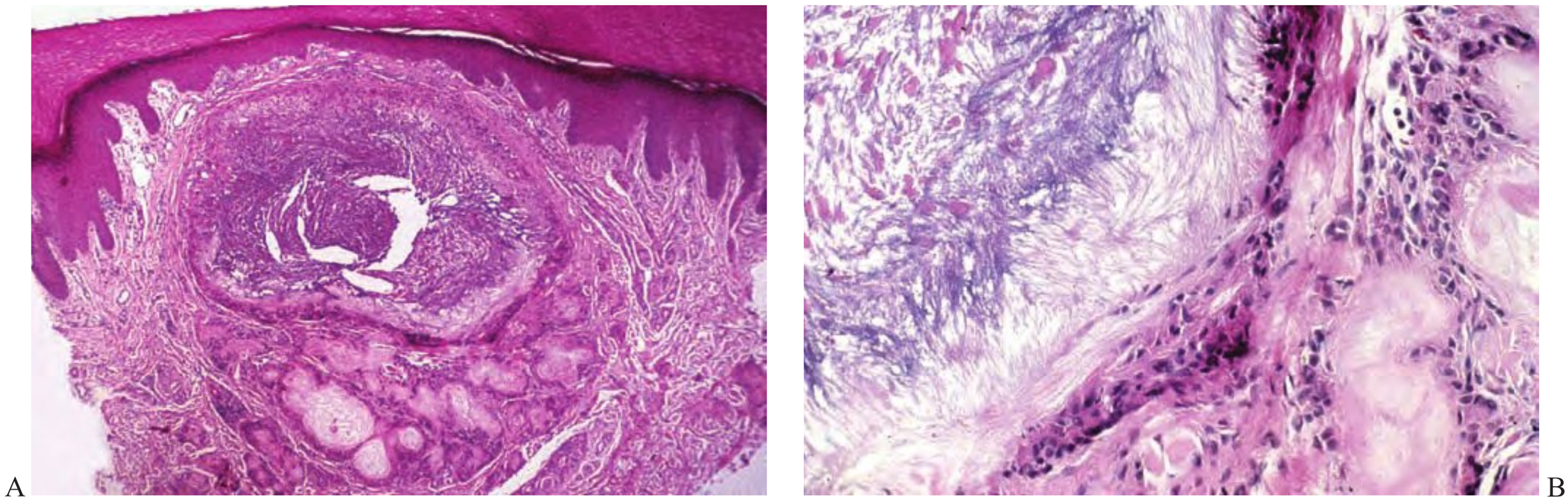


FIGURE 17-17. Gouty tophus. A: There are deposits of urate crystals in the reticular dermis that have a radial array. The lucent areas show where some urate crystals were removed during processing of the tissue (H&E). B: There are macrophages and multinucleated giant cells surrounding the urate deposits in the dermis (H&E).

characteristic rim of foreign body giant cells and macrophages surrounding the aggregates of amorphous material. As a secondary phenomenon, calcification, and occasionally ossification, may take place in the sodium urate aggregates.

Histogenesis. Gout, a dominantly inherited disorder, is characterized by hyperuricemia. An asymptomatic stage of hyperuricemia precedes the development of gouty arthritis by many years. Patients with gout are a heterogeneous group. In some patients, diminished renal excretion of uric acid accounts for the hyperuricemia; in others, an excessive production of uric acid from increased purine biosynthesis is found. In still other patients with gout, both excessive synthesis of uric acid and decreased renal excretion of uric acid are found (189). The deposits of urate crystals stimulate cytokine production, chiefly interleukin-1 (IL-1). IL-1 is a central mediator of the neutrophil recruitment and activation that is characteristic of joint disease (but not a feature in dermal disease) (190).

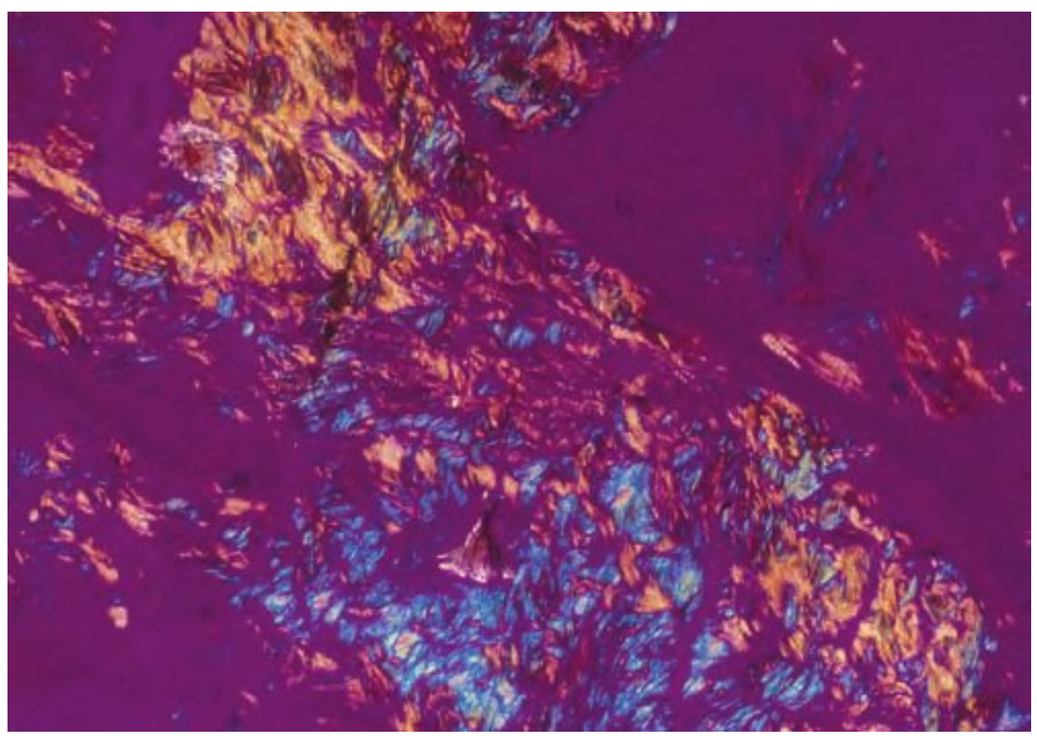


FIGURE 17-18. Gouty tophus. Polarization with a red filter reveals birefringent blue urate crystals in a gouty tophus.

OCHRONOSIS

There are two types of ochronosis: endogenous ochronosis (alkaptonuria), which is inherited as an autosomal recessive trait, and localized exogenous ochronosis, which is prototypically caused by the topical application of a hydroquinone cream to exposed parts of the skin in order to lighten the color of dark skin.

As the result of the lack of homogentisic acid oxidase in endogenous ochronosis, homogentisic acid accumulates over the course of years in many tissues—especially in the cartilages of the joints, the ears, and the nose; in ligaments and tendons; and in the sclerae. This results in osteoarthritis; in blackening of cartilages, ligaments, and tendons; and in patchy pigmentation of the sclerae. In one unusual case, the presenting complaint was pigmentation of the palms and soles with overlying hyperkeratosis and pitting (191). Intervertebral calcification is a characteristic x-ray finding (191–193). In the course of time, homogentisic acid accumulates in the dermis in sufficient amounts to cause patchy brown pigmentation of the skin. The gene for homogentisic acid oxidase maps to chromosome 3q (193,194).

In localized exogenous ochronosis, there is a macular blue-black hyperpigmentation of portions of the face to which the hydroquinone cream or other responsible agent was applied (195) (Fig. 17-19). In more severely involved areas, blue-black papules, milia, and nodules can occur. A condition termed *pseudo-ochronosis* has been recently described as a histopathologic finding in localized argyria occurring primarily in jewelry workers. Clinically, these patients present with blue-black macules ("blue nevus-like") typically on the upper extremities (196).

Histopathology. Involvement of the skin is essentially identical in endogenous and exogenous ochronosis, although it is often more pronounced in exogenous ochronosis (197). The ochronotic pigment, as seen in sections of the dermis stained

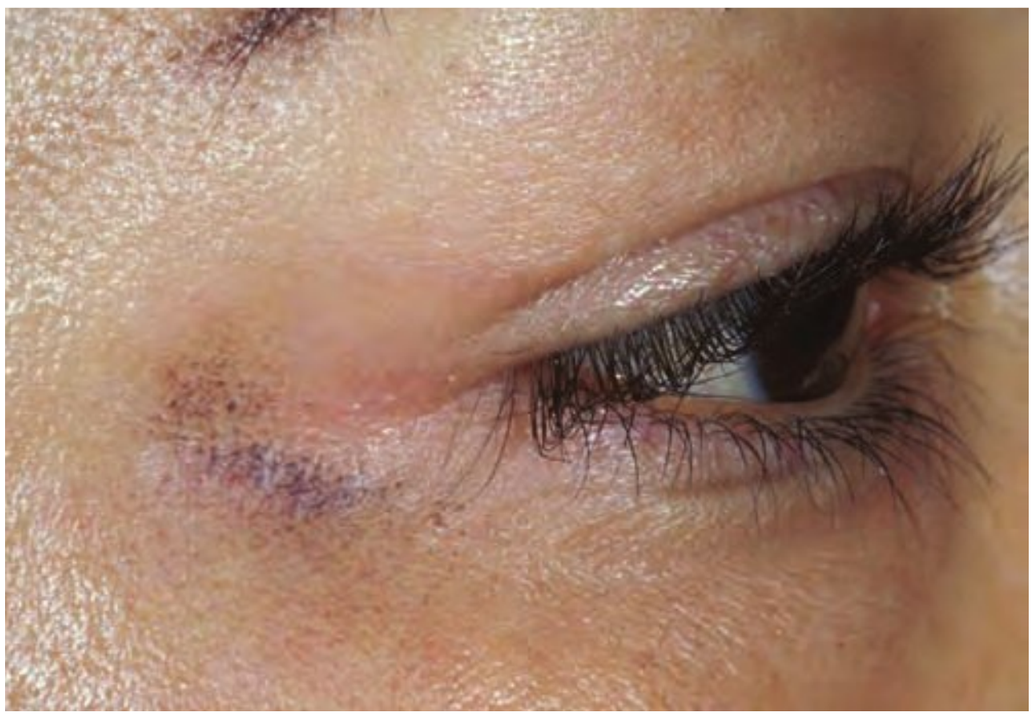


FIGURE 17-19. Exogenous ochronosis. There is stippled, blue-gray pigmentation following long-term use of topical hydroquinone.

with H&E, has a yellow-brown or ochre color; thus, the name *ochronosis*.

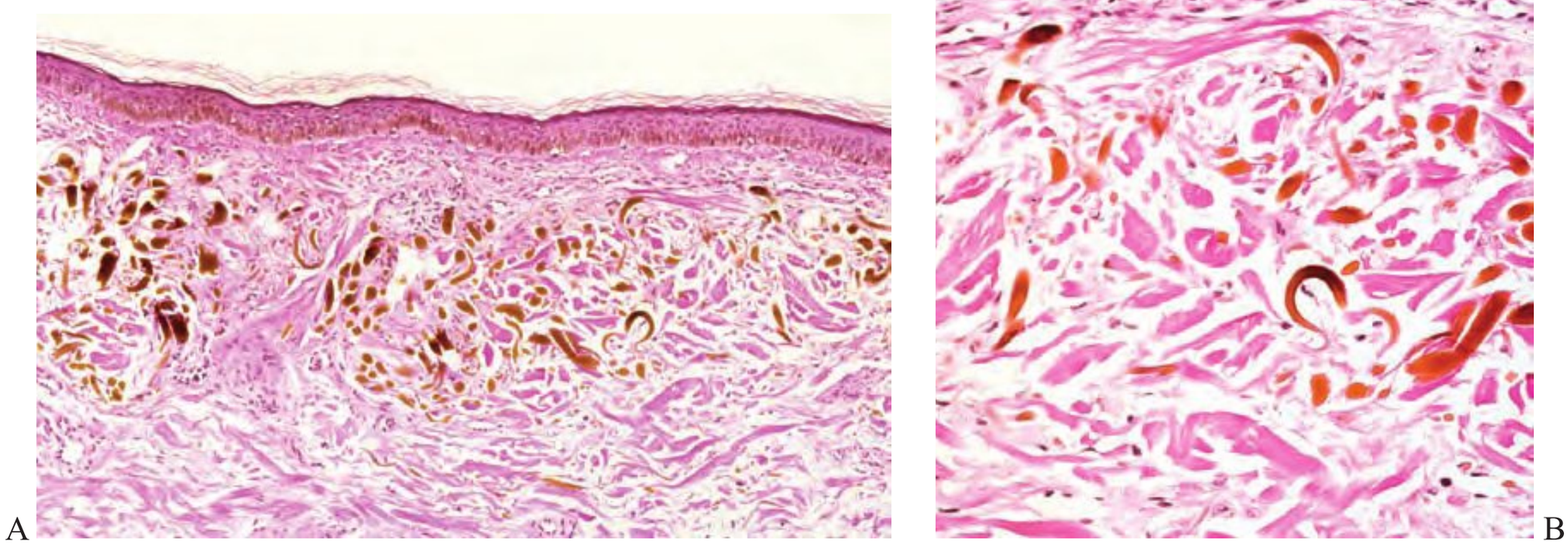
The skin shows ochronotic pigment as fine granules free in the tissue and in the endothelial cells of blood vessels, in the basement membrane and the secretory cells of sweat glands, and within scattered macrophages (198). The most striking finding, however, is the ochronotic pigment within collagen bundles, causing homogenization and swelling of the bundles. Some collagen bundles assume a bizarre shape; they appear rigid and tend to fracture transversely with jagged or pointed ends (199) (Fig. 17-20). As the result of the breaking up of degenerated collagen bundles, irregular, homogeneous, light brown clumps lie free in the tissue. The altered dermal connective tissue does not stain with silver nitrate as melanin does but becomes black when stained with cresyl violet or methylene blue (200). In addition, ochronotic pigment can be found within elastic fibers (201). In nodular ochronosis, a granulomatous response surrounds this material (202). Transfollicular elimination of ochronotic fibers may occur in patients with severe disease (203).

In pseudo-ochronosis, features similar to ochronosis are present in the form of prominent collagen bundles that are yellow-brown in color. In addition, most cases have shown "ellipsoid black globules" of silver within the dermis (196).

Pathogenesis. In *endogenous ochronosis*, because of an inborn lack of homogentisic acid oxidase, the two amino acids tyrosine and phenylalanine cannot be catabolized beyond homogentisic acid. Most of the homogentisic acid is excreted in the urine. The urine, on standing or after the addition of sodium hydroxide, turns black (alkaptonuria) because, through oxidation and polymerization, homogentisic acid is converted into a dark-colored insoluble product. However, some of the homogentisic acid gradually accumulates in certain tissues. It is bound irreversibly to collagen fibers as a polymer after oxidation to benzoquinone-acetic acid (190,204).

In *exogenous ochronosis*, a topical agent such as hydroquinone, resorcinol, phenol, mercury, picric acid or benzene, or a systemic medication such as quinine or antimalarials inhibits the activity of homogentisic acid oxidase in the skin, resulting in the local accumulation of homogentisic acid, which polymerizes to form ochronotic pigment (205,206). In effect, this process mimics the cutaneous manifestation of endogenous ochronosis (197).

Pseudo-ochronosis appears to be due to deposits of traumatically implanted silver onto collagen bundles (196).



A B

FIGURE 17-20. Exogenous ochronosis. Yellowish orange–colored collagen bundles are present in the superficial reticular dermis. Some are abnormally thickened (A: H&E, original magnification ×100; B: H&E, original magnification ×200.)

On electron microscopic examination of early lesions, deposition of amorphous, electron-dense ochronotic pigment around individual collagen fibrils within collagen fibers is observed (192). This causes the collagen fibrils to lose their periodicity and to degenerate. Gradually, the collagen fibrils disappear as they are replaced by ochronotic pigment. Ultimately, the ochronotic pigment occupies entire collagen fibers and, by fusion, entire collagen bundles (207). Cross-sections of the bundles then reveal a large, homogeneous, electron-dense aggregate that in some instances shows remnants of collagen fibrils at its periphery as well as macrophages containing particles of ochronotic pigment (201,208). Particles of ochronotic pigment can also be found in elastic fibers (201). In pseudoochronosis, scanning electron microscopy demonstrates silver deposited on collagen fibers (196).

MUCINOSES

There are six types of cutaneous mucinosis: (a) generalized myxedema, (b) pretibial myxedema, (c) lichen myxedematosus or papular mucinosis, (d) reticular erythematous mucinosis or plaquelike mucinosis, (e) self-healing juvenile cutaneous mucinosis, and (f) scleredema.

Regular demonstration of the presence of mucin in the dermis is possible only in pretibial myxedema, self-healing juvenile cutaneous mucinosis, and lichen myxedematosus. In reticular erythematous mucinosis, it is possible in most cases. In generalized myxedema, the amount of mucin usually is too small to be demonstrable, and in scleredema, mucin may be present only in the early stage.

The mucin found in these six diseases represents an increase in the mucin that is normally present in the ground substance of the dermis. It consists of proteins bound to hyaluronic acid (hyaluronan), which is an acid mucopolysaccharide or glycosaminoglycan. As a result of the great water-binding capacity of hyaluronic acid, dermal mucin contains a considerable amount of water. This water is largely removed during the process of dehydration of the specimen; consequently, in routine sections, the mucin, because of its marked shrinkage, appears largely as threads and granules.

The mucin present in the six types of mucinosis stains a light blue in sections stained with H&E. It also stains with colloidal iron. It is Alcian blue–positive at pH 2.5 but negative at pH 0.5 and shows metachromasia with toluidine blue at pH 7.0 and 4.0 but no metachromasia below pH 2.0 (209). It is PAS negative (indicating the absence of neutral mucopolysaccharides) and aldehyde fuchsin negative (indicating the absence of sulfated acid mucopolysaccharides). The mucin is completely removed on incubation of histologic sections with testicular hyaluronidase for 1 hour at 37°C (210).

Generalized Myxedema

In generalized myxedema, caused by hypothyroidism, the entire skin appears swollen, dry, pale, and waxy. It is firm to the touch. Despite its edematous appearance, the skin does not pit on pressure. There is often a characteristic facial appearance: the nose is broad, the lips are swollen, and the eyelids are puffy.

Histopathology. The epidermis may show slight orthohyperkeratosis and follicular plugging. Usually, routinely stained sections show no abnormality in the dermis, except in severe cases, in which one may observe swelling of the collagen bundles with splitting up of the bundles into individual fibers with some blue threads and granules of mucin interspersed (211). However, with histochemical stains, such as colloidal iron, Alcian blue, or toluidine blue, it is possible, at least in severe cases, to demonstrate small amounts of mucin, mainly in the vicinity of the blood vessels and hair follicles.

Pretibial Myxedema

Usually, the lesions are limited to the anterior aspects of the legs, but they may extend to the dorsa of the feet. They consist of raised, nodular, yellow, waxy plaques with prominent follicular openings that give a peau d'orange appearance (Fig. 17-21). Similar lesions rarely occur on the radial aspect of the forearms (212).

Pretibial myxedema usually occurs in association with thyrotoxicosis and not infrequently becomes more pronounced after treatment of the thyrotoxicosis. It nearly always occurs in association with exophthalmos, and 15% to 20% also have acropachy (213). Complete remission occurs in about 25% of cases (213). Rarely, pretibial myxedema, with or without exophthalmos, occurs in nonthyrotoxic thyroid disease such as chronic lymphocytic thyroiditis; the patient is then either euthyroid or hypothyroid (214).

Histopathology. The epidermis and papillary dermis are usually normal. Mucin in large amounts is present in the dermis,

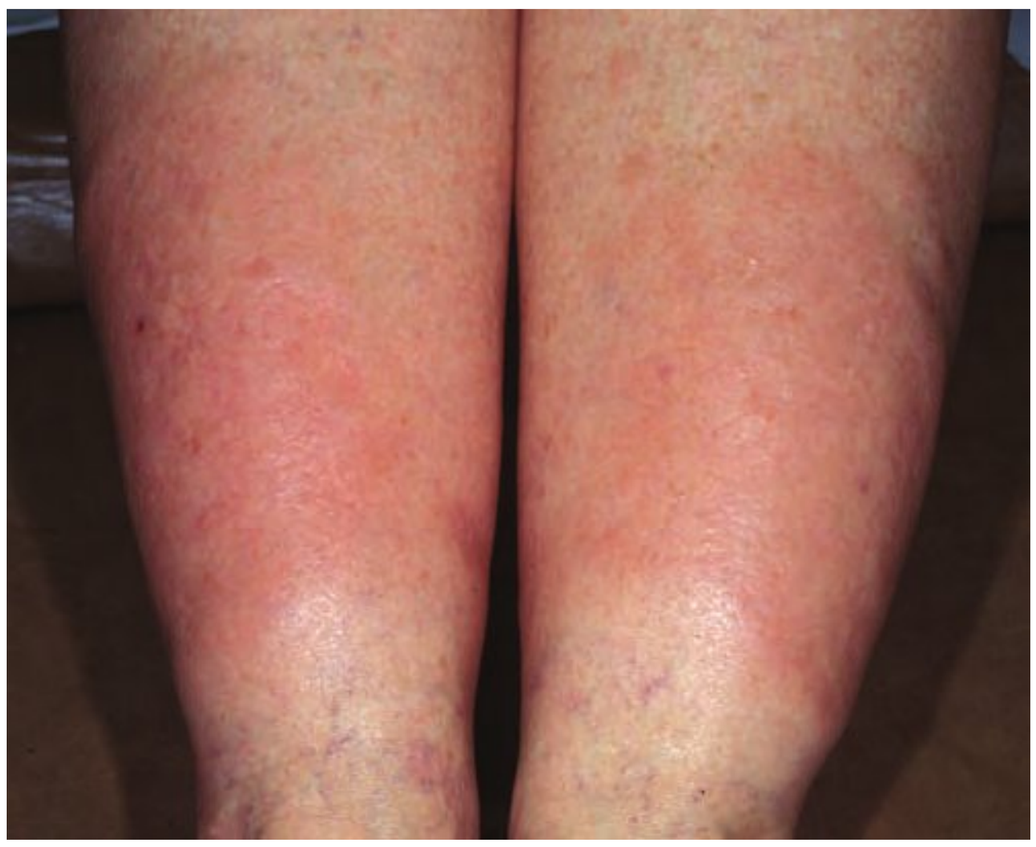


FIGURE 17-21. Pretibial myxedema. There are waxy infiltrated yellow-erythematous plaques on the anterior lower legs.

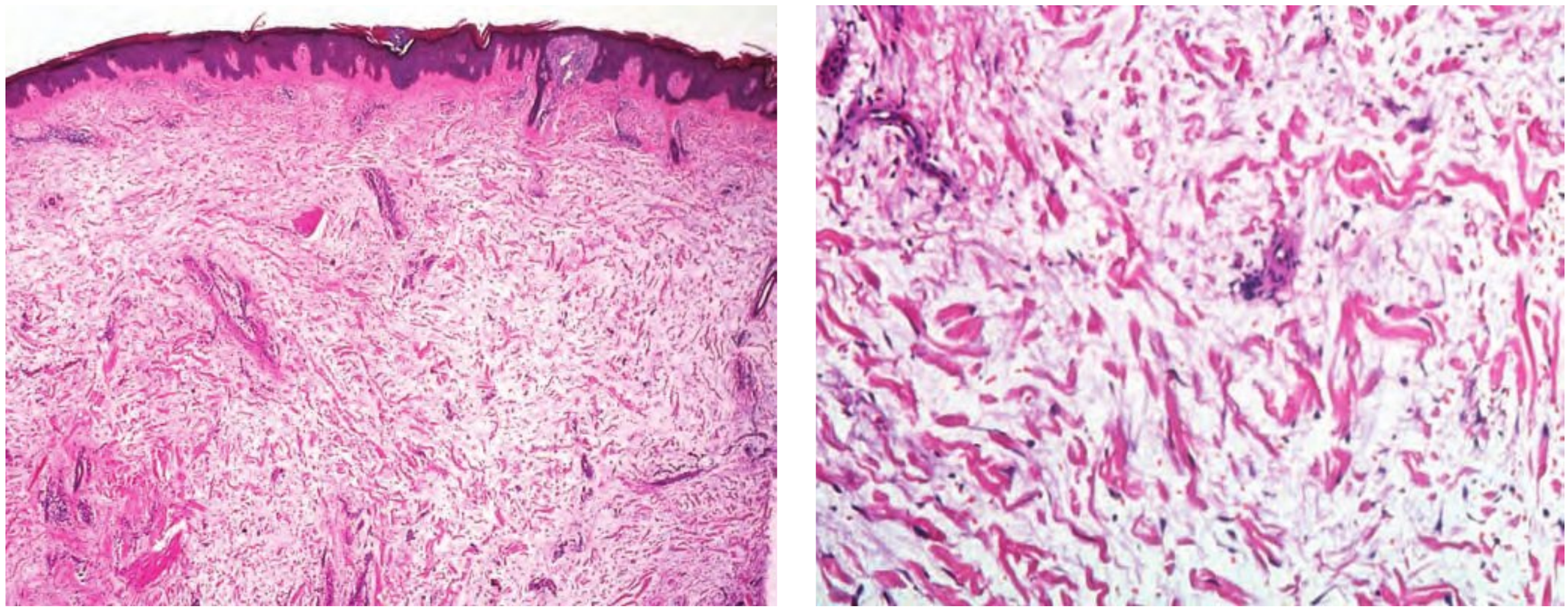


FIGURE 17-22. Pretibial myxedema. A: At scanning magnification, the epidermis and papillary dermis are normal. The collagen fibers in the reticular dermis are widely separated by deposits of mucin (H&E). B: At higher magnification, stellate fibroblasts are evident among the separated collagen fibers (H&E).

particularly in the upper half (Fig. 17-22). As a result, the dermis is greatly thickened. The mucin occurs not only as individual threads and granules but also as extensive deposits resulting in the splitting up of collagen bundles into fibers and wide separation of the fibers. As a result of shrinkage of the mucin during the process of fixation and dehydration, there are empty spaces within the mucin deposits. The number of fibroblasts is not increased as a rule, but in areas where there is much mucin, some fibroblasts have a stellate shape and are then referred to as *mucoblasts* (213,215). A perivascular infiltrate of lymphocytes may be seen in some cases, and mast cells are moderately increased in number (213,215).

Pathogenesis. On electron microscopic examination, the collagen bundles and fibers are separated by wide, electron-lucent, empty spaces. The fibroblasts that produce the mucin are stellate shaped with long, thin cytoplasmic processes and exhibit dilated cisternae of the rough endoplasmic reticulum. An amorphous, moderately electron-dense material coats the surface of the fibroblasts. This material is also present in small, irregular clumps within the otherwise empty-appearing spaces (216). At high magnification, the amorphous material appears as a complex of microfibrils and granules, forming a network (217).

Of interest is the almost invariable presence of long-acting thyroid stimulator (LATS) in the serum of patients with pretibial myxedema. There is, however, a rather poor correlation between the severity of the skin lesions and the level of serum LATS; furthermore, LATS is detected in 40% to 60% of patients with an active exophthalmic goiter but without pretibial myxedema. Thus, LATS cannot be regarded as the cause of pretibial myxedema (218). It is likely that the IgG LATS represents an autoantibody that is produced by lymphocytes in thyroid disease, especially in thyrotoxicosis, and is a reflection rather than a cause of the underlying disease (214).

The restriction of the myxedema largely to the pretibial area may be explained by the finding that fibroblasts from the pretibial area synthesize two to three times more hyaluronic acid than do fibroblasts from other areas when incubated with serum from patients with pretibial myxedema (219). The receptor for thyroid-stimulating hormone (TSH-R) is a candidate as the common tissue antigen in Grave's disease, exophthalmos, and pretibial myxedema. TSH-R immunoreactivity has been detected on fibroblasts in the dermis of control patients without thyroid disease (216).

Differential Diagnosis. Pretibial myxedema must be differentiated from pretibial mucinosis associated with venous stasis. In pretibial mucinosis, the excess mucin is localized to the thickened papillary dermis and is accompanied by angioplasia and siderophages (220).

Lichen Myxedematosus

Lichen myxedematosus, or papular mucinosis, is characterized by a more or less extensive eruption of asymptomatic, soft papules generally 2 to 3 mm in diameter, associated with a monoclonal gammopathy. Although densely grouped, they usually do not coalesce. The face and arms are the most commonly affected areas (Fig. 17-23). In some instances, in addition to papules, large nodules may be present, especially on the face (221). Although the disease is very chronic, spontaneous resolution has been reported (222).

In a variant of lichen myxedematosus called *scleromyxedema*, a generalized eruption of papules as in lichen myxedematosus and, in addition, diffuse thickening of the skin associated with

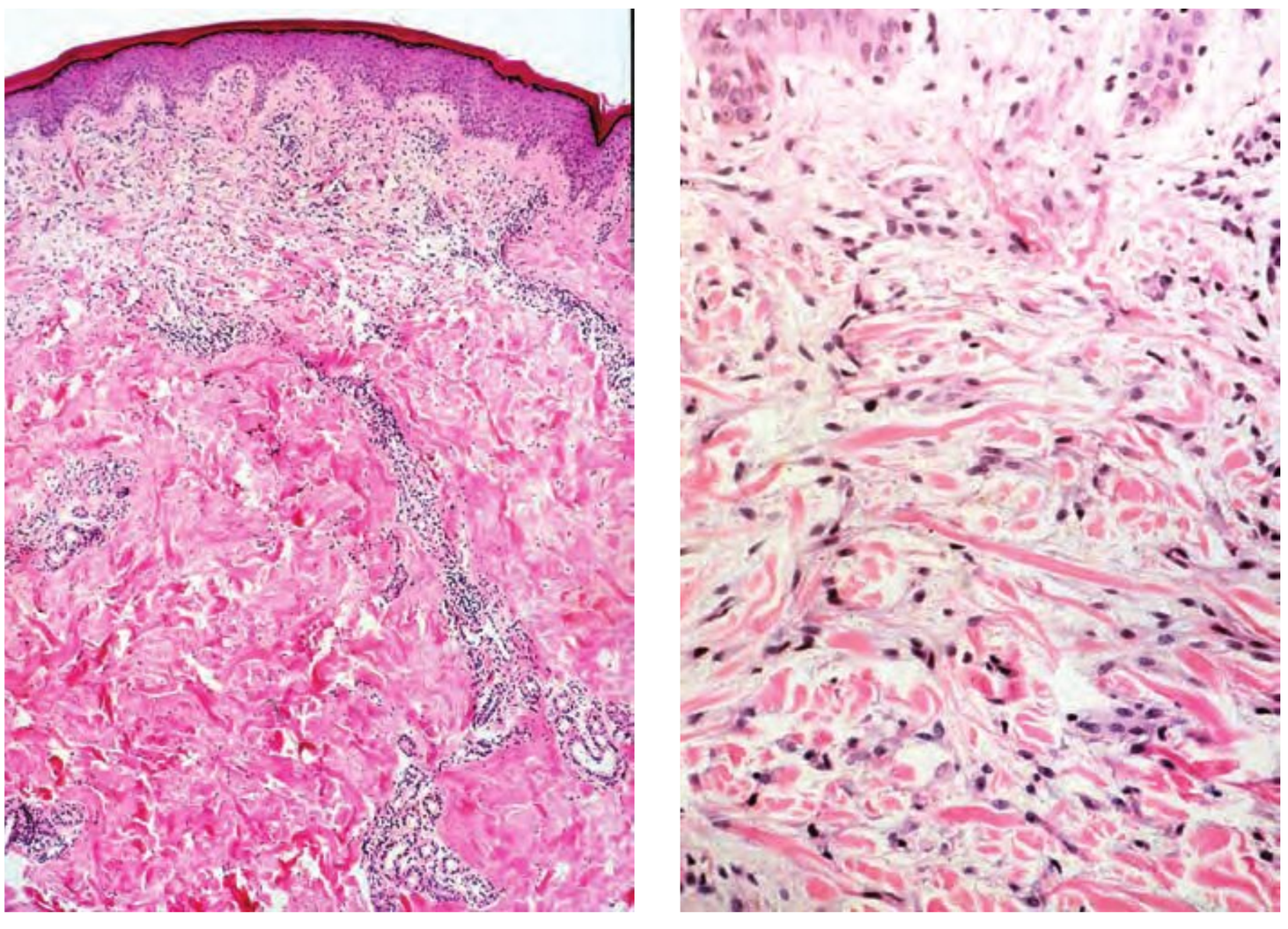


FIGURE 17-23. Lichen myxedematosus. There are numerous firm papules on the face and ear. Note the linear arrangement of the papules near the angle of the jaw.

erythema are found. There is marked accentuation of the skin folds, particularly on the face. Scleromyxedema can be differentiated from scleroderma clinically by the papular component and the absence of telangiectasias. Transitions of lichen myxedematosus to scleromyxedema do occur. Acral persistent papular mucinosis presents multiple small papular lesions on the hands and forearms (223). The clinical and histopathologic features resemble the discrete papular form of lichen myxedematosus (224). The detection of immunoglobulin A (IgA) monoclonal gammopathy in one case also suggests that it is a localized variant of lichen myxedematosus (225). Cutaneous mucinosis of infancy may also represent a localized form of papular mucinosis on the upper extremities unassociated with monoclonal gammopathy (226). It may remit spontaneously (227).

Multiple dome-shaped papules with histopathologic features suggestive of papular mucinosis have been noted in Birt-Hogg-Dube syndrome (228).

Histopathology. In lichen myxedematosus, fairly large amounts of mucin are present. In contrast with pretibial myxedema, however, the mucinous infiltration is found only in circumscribed areas, is most pronounced in the upper dermis, and is associated with an increase in fibroblasts and collagen (229,230) (Fig. 17-24). The collagen bundles may show a rather irregular arrangement.



A B

FIGURE 17-24. Lichen myxedematosus. A: At scanning power, a dome-shaped papule is evident. The papillary and superficial reticular dermis contain abundant mucin (H&E). B: In addition to mucin, there is an increased number of plump fibroblasts in the upper dermis (H&E).

Scleromyxedema

The histologic picture found in the papules in scleromyxedema resembles that observed in lichen myxedematosus. In the diffusely thickened skin, there is extensive proliferation of fibroblasts throughout the dermis associated with irregularly arranged bundles of collagen. In many areas, the collagen bundles are split into individual fibers by mucin. As a rule, the amount of mucin is greater in the upper half than in the lower half of the dermis.

Scleromyxedema may be difficult to distinguish from nephrogenic fibrosing dermopathy without clinicopathologic correlation. Both conditions are characterized by a dermal infiltrate of spindle cells with increased mucin and collagen. In both conditions, the spindle cells label for either factor XIIIa or CD34 and procollagen1 without demonstrating a pattern that could be utilized to discriminate between these diseases (231). However, in scleromyxedema, the infiltrate is limited to the dermis whereas in nephrogenic fibrosing dermopathy the infiltrate usually also extends down the subcutaneous septa (231).

Autopsy examination of patients with lichen myxedematosus and scleromyxedema usually has not shown mucinous deposits in any internal organs (230,232). However, in one case, mucin was detected in renal papillae, and in others, it was found in the adventitia and media of blood vessels in several organs (233–235).

Pathogenesis. Electron microscopic examination of scleromyxedema reveals an increase in the number of fibroblasts. They show considerable activity, as indicated by the presence of a markedly dilated rough endoplasmic reticulum and long cytoplasmic processes. These fibroblasts produce both collagen and ground substance. The presence of many collagen fibrils with reduced diameter, similar to those in scleroderma, indicates that it is young collagen. In many areas, there are small bundles of young collagen fibrils, with each fibril richly coated with ground substance (236).

The presence of a *monoclonal component* (M component) or paraprotein in the sera of patients with lichen myxedematosus and scleromyxedema has been noted in nearly all cases that have been adequately tested. Its absence has been noted in a few cases (237); in another case, it was absent at first but present later on (238).

In nearly all instances, the paraprotein is an IgG, although other immunoglobulin classes occur on rare occasions (232,239). The IgG paraprotein is a very basic protein because of an increased lysine content in its light chains (240). Thus, in most instances, it migrates more slowly than gamma globulin on serum electrophoresis and may even migrate toward the cathode rather than toward the anode (241). In instances in which it migrates with the same speed as gamma globulin, immunoelectrophoresis is required for its recognition (242). The IgG of lichen myxedematosus differs from the IgG of multiple myeloma not only by usually showing slower electrophoretic migration but also by the fact that its IgG molecules nearly always possess light chains of the lambda type, although light chains of the kappa type have occasionally been found (243,244). In contrast, in multiple myeloma with elevated values for IgG, only about one third of the reported cases with IgG molecules have lambda light chains, and two thirds have kappa light chains (245). In addition to showing a monoclonal IgG, many cases of lichen myxedematosus show hyperplasia of plasma cells in the bone marrow (232,233,242,246). These plasma cells have been shown to synthesize the monoclonal IgG (244). In some cases, the plasma cells in the bone marrow have been regarded as atypical in appearance (247). However, only one case fulfilling the criteria for coexisting multiple myeloma has been documented (248).

The role of the monoclonal IgG in lichen myxedematosus is not clear. Its presence in the dermal mucin has been demonstrated by direct immunofluorescence (247,249,250). Furthermore, the serum containing the paraprotein stimulates the production of hyaluronic acid and prostaglandin E by fibroblasts *in vitro* (251). However, although the serum from patients with lichen myxedematosus stimulates fibroblast proliferation *in vitro*, the purified IgG paraprotein itself has no direct effect on fibroblast proliferation (252).

Reticular Erythematous Mucinosis

Erythematous, reticulated areas with irregular but well-defined margins are present, usually in the center of the chest and of the upper back (Fig. 17-25). This disorder was first described in 1960 as being composed of confluent papules and was called *plaquelike mucinosis*, but similar cases showing coalescent macules, rather than papules, were designated as *reticular erythematous mucinosis* in 1974 (253,254). It has since become apparent that macular and papular lesions can coexist (255). In rare instances, lesions spare the trunk and are present on the arms and face (256). The eruption is asymptomatic. It is chronic but usually responds well to small doses of antimalarial drugs of the 4-aminoquinoline group, such as chloroquine. It may be a presenting sign of systemic lupus erythematosus (257).

Histopathology. Two histologic features are usually present: small amounts of dermal mucin and a mild or moderately pronounced mononuclear infiltrate situated predominantly



FIGURE 17-25. Reticular erythematous mucinosis. There is a netlike (reticulated) pattern of erythema involving the neck and upper chest.

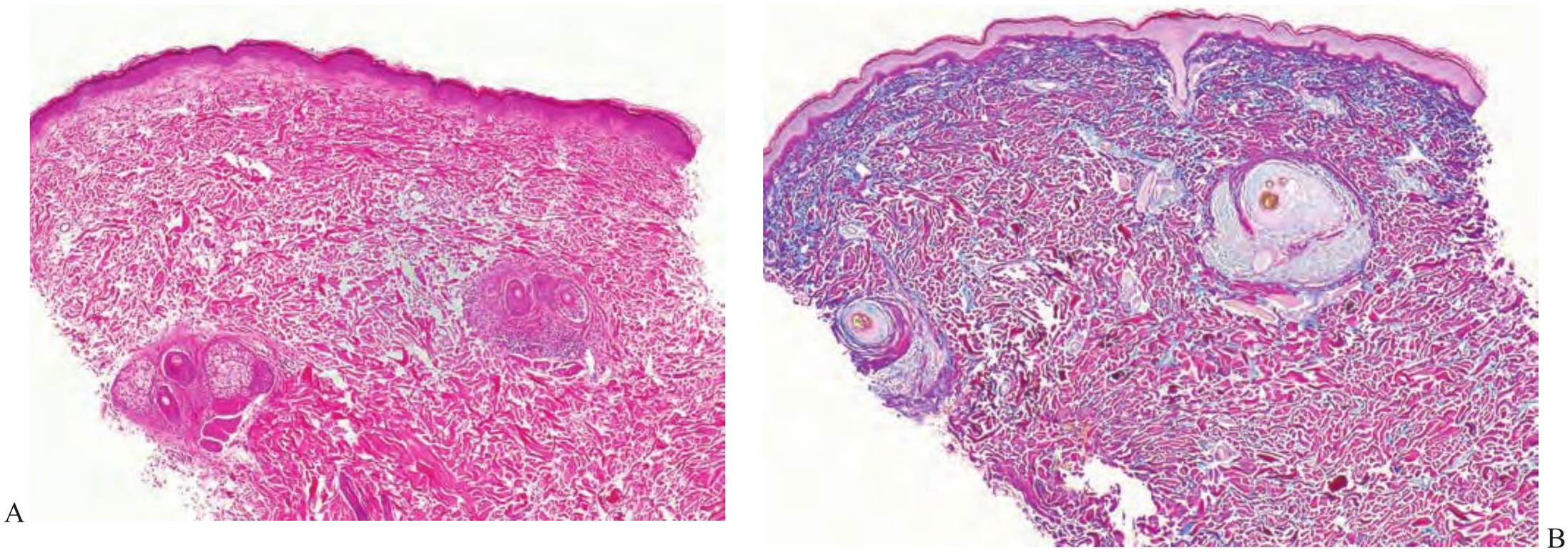


FIGURE 17-26. Reticular erythematous mucinosis. A: There is a sparse superficial perivascular and perifollicular infiltrate of lymphocytes around blood vessels in the dermis (H&E). B: Colloidal iron staining reveals abundant mucin among collagen fibers.

around blood vessels and hair follicles (253,254). The infiltrate is composed of helper T cells (258).

In papular lesions, the mucin usually is fairly conspicuous. As a rule, mucin can be recognized even in routinely stained sections (Fig. 17-26). The mucin stains with Alcian blue and usually also with mucicarmine. In addition, there often is metachromasia on staining with toluidine blue or with the Giemsa stain (253,254). Fibroblasts with bipolar processes are located in the mucinous deposits (259). Immunohistochemistry has revealed a significantly increased number of factor XIIIa dendritic cells in the lesional skin of a patient with reticular erythematosus mucinosis but not in the patient's uninvolved skin or normal control skin samples (260). These same cells also demonstrated immunoreactivity for one isoform of hyaluronan synthase (260).

In macular lesions, the mucin may be missed in routinely stained sections and become apparent only on staining with Alcian blue. In some instances, no mucin is found, even on staining with Alcian blue (261), but if an Alcian blue stain is negative in paraffin-embedded sections, it may be positive in unfixed, frozen sections (262). If this is negative as well, the diagnosis depends on the presence of the mononuclear infiltrate, the clinical appearance, and the response of the patient to treatment with antimalarial drugs.

Differential Diagnosis. Reticular erythematous mucinosis, Jessner's lymphocytic infiltrate of skin, and lupus erythematosus may share in common a perivascular and perifollicular lymphocytic infiltrate and increased mucin among collagen bundles. In Jessner's lymphocytic infiltrate, the lymphocytic infiltrate is usually much denser than that in reticular erythematous mucinosis. Lupus erythematosus almost always shows vacuolar changes in the basal layer of the epidermis and follicular units, but in the rare tumid lesions, vacuolar changes may be inconspicuous. Thus, it may not be possible to distinguish between the tumid lesions of lupus erythematosus and reticular erythematous mucinosis by conventional microscopy. Furthermore, flesh-colored papules and nodules situated on the trunk and demonstrating increased dermal mucin may precede or accompany systemic lupus erythematosus or progressive systemic sclerosis (263). Clinicopathologic correlation is essential in distinguishing these conditions.

Self-Healing Juvenile Cutaneous Mucinosis

Self-healing juvenile cutaneous mucinosis is a rare dermatosis that has been described only in children. It has a sudden onset and undergoes spontaneous resolution within a few months. Infiltrated plaques with a corrugated surface are observed on the torso, and nodules occur on the face and in the periarticular region. Nontender ivory papules in a linear configuration may also occur. There may be associated fever, arthralgias, muscle tenderness, and weakness (264).

Histopathology. Abundant mucinous material, which is Alcian blue positive at pH 2.5, is present mainly in the upper reticular dermis. There may be a superficial perivascular lymphocytic infiltrate and a slight increase in the number of mast cells and fibroblasts in the zone of mucin deposition. Nodular lesions may show a septolobular panniculitis-like pattern with abundant mucin in the expanded fat lobules (265). There may be a proliferation of delicate spindle cells and an infiltrate of lymphocytes. Epithelioid gangliocyte-like mononuclear cells may be present. The histopathologic changes can be confused with proliferative fasciitis. The presence of increased mucin in the papillary and reticular dermis favors self-healing mucinosis.

Scleredema

Scleredema, occasionally called *scleredema adultorum* even though it may occur in children and infants, is characterized by diffuse, nonpitting swelling and induration of the skin (266,267). Three groups can be recognized (268): one with abrupt onset, one with insidious onset, and one preceded by diabetes. In the first group, the scleredema starts abruptly during or within a few weeks after an upper respiratory tract infection. The

skin lesions may clear within a few months, or the disease may take a prolonged course. In the second group, the scleredema starts insidiously, for no apparent reason; spreads gradually; and takes a chronic course. The disease in the third group is preceded by diabetes for years, starts insidiously, and persists indefinitely. Usually, the scleredema starts on the face and extends to the neck and upper trunk. Unlike scleroderma, the hands and feet are always spared. In about 75% of patients, complete resolution takes place within a few months; in the remaining 25%, the disease may persist for as long as 40 years (269). Although visceral lesions may occur, death from scleredema is rare.

Diabetes is commonly associated with persistent scleredema and in most of these instances is quite resistant to antidiabetic therapy (269). It has been suggested that the association of persistent scleredema with maturity-onset diabetes be recognized as a special form of scleredema (270).

Histopathology. The dermis in scleredema is about three times thicker than normal (Fig. 17-27). The collagen bundles are thickened and separated by clear spaces, causing "fenestration" of the collagen. The secretory coils of the sweat glands, surrounded by fat tissue, are located in the upper dermis or mid dermis rather than, as normally, in the lower dermis or at the junction of the dermis and the subcutaneous fat. Because the distance between the epidermis and the sweat glands is unchanged, it can be concluded that much of the subcutaneous fat in scleredema has been replaced by dense collagenous bundles (271). No increase in the number of fibroblasts is noted in association with the hyperplasia of the collagen; in fact, their number may be strikingly decreased (272).

In many instances, especially in early cases, histochemical staining reveals the presence of hyaluronic acid between the bundles of collagen, particularly in the areas of fenestration. Staining with toluidine blue usually reveals metachromasia, which is most evident at pH 7.0, weaker at pH 5.0, and absent at pH 1.5, indicating the presence of only nonsulfated acid mucopolysaccharides (209). Although the hyaluronic acid is usually present throughout the dermis, it may be present only in the deeper portion of the dermis (273) (Fig. 17-28).

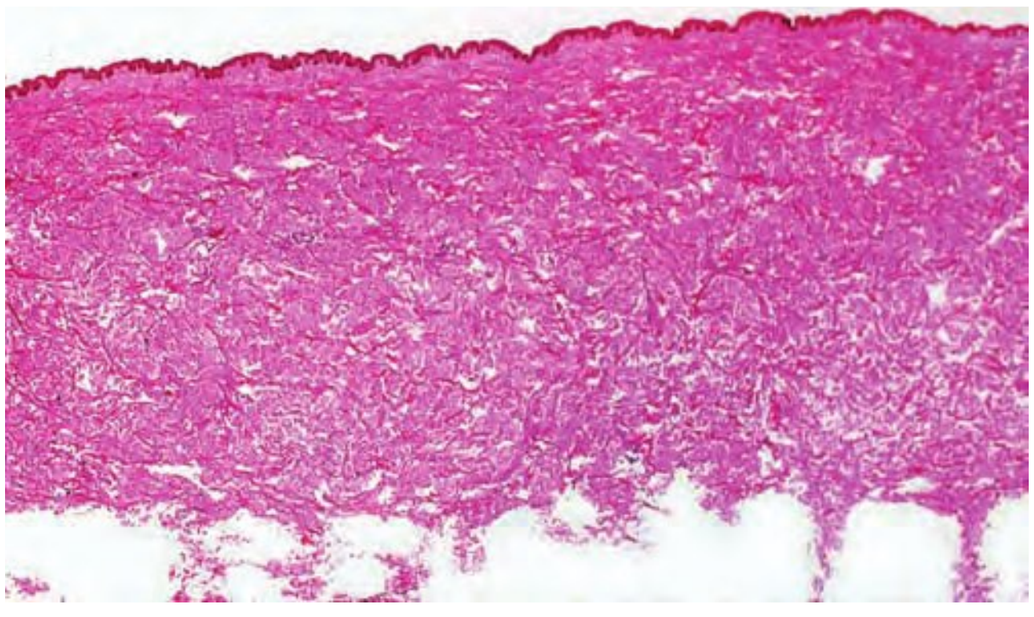


FIGURE 17-27. Scleredema. Panoramic view showing only a greatly thickened reticular dermis. The subcutis is not involved as in scleroderma (H&E).

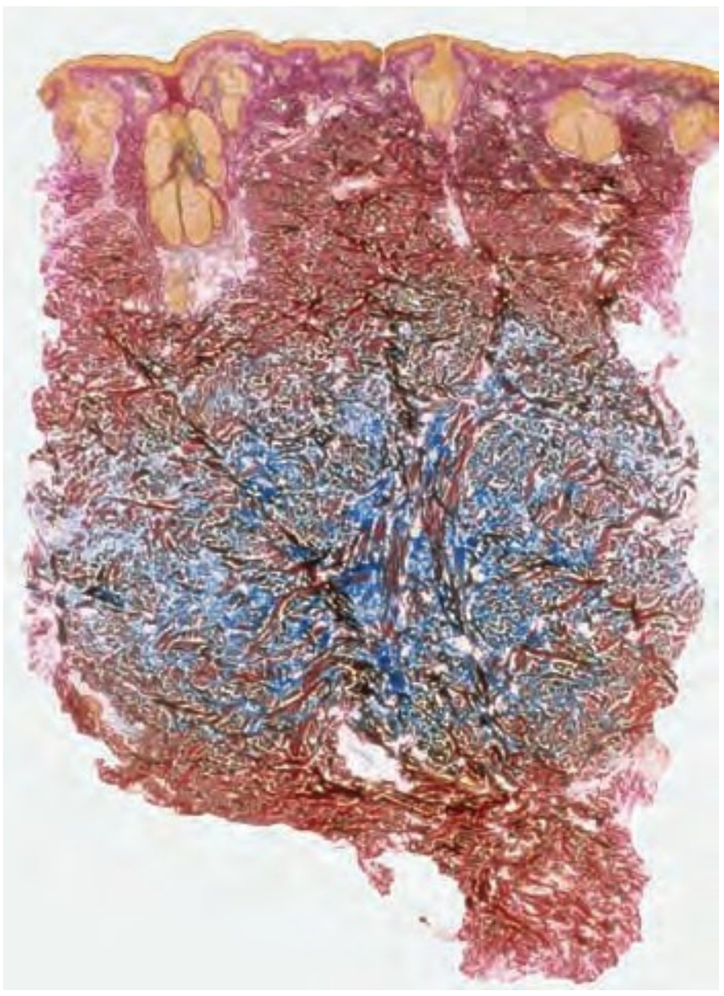


FIGURE 17-28. Scleredema. Colloidal iron staining of an early case reveals increased mucin in the middle and lower dermis.

In some instances, staining with toluidine blue at pH 7.0 is more intense if unfixed cryostat sections are used in place of formalin-fixed material (274). In some cases, even frozen sections have failed to stain with Alcian blue or toluidine blue (275). It may be postulated that in long-standing cases in which the disease has reached a steady stage of collagen turnover, staining for hyaluronic acid may give negative results (271). In cases of scleredema in which formaldehyde-fixed specimens fail to show acid mucopolysaccharides, they may show them on fixation in 0.05% cetylpyridinium chloride solution and staining with Alcian blue at pH 2.5 (267). It has been stated that fixation with 1% cetylpyridinium chloride solution in standard formalin fixative combined with colloidal iron staining gives the best results (276).

Systemic Lesions. Occasionally, the tongue and some skeletal muscles are involved, and on histologic examination, the muscle bundles show edema and loss of striation (275,277). In a few reported cases, pleural and pericardial effusions were present (275,278). In one case, the disease terminated in death, and autopsy revealed diffuse edema of the heart, liver, and spleen in addition to pleural and pericardial effusions (279).

Pathogenesis. In many patients with long-standing scleredema, a monoclonal gammopathy is found in the serum. Usually, the paraprotein is either IgG kappa or IgG lambda (272). In other cases, it has been IgA kappa, IgA lambda, or IgM lambda (280). There can be coexistence of scleredema with multiple myeloma (281). No immunoglobulin deposits have been found in involved skin sites (272). A marked increase in type 1 collagen gene expression occurs in scleroderma, leading to increased collagen synthesis (282).

Differential Diagnosis. It can be difficult to differentiate between end-stage scleroderma in which inflammation is no

longer present and scleredema. As a rule, however, in scleroderma, the collagen in the reticular dermis and subcutaneous tissue appears homogenized and hyalinized and stains only lightly with eosin and with the Masson trichrome stain, but in scleredema, the collagen bundles are thickened without being hyalinized and stain normally with eosin and the trichrome stain (271). A marked increase in type 1 collagen gene expression occurs in scleroderma, leading to increased collagen synthesis (282).

MUCOPOLYSACCHARIDOSIS

Mucopolysaccharidosis (MPS) comprises a group of storage diseases in which, as the result of a deficiency of specific lysosomal enzymes, there is inadequate degradation of mucopolysaccharides, or glycosaminoglycans. Consequently, this material accumulates within lysosomes of various cells in many organs, including the skin. Greatly elevated levels of mucopolysaccharides are present in the blood, serum, and urine. There are 11 different enzyme deficiencies implicated in development of the 7 major types of MPS (283). Thus, there is marked variation in the manifestations not only from type to type but also within the same type (284). The most common features, any or all of which may be present or absent, include dwarfism, skeletal deformities, hepatosplenomegaly, corneal clouding, and progressive mental deterioration with premature death from cardiorespiratory complications. In many instances, there is a characteristic facial appearance—thick lips, flattened nose, and hirsutism—referred to as *gargoylism*. The mode of transmission is autosomal recessive in all types of MPS except type II, the Hunter syndrome, which is X-linked recessive.

Only MPS types I to III will be discussed in this chapter. MPS I presents as three distinctive variants, even though they are all caused by a deficiency of the same enzyme. MPS I H, Hurler's syndrome, causes severe mental retardation and death, usually within the first decade of life (285). In contrast, persons with MPS I S, Scheie's syndrome, have normal intelligence, no dwarfism, and a normal life expectancy (286). MPS I H/S, the Hurler-Scheie syndrome, is intermediate between MPS I H and MPS I S. MPS II, Hunter's syndrome, occurs in a severe form, with mental retardation and early death, and in a mild form, in which mental function is normal and survival to adult life is the rule (287). MPS III, Sanfilippo's syndrome, has mild somatic changes but severe mental retardation (288).

The skin in all types of MPS usually appears thickened and inelastic. However, the only type in which distinctive cutaneous lesions are found frequently, although not invariably, is MPS II, Hunter's syndrome. These lesions consist of ivory white papules or small nodules, usually 3 to 4 mm in diameter, that may coalesce to form ridges in a reticular pattern on the upper trunk, especially in the scapular region (287,289). This condition has been referred to as *pebbling of the skin*. Grouped papules on the extensor surfaces at the upper portions of the arms and legs has been noted in one patient with the Hurler-Scheie syndrome (MPS I H/S) (290).

Histopathology. In all types of MPS, the normal-appearing or slightly thickened skin, on staining with the Giemsa stain or toluidine blue, shows metachromatic granules within fibroblasts, so the fibroblasts resemble mast cells (285). The granules also stain with Alcian blue and with colloidal iron (286). Fixation in absolute alcohol in some instances demonstrates the metachromasia better than fixation in formalin (291). In addition, metachromatic granules are occasionally present in some epidermal cells and in the secretory and ductal cells of eccrine glands (285,292,293).

The cutaneous papules observed only in Hunter's syndrome show not only metachromatic granules within dermal fibroblasts but also extracellular deposits of metachromatic material between collagen bundles and fibers (289,291).

In all types of MPS, metachromatic granules are visible also in the cytoplasm of circulating lymphocytes when smears of them are stained with toluidine blue after fixation in absolute methanol, a finding that aids in the rapid diagnosis of MPS (294).

Histogenesis. Biochemical studies have shown that in MPS I, as a result of a deficiency in alpha-l-iduronidase, there is an accumulation of heparan sulfate and dermatan sulfate (chondroitin sulfate) (283). Accumulation of dermatan sulfate but not heparan sulfate is linked to impaired elastic fiber assembly, which is thought to contribute to the clinical phenotype in Hurler disease (295). In MPS II, the same two substances are excessively accumulated owing to a deficiency in iduronate sulfatase. In MPS III, there is excessive accumulation of heparan sulfate. Successful bone marrow transplantation in children with Hurler's syndrome can restore the previously deficient alpha-1-iduronidase level (296).

By staining for acid phosphatase and by electron microscopy, the metachromatic granules in the skin and in the lymphocytes have been identified as lysosomes that contain acid mucopolysaccharides, which they are incapable of degrading (293,294).

Electron microscopic examination of the skin reveals in most fibroblasts numerous electron-lucent, greatly dilated, membrane-bound vacuoles representing lysosomes. Some of the vacuoles contain granular material or, less commonly, myelin-like structures representing residual bodies (286). Lysosomes are present also in macrophages, showing the same characteristics as in fibroblasts (288). In addition, from 5% to 20% of the epidermal cells contain lysosomal vacuoles, with acid phosphatase activity, varying from a solitary vacuole to 20 or 30 vacuoles per cell (292).

The dermal Schwann cells also contain electron-lucent lysosomes. In addition, some Schwann cells occasionally show laminated membranous structures ("zebra bodies"). These structures resemble those found in the brains of some patients with MPS. In the brain, they contain gangliosides as the result of a deficiency in the lysosomal hydrolase beta-d-galactosidase (292). The deposition of gangliosides in the brain leads to mental deterioration through the degeneration and loss of neurons.

ACANTHOSIS NIGRICANS

Acanthosis nigricans can be seen in multiple clinical settings: malignancy associated, benign, inherited, obesity associated, syndromic, drug induced, and mixed (297). The malignant

type differs from the benign types by showing more extensive and more pronounced lesions, by its progressiveness, and by its onset usually after 40 years of age. The histologic picture is essentially the same in all types.

The *malignant* type is associated with a malignant tumor—most commonly an abdominal, and particularly a gastric, carcinoma (298). However, it may also occur with squamous cell carcinoma, with sarcomas, and with Hodgkin and non-Hodgkin's lymphomas (297). In some cases, the skin lesions precede the symptoms of malignancy. The sign of Leser-Trélat, which is characterized by the sudden appearance of numerous seborrheic keratoses in association with a malignant tumor, may be an early stage or incomplete form of the malignant type of acanthosis nigricans. The seborrheic keratoses observed in this sign may be accompanied or followed by lesions of acanthosis nigricans (297).

The *benign inherited* type usually has its onset during infancy or early childhood. It is an autosomal dominant trait (299).

Syndromic acanthosis nigricans is especially linked to syndromes associated with insulin resistance (300). In the HAIR-AN syndrome, which affects younger women, there is hyperandrogenemia (HA), insulin resistance (IR), and acanthosis nigricans (AN) (297). Another subset links autoimmune states such as lupus erythematosus with uncontrolled diabetes mellitus, acanthosis nigricans, and ovarian hyperandrogenism. These patients have antibodies to the insulin receptor. Acanthosis nigricans has also been associated with insulin resistance in obesity, hypothyroidism, and congenital generalized lipodystrophy (301–303).

Acanthosis nigricans–like lesions have been induced by high dosages of nicotinic acid (304). Acanthosis nigricans has also occurred following use of oral contraceptives, following use of the folic acid antagonist triazinate, and as a localized reaction to insulin (299,305,306).

Clinically, acanthosis nigricans presents as papillomatous brown patches, predominantly in the intertriginous areas such as the axillae, the neck, and the genital and submammary regions (Fig. 17-29). In extensive cases of acanthosis nigricans of the malignant type, mucosal surfaces, such as the mouth, the vulva, and the palpebral conjunctivae, may be involved (298). In the acral type, there is velvety hyperpigmentation of the dorsa of the hands and feet.



FIGURE 17-29. Acanthosis nigricans. There is a velvety, hyperpigmented plaque in the axillary fossa.

Histopathology. Histologic examination reveals hyperkeratosis and papillomatosis but only slight, irregular acanthosis and usually no hyperpigmentation. Thus, the term *acanthosis nigricans* has little histologic justification.

In a typical lesion, the dermal papillae project upward as finger-like projections. The valleys between the papillae show mild to moderate acanthosis and are filled with keratotic material (Fig. 17-30). Horn pseudocysts can occur in some cases (307). The epidermis at the tips of the papillae and often also on the sides of the protruding papillae appears thinned.

Slight hyperpigmentation of the basal layer is demonstrable with silver nitrate staining in some cases but not in others (308). The brown color of the lesions is caused more by hyperkeratosis than by melanin.

In the acanthosis nigricans lesions of the polycystic ovary syndrome, there are prominent deposits of glycosaminoglycan consisting mostly of hyaluronic acid in the papillary dermis (309).

Histogenesis. The inherited type of acanthosis nigricans can be classified as a type of epidermal nevus. In persons who have acanthosis associated with insulin resistance, high levels of insulin may activate insulin-like growth factor-1 receptors and thereby mediate epidermal proliferation (310). Malignant acanthosis nigricans most likely is mediated by growth factors that are secreted by the associated neoplasm, such as transforming growth factor-alpha (311,312). The basal cells from one patient with syndromic acanthosis nigricans demonstrated unusually high expression of the rare keratins 18 and 19 (307).

Differential Diagnosis. Differentiation of acanthosis nigricans from other benign papillomas, particularly from linear epidermal nevi and from the hyperkeratotic type of seborrheic keratosis, may be difficult. As a rule, however, linear epidermal nevi show more marked acanthosis than acanthosis nigricans and have a more compact orthokeratotic stratum corneum. Furthermore, the pilosebaceous units in linear epidermal nevi are rudimentary. Acanthosis nigricans cannot be distinguished histologically from confluent and reticulated papillomatosis.

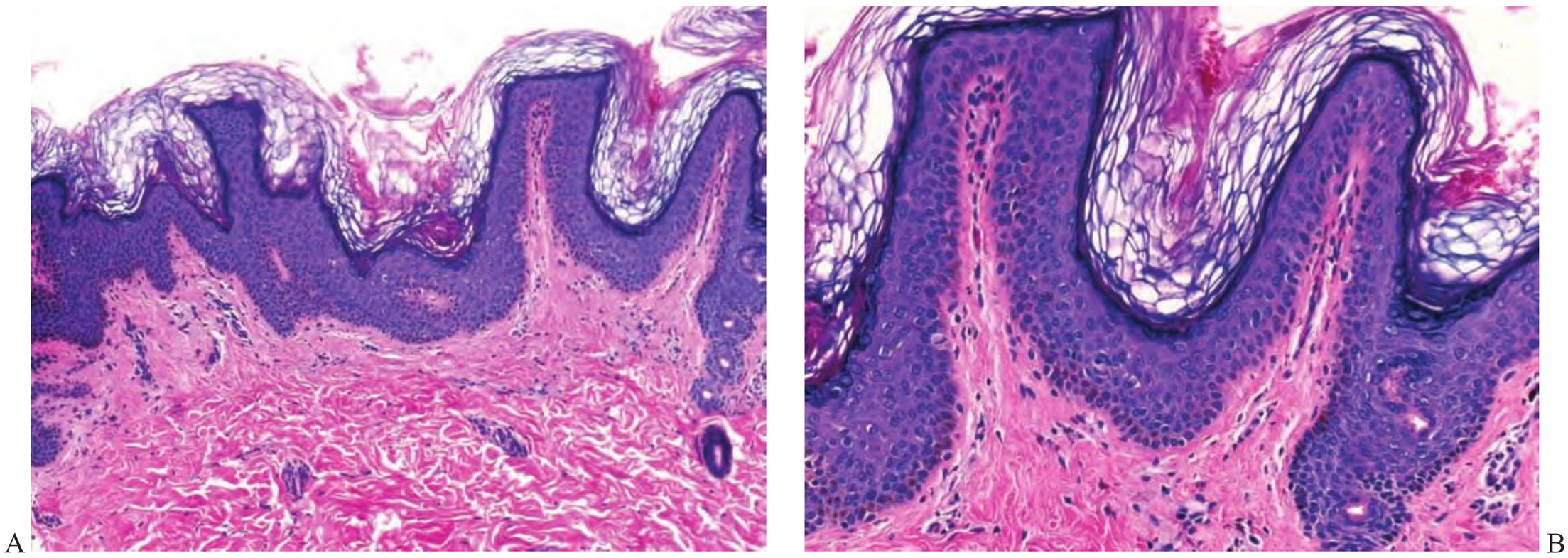


FIGURE 17-30. Acanthosis nigricans. A: There are papillomatous projections of the dermis (H&E). B: The epidermis is not increased in thickness above the papillomatous projections. The stratum corneum shows loose, basket-weave orthokeratosis (H&E).

Confluent and Reticulated Papillomatosis

Confluent and reticulated papillomatosis shows slightly hyperkeratotic and papillomatous pigmented papules that are confluent in the center and reticulated at the periphery (313). The site of predilection is the sternal region (Fig. 17-31). In the view of some authors, this disorder represents a variant of acanthosis nigricans (314). However, its location and reticulated pattern are distinctive.

Histopathology. Mild hyperkeratosis and papillomatosis are present, as is focal acanthosis, limited largely to the valleys between elongated papillae (314). Thus, the histologic changes are similar to but milder than those of acanthosis nigricans.

Histogenesis. Heavy colonization with *Pityrosporum orbiculare* has been observed in patients with confluent and reticulated papillomatosis; thus, this disorder has been regarded as a peculiar host reaction to *P. orbiculare* (315,316). However, in a review of the literature, it was found that even though potassium hydroxide preparations had yielded positive findings for yeast in 10 cases, there were positive findings for yeast and hyphae in only one case and negative results in 20 cases (317). Considering the common presence of the yeast phase as a nonpathogen, the role of *Malassezia* (*Pityrosporum*) as the cause of confluent and reticulated papillomatosis can be discounted. Reports of a variety of antibiotics that have been used successfully in the treatment of this condition raise the possibility that bacteria play a role in inducing the observed changes, although this is speculative (318).



FIGURE 17-31. Confluent and reticulated papillomatosis. There are discrete, flat, brown papules distributed over the sternal region, a characteristic location. Note the coalescence of papules into plaques in some areas and the reticulated appearance inferiorly.

HEREDITARY HEMOCHROMATOSIS

In hereditary hemochromatosis, large amounts of iron are deposited in various organs of the body, especially in the parenchymal cells of the liver and pancreas and in the myocardial fibers. The classic tetrad of hereditary hemochromatosis consists of hepatic cirrhosis, diabetes, hyperpigmentation of the skin, and cardiac failure.

Unless there is early recognition and adequate treatment by phlebotomy, hemochromatosis is a fatal disorder as the result of liver failure, heart disease, or hepatocellular carcinoma, which occurs in about one third of patients with advanced hemochromatosis (319).

Pigmentation of the skin is present in more than 90% of patients with hereditary hemochromatosis at the time the diagnosis is made, but it is often so mild as to attract little attention (320,321). The pigmentation is most pronounced in exposed

areas, especially on the face. Its color usually is brown or bronze but may be blue-gray. The pigmentation is caused largely by melanin and not by iron. In addition to pigmentation, ichthyosis-like changes, koilonychia, and hair loss are common.

Histopathology. Histologic examination of pigmented skin, especially from exposed areas, shows melanin to be present in increased amounts in the basal layer of the epidermis (320,322). Hemosiderin can be demonstrated in the skin of most patients with the aid of an iron stain, such as Perls' stain. It is found as blue-staining granules, mainly around blood vessels, both extracellularly and within macrophages, and in the basement membrane zone of the sweat glands and within cells of the connective tissue surrounding these glands (322). Siderosis around eccrine glands appears specific for hereditary hemochromatosis (320). In rare instances, some iron is present in the epidermis, particularly in the basal cell layer, and in the epithelial cells of the sweat glands (323).

In selecting a site for biopsy, it is not necessary to choose a pigmented area, because if deposits of iron are present in the skin, they are not limited to the areas of pigmentation. However, it is important not to take a specimen from the legs, where deposits of iron are frequently found in association with even minor venous stasis or as a consequence of a preceding inflammation that may no longer be evident.

A skin biopsy no longer represents an important test for establishing the diagnosis of hereditary hemochromatosis; it is merely of confirmatory value. Determinations in the serum of the level of iron, of the iron-binding capacity, as measured by the degree of saturation of transferrin with iron, of the plasma ferritin concentration, and, above all, biopsy of the liver, have replaced the skin biopsy in importance (321). Before liver biopsy, however, genotyping of patients who have abnormal screening exams for iron overload is now being performed. If the person is homozygous for the most common mutation in the hemochromatosis gene (HFE) and has persistently elevated transaminase levels, a biopsy of the liver is considered to evaluate whether fibrosis is present. Phlebotomy can prevent iron overload and development of fibrosis or can prevent further hepatic injury (324).

Histogenesis. Hereditary hemochromatosis is an autosomal recessive disease caused by mutation in the HFE gene. It is the most common genetically inherited disease in people of northern European ancestry (325). About 10% of the U.S. population are carriers of the disease (326). This figure implies a homozygote frequency of 2 or 3 per 1,000 persons. The gene for hemochromatosis is located on chromosome 6 and is most commonly altered by a point mutation that results in a cysteine to tyrosine switch at amino acid position 282 of the HFE protein (327). Homozygosity is present in approximately 90% of affected persons (327).

The amino acid substitution responsible for the vast majority of cases results in the inability of HFE to bind to β-2 microglobulin, a required step in the shuttling of HFE to the cell surface, the site of interaction of HFE and transferrin. The precise role of HFE in regulating iron stores is not known (324). Although iron absorption through duodenal mucosa is excessive, it is not known if this is the primary event. The degree of saturation of transferrin with iron is very high. Consequently, not all of the iron passing from the intestinal tract can be bound to transferrin, and it is therefore deposited in a variety of organs. Iron accumulates particularly in the parenchyma of the liver and pancreas and in the myocardium, and by damaging the cells in which it accumulates, it causes hepatic cirrhosis, diabetes, and cardiac insufficiency.

Two observations indicate that the cutaneous pigmentation in hereditary hemochromatosis is caused by melanin and not by hemosiderin. The first observation concerns a patient who in addition to having hemochromatosis had vitiligo. The areas of vitiligo were fully depigmented despite the finding on histologic examination that they contained just as much iron as deeply pigmented areas (322). The second observation was made in a black patient with idiopathic hemochromatosis who had three epidermal cysts. Although the patient had noticed no change in his skin color, he had observed progressive darkening of the cysts, and histologic examination revealed considerable amounts of melanin both in the walls of the cysts and in their keratinous contents (328). Although pigmented epidermoid cysts have been attributed to hemochromatosis, in a series of 125 epidermal cysts in Indian patients, pigmentation was found in 79 of them, none of which was attributed to hemochromatosis or iron deposition (329).

The increase in the amount of melanin found in the skin of patients with hemochromatosis is brought about by iron in the skin. The iron stimulates melanocytic activity either by increasing oxidative processes or by reacting with epidermal sulfhydryl groups and reducing their inhibitory effect on the enzyme system governing melanin synthesis (330,331).

VITAMIN A DEFICIENCY (PHRYNODERMA)

Deficiency of vitamin A is very rare in the United States, occurring mainly in Asia and Africa. It has been described, however, as occurring after small bowel bypass surgery for obesity (332,333). Vitamin A deficiency results in cutaneous changes to which the name *phrynoderma* (toad skin) has been given. These changes consist of dryness and roughness of the skin and the presence of conical, follicular keratotic lesions usually most prominent in the elbows and knees. Clinically, phrynoderma may at times simulate a perforating disorder (334). In addition to causing cutaneous changes, deficiency of vitamin A may cause night blindness, xerophthalmia, and keratomalacia.

Histopathology. The skin shows moderate hyperkeratosis with marked distention of the upper parts of the hair follicles by large, horny plugs (332,335). The horny plugs may perforate the follicular epithelium (333). The sebaceous gland lobules are greatly reduced in size. There may also be atrophy of the sweat glands, such as flattening of the secretory cells (336).

In severe cases, the sweat glands and sebaceous glands may undergo keratinizing metaplasia (337).

Differential Diagnosis. Histologic differentiation of phrynoderma from ichthyosis vulgaris and keratosis pilaris is impossible, except in very severe cases of phrynoderma, in which the sweat glands and the sebaceous glands show keratinizing metaplasia. Pityriasis rubra pilaris differs from phrynoderma by showing, in addition to hyperkeratosis and follicular plugging, stuttering parakeratosis, irregular epidermal hyperplasia, and an inflammatory infiltrate in the upper dermis.

PELLAGRA

Pellagra is caused by a deficiency of nicotinic acid (niacin) or its precursor, the essential amino acid tryptophan. As a dietary deficiency disease, it may occur in chronic alcoholics and patients with anorexia nervosa (338). It may also occur in patients with the carcinoid syndrome; the tumor cells divert tryptophan toward serotonin, thus depressing endogenous niacin production (339). In addition, pellagra is a well-recognized complication of isoniazid therapy for tuberculosis. Because isoniazid is a structural analog of niacin, it can cause the suppression of endogenous niacin production (340). Because 5-fluorouracil inhibits the conversion of tryptophan to nicotinic acid, it also may precipitate pellagra (341). Recently, multiple anticonvulsants have been reported to induce pellagra as well, although the precise mechanism for this is not known (342,343). Deficiencies of other vitamins such as B_6 and thiamine that are involved in the synthesis or utilization of niacin or excess dietary intake of substances (e.g., leucine) that directly inhibit niacin synthesis can result in clinical symptoms as well (342).

Pellagra presents with cutaneous lesions, gastrointestinal symptoms, and mental changes, resulting in the triad of the three Ds: dermatitis, diarrhea, and dementia.

The cutaneous lesions are precipitated by sunlight. A symmetrical photosensitive dermatitis predominantly involves the dorsa of the hands, wrists, and forearms; the face; and the nape of the neck. In the early stage, there is erythema, which usually is sharply demarcated; in severe cases, it may be accompanied by vesicles or bullae. Later, the skin becomes thickened, scaly, and pigmented.

Histopathology. The histologic changes of the skin are nonspecific. Early lesions present a superficial perivascular lymphocytic inflammatory infiltrate in the upper dermis. Vesicles, if present, arise as in erythema multiforme either subepidermally, owing to vacuolar degeneration of the basal layer and edema in the papillary dermis, or intraepidermally, owing to degenerative changes in the epidermis (344). Sometimes, there is a distinct pallor of the upper layers of the epidermis with or without an infiltrate of neutrophils. The differential diagnosis of this pattern includes acrodermatitis enteropathica (zinc deficiency), necrolytic migratory erythema of the glucagonoma syndrome, and occasionally psoriasis (345). There is one report of a contact dermatitis due to topical application of a eutectic mixture of local anesthetics (EMLA cream) that resembled pellagra microscopically (346).

In older lesions, hyperkeratosis with areas of parakeratosis and prominent but irregular epidermal hyperplasia is observed. The amount of melanin in the basal layer of the epidermis often is increased. Late lesions may show epidermal atrophy, and the dermis may show fibrosis in addition to chronic inflammation (344).

Hartnup Disease

First described in 1956 and named in 1957 after the family in which it was first observed, Hartnup disease is transmitted as an autosomal recessive trait (347,348). It first manifests itself in early childhood and often improves with advancing age. A photosensitivity eruption is present that usually is indistinguishable from pellagra (349). However, in some cases, the cutaneous reaction to sun exposure resembles poikiloderma atrophicans vasculare or, because of the prominence of vesicles, hydroa vacciniforme (350,351). In addition, there may be cerebellar ataxia and mental retardation. Niacin is used to treat Hartnup disease (349).

Histopathology. The cutaneous eruption in Hartnup disease usually shows the same histologic changes observed in pellagra (see previous section) (345). In patients with poikiloderma-like changes, atrophy of the epidermis and the presence of a chronic inflammatory infiltrate and of melanophages in the upper dermis are observed (350).

Histogenesis. The sun-sensitivity eruption with its resemblance to pellagra is caused by an enzymatic defect in the transport of tryptophan and a resultant decrease in the endogenous production of niacin. Specifically, the defective transporter is a transporter of monoamino-monocarboxylic acids, which is encoded by a gene which maps to chromosome 5p (352). The defect in tryptophan transport consists of both an intestinal defect in tryptophan absorption and a renal tubular defect causing inadequate reabsorption of amino acids, including tryptophan. Chromatographic study of the urine shows a constant aminoaciduria, particularly the presence of tryptophan and of indolic substances derived from tryptophan—a finding that establishes the diagnosis (350).

TYROSINEMIA TYPE II (OCULOCUTANEOUS TYROSINOSIS)

Tyrosinemia type II, also referred to as the *Richner-Hanhart syndrome* and *oculocutaneous tyrosinosis*, is transmitted as an autosomal recessive trait. It is characterized by very tender hyperkeratotic papules and plaques on the palms and soles arising in infancy or childhood; bilateral keratitis, which may lead to corneal opacities; and mental retardation. Palmoplantar lesions may begin as bullae and erosions (353). Ocular changes

are absent in some families (354). A diet low in tyrosine and phenylalanine improves the disease manifestations.

Histopathology. In most instances, the histologic findings in the keratotic lesions are not diagnostic, showing merely orthokeratotic hyperkeratosis with hypergranulosis and acanthosis (355). In one reported case, vertical parakeratotic columns were present over the openings of the acrosyringia. Multinucleated keratinocytes and dyskeratotic cells were noted in the spinous layer (356). A large intraepidermal bulla seen in another patient probably was also the result of irritation (357).

Histogenesis. Tyrosinemia maps to chromosome 16q 22.1 to 16q 22.2 (349). As a result of a genetic deficiency in hepatic tyrosine aminotransferase, excessive amounts of tyrosine are found in the blood, urine, and tissues. It can be assumed that excessive amounts of intracellular tyrosine enhance cross-links between aggregated tonofilaments. On electron microscopic examination, aggregations of tonofilaments and needle-shaped tyrosine crystalline inclusions are found in keratinocytes (356).

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CHAPTER 18

Michael D. Ioffreda

Inflammatory Diseases of Hair Follicles, Sweat Glands, and Cartilage

INFLAMMATORY DISEASES OF HAIR FOLLICLES: FOLLICULITIS

There are various types of folliculitis, or inflammation of the hair follicle, many of which are covered in other areas of this book. Folliculitis can have an infectious etiology due to bacteria (see Chapter 21), viruses such as herpes (see Chapter 25), and fungi (see Chapter 23), including dermatophytes (tinea capitis, tinea barbae, Majocchi's granuloma) and yeast (*Pityrosporum*). Chapter 21 discusses pseudofolliculitis barbae, folliculitis ("*acne*") keloidalis nuchae, and the follicular occlusion triad. Perforating folliculitis is discussed with the other perforating disorders in Chapter 15. The present chapter reviews the types of acneiform folliculitis and miscellaneous follicular disorders.

Acne Vulgaris

Acne vulgaris is a disease of adolescence and early adulthood that only occasionally persists into later adult life, when it is found more often in women (1). Chiefly affecting the face, upper back, and chest, it manifests as two types of lesions—comedones and inflammatory lesions, both of which are follicular based. Comedones may be closed ("whiteheads") or open ("blackheads"). Inflammatory lesions evolve from ruptured comedones or microcomedones, which are not clinically apparent, and they originate more frequently from closed than open comedones. Once developed, inflammatory papules may become pustules or nodules, which develop from cysts. Cystic acne can result in severe scarring. In acne fulminans—a rare variant occurring mainly in young male patients—lesions rapidly become tender, ulcerated, and crusted, and eventually scar. It may be associated with fever and polyarthralgia (2).

Histopathology. The development of a comedone involves a complex but incompletely understood process that results in infundibular dilation and thinning of the follicular wall. A plug composed of loosely arranged keratinized cells and sebum forms (Fig. 18-1). Sebum is made up of sebaceous lipids that empty into the follicular lumen and microorganisms. Solvents used in histologic processing remove these lipids.

In closed comedones, the follicular orifice remains more or less normal in size, but when the follicular ostium widens, an open comedone results. Both types of comedones are associated with mild mononuclear inflammation around vessels in the adjacent papillary dermis. Attenuation of the follicular wall may be so extreme as to lead to rupture (3). Release of follicular contents into the dermis generates an inflammatory response initially mediated by neutrophils and later by histiocytes and foreign-body giant cells. When rupture occurs superficially, it tends to lead to the development of a clinical pustule (Fig. 18-2), but when it occurs in the deeper dermis, an inflammatory nodule forms (Fig. 18-3). If the follicular damage and inflammatory response are severe, scarring can result. This is the norm in severe forms of acne (cystic acne and acne fulminans), in which extensive inflammation can result in dermal necrosis with large abscesses.

Pathogenesis. Several reviews highlight important advances that have affected our understanding of acne (4,5). Acne is a multifactorial condition, initially requiring sex hormone release during puberty and activation of the sebaceous glands. The major factors contributing to acne development are follicular hyperkeratinization, androgens, sebum, *Propionibacterium acnes*, and inflammation.

Comedones exhibit hyperkeratinization, and the keratin is bound more avidly as a result of increased levels of intercellular adhesion materials (6). Follicular linoleic acid deficiency, androgens, and interleukin-1 may all play a role in follicular hyperkeratinization (5,7). Ultrastructurally, follicular keratinocytes in comedones possess increased numbers of desmosomes and tonofilaments, which contribute to hypercornification (8). The black color of open comedones ("blackheads") appears to be related to densely packed keratinocytes, bacteria, and bacterial breakdown products located at the surface. If dilation of the follicular orifice does not occur (closed comedone), continued thinning and ultimate rupture of the infundibular wall becomes more probable.

Comedone development is associated with increased epithelial cell proliferation in the lower portion of the infundibulum, as measured by tritium-labeling techniques (9). Based on the use of Ki-67, increased keratinocyte proliferation was demonstrated in normal follicles from acne-affected areas (as compared to areas free of acne), suggesting that some follicles may be "acne-prone" (10). Ki-67 was also increased in comedones.

Generation of inflammation in acne lesions is also a complex process. Potential instigators of inflammation may be



FIGURE 18-1. Comedone, open. A dilated follicular infundibulum with an attenuated wall is plugged with keratin and sebum. The follicular orifice is widened.

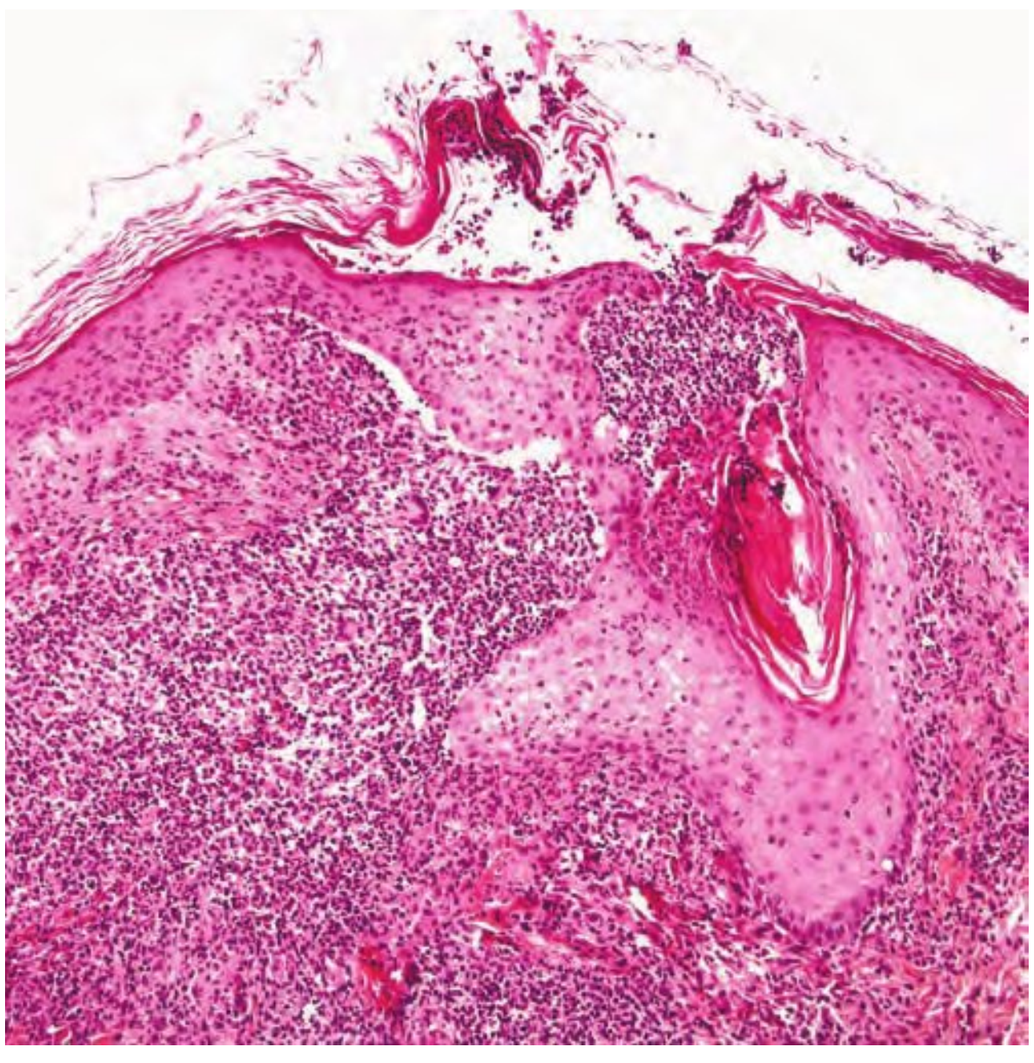


FIGURE 18-2. Acne vulgaris, pustule. Superficial follicular rupture incites suppurative and granulomatous inflammation, with neutrophils predominating in early lesions.

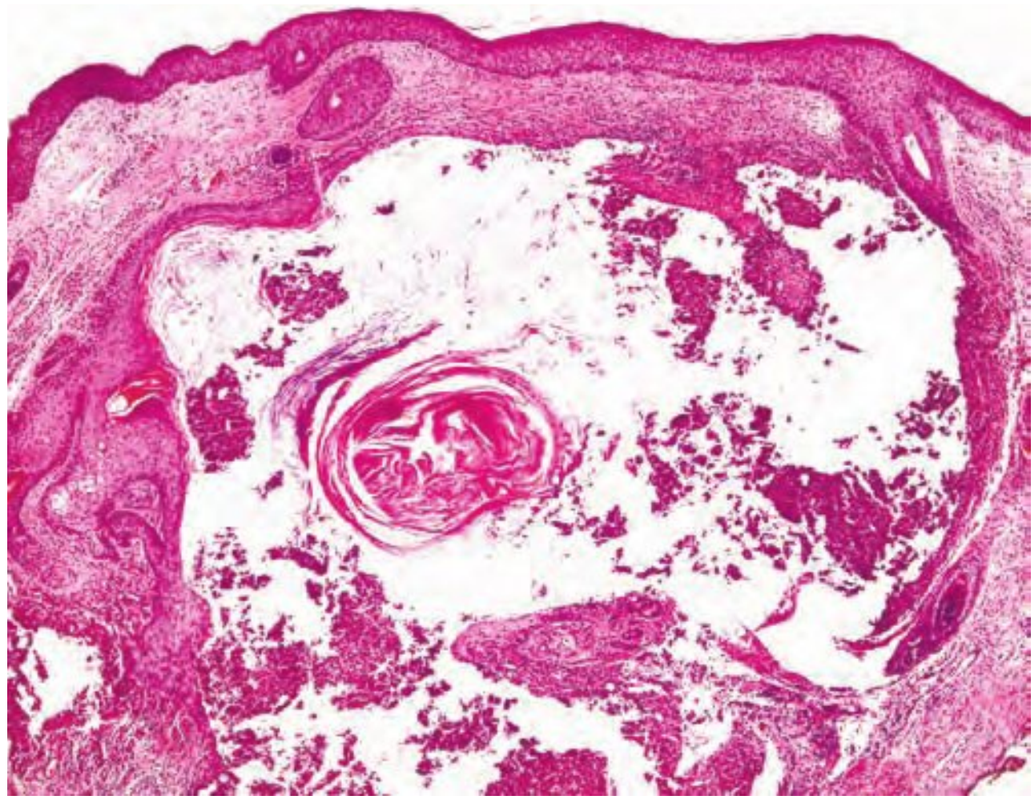


FIGURE 18-3. Acne vulgaris, nodule. Cystlike follicular dilation with deep rupture leads to neutrophilic and granulomatous inflammation throughout the dermis.

derived from the breakdown products of sebaceous lipids, from byproducts derived from *P. acnes*, and from various immunologic mechanisms directed against this organism (11). The expression of adhesion molecules and inflammatory infiltrates was studied by immunohistochemistry in evolving lesions of acne vulgaris (12). There was vascular expression of intercellular adhesion molecule-1, E-selectin, vascular cell adhesion molecule-1, and human leukocyte antigen (HLA)-DR, and the inflammatory cells consisted of $CD4^+$ T lymphocytes.

There is substantial evidence linking the activation of sebum production to androgens, specifically testosterone and dihydrotestosterone (DHT) (13). Circulating testosterone is converted in tissues to the more potent DHT by the enzyme 5α-reductase (14). The type 1 isoform of 5α-reductase is located primarily in sebocytes [but is also found in the epidermis, infundibular hair follicle keratinocytes (15), dermal papilla cells, sweat glands, and fibroblasts]. The gene encoding the type 1 isozyme is found on chromosome 5p (16). Activity of the type 1 isoform of 5α-reductase was greater in sebaceous glands from acne-prone areas of the skin than in those from non–acne-prone areas, suggesting that regional differences in pilosebaceous production of DHT may play a role in acne (17).

The precise role of androgenic hormones in the production of acne lesions is controversial. Androgens are derived from two sources: precursor serum androgens of glandular origin (gonadal and adrenal) and target tissue androgens derived from conversion of circulating precursors. It has been suggested that in patients with mild acne the serum levels of precursor androgens are normal and that in these circumstances only tissue androgen levels are elevated (18). In severe cystic acne, increased serum androgen levels have been found, although the majority of acne patients—especially male patients—do not show abnormal levels. Elevated serum

androgen levels occur more frequently in women with acne, but similar elevations have been found in hirsute women without acne (19). Another study found significantly higher mean serum androgen levels in females with acne than in those without acne, although values were in the range of normal; in addition, sebaceous glands from the women with acne showed higher mean 5α-reductase type 1 activity, although the difference was not statistically significant (20). This study suggests that women with acne may have higher serum androgen levels and perhaps a greater capacity to produce DHT within sebaceous glands.

One author emphasized the importance of sebum in acne with a simple statement: "remove sebum and you remove acne" (21). Sebum production in acne is elevated and appears to correlate with disease severity. An *in vitro* study of sebaceous gland ultrastructure after exposure to substance P found that this stress-induced neuropeptide promoted the proliferation and differentiation of sebaceous glands, implicating a role for stress in acne (8). The beneficial effect of isotretinoin (13-*cis*-retinoic acid) appears to result largely from reduction in sebum production, although a substantial decrease in *P. acnes* levels was detected in one study (22) and follicular hyperkeratinization was found to be reduced in another study (23). After 2 months of treatment with oral isotretinoin, a 70% reduction in sebum excretion is achieved (22), and after 4 months a reduction of 88% may be attained (24). These changes are associated histologically with a marked reduction in sebaceous gland size (24).

Of all the microorganisms identified in the follicular infundibulum, only *P. acnes* appears to be consistently involved in the pathogenesis of acne lesions (25). Nevertheless, levels of this organism may not be consistently greater in lesional skin than in normal skin (26). Immunologic reactivity to this organism may contribute to the inflammation in acne lesions. In response to *P. acnes*, acne patients may exhibit elevated serum antibody levels, increased immediate hypersensitivity, and augmented cell-mediated immunity (27). The beneficial effects of systemic and topical antibiotics in acne patients are generally attributed to their suppression of *P. acnes*, although some studies suggest that oral tetracycline and topical erythromycin may improve acne without reducing the population of *P. acnes*.

Peroxisomal proliferator activator receptors (PPARs) may play a role in acne. PPARs modulate various functions of peroxisomes (small organelles that are important in regulating cell proliferation, differentiation, metabolism, and inflammation) (28,29). In addition, *P. acnes* has been shown to elicit inflammatory cytokines in acne through activation of Toll-like receptor 2; Toll-like receptors initiate immune reactions in response to pathogen-associated molecular patterns (30).

Steroid Acne

Steroid acne is a folliculitis caused by the use of corticosteroids, including systemic, topical, inhaled (31), and intranasal (32) steroids. Despite its well-known existence, steroid acne has become more prevalent with the creation of increasingly potent topical preparations and the introduction of organ transplant surgery and various treatment regimens for cancer (33). Although other medications have been implicated in acneiform eruptions, steroid acne results in a distinctive clinical picture characterized by the sudden appearance of monomorphous papulopustules predominantly on the upper trunck and arms but also on the face (34). Comedones are not apparent. The underlying rash for which topical steroids are used initially improves, followed by exacerbation of the rash (35). The exacerbation is controlled only by continued use of topical steroids (physical dependence). Resolution typically occurs without scarring. Perioral dermatitis may be caused by topical corticosteroids (see the later discussion of perioral dermatitis).

Histopathology. Acne due to both topical and systemic corticosteroids shows similar histologic features. Despite the apparent absence of comedones clinically, Hurwitz described histologic features that resembled those of acne vulgaris (Fig. 18-4), albeit with an accelerated rate of development (33). In chronologic order, biopsied flesh-colored papules that measured 1 mm showed infundibular spongiosis, hyperkeratosis, perifollicular edema, microcomedo formation, and infundibular wall thinning, sometimes with infundibular rupture. It was more common, however, to see only infundibular dilation with compact hyperkeratosis. Biopsied lesions that were 2 mm or greater and clinically inflamed frequently showed infundibular rupture, necrotic keratinocytes, and surrounding suppurative and granulomatous inflammation that included multinucleated giant cells amid keratinous debris. Dilated blood vessels were also seen.

Pathogenesis. Although the exact pathogenesis is not known, three phases of lesion development have been described as a result of "addiction" to topical steroids (35): (a) initial improvement of the rash is due to the antiinflammatory properties of topical corticosteroids, (b) local immunosuppressive

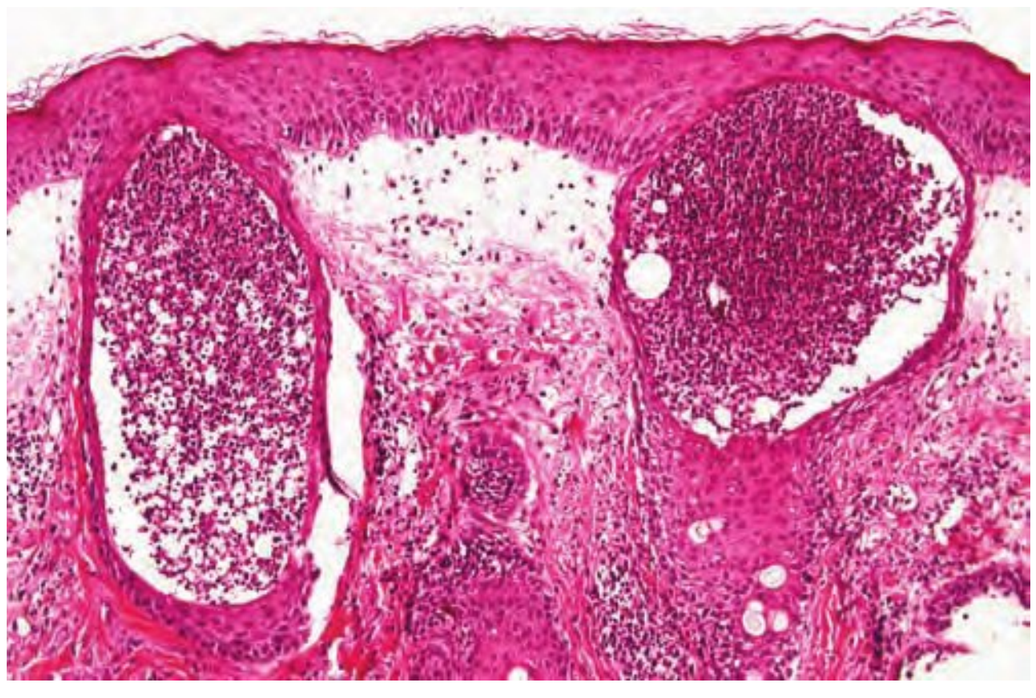


FIGURE 18-4. Steroid acne. Pustules in steroid acne are monomorphous and are indistinguishable from acne vulgaris.

effects of the steroids result in bacterial overgrowth, and (c) on withdrawal of steroids there is rebound and flaring secondary to bacterial overgrowth. In addition to the chronologic sequence described under Histopathology, some authors have described a pathologic process that is the reverse of acne vulgaris, beginning with folliculitis that proceeds to rupture and concludes with comedone formation (a so-called "secondary" comedone) (36). In a study of steroid acne due to systemic therapy, 80% of 125 patients showed significant numbers of *Pityrosporum ovale* in lesional follicles, and itraconazole, an oral antifungal agent, proved more efficacious than other medications (37).

Perioral Dermatitis

Recognition of this relatively common facial eruption is important because of its resemblance to rosacea, seborrheic dermatitis, and occasionally lupus erythematosus. Predominantly affecting white women of European extraction ranging in age from the mid teens into middle age, it results in fine, follicular-based papules perioral and, more rarely, in a periocular distribution (*periocular dermatitis*) (38,39). The papules are single, grouped, or confluent, with minimal scaling. Pinhead-sized pustules may occur in more severe cases. There is sparing of a 5-mm zone around the vermilion border (34). The condition lacks significant telangiectasia. It is commonly associated with topically applied preparations, especially topical corticosteroids and cosmetics. Perioral dermatitis in children occurs primarily as a result of topical steroid use and is almost identical to the disease in adults (40–43).

Childhood granulomatous periorificial dermatitis is an acneiform facial eruption that shows some similarity to granulomatous rosacea and perioral dermatitis in children but does have some distinctive features (44–46). The current terminology was first coined in 1989 (44), although other terms have been proposed, such as facial Afro-Caribbean childhood eruption, reflecting its usual incidence on the face of black children (47). Other features that distinguish childhood granulomatous periorificial dermatitis from childhood perioral dermatitis and acne vulgaris include (a) exclusive incidence in healthy prepubertal children and (b) absence of pustules and lack of circumoral sparing. Another entity producing clinically similar lesions—lupus miliaris disseminatus faciei—has not been reported in children (47). Clinical lesions may be flesh colored, hypopigmented, or reddish yellow; are small (1 to 3 mm); are monomorphous; and occur periorally, perinasally, and periorbitally. Lesions are asymptomatic and self-limited but may last for years, typically healing without residual except for some small, pitted scars in a small number of patients (48). Cases with extrafacial and generalized lesions have been reported (48).

Histopathology. Some authors consider perioral dermatitis to be a variant of rosacea, with indistinguishable histologic features (42,49), whereas others consider the two entities to be distinct (50,51), with some histologic overlap. A proposed clinical classification scheme for rosacea published in 2002 did not classify steroid-induced acneiform eruptions or perioral dermatitis as rosacea variants, citing insufficient evidence (51).

The following histologic characteristics of perioral dermatitis have been described (50). Fully developed lesions show spongiosis of the follicular infundibulum with mild mononuclear cell exocytosis (Fig. 18-5), with similar changes sometimes observed in the epidermis adjacent to the involved follicle. The epidermis may show mild acanthosis and parakeratosis, particularly about follicular ostia. The perifollicular dermis shows lymphohistiocytic inflammation around vessels, and in rare cases plasma cells may be prominent. Less developed lesions may exhibit only dermal inflammation. Lesions tend to lack the dermal edema and telangiectasias characteristic of rosacea and show more noticeable epidermal changes. Acute folliculitis is uncommon.

Lesions of *childhood granulomatous periorificial dermatitis* often resemble granulomatous rosacea, with noncaseating perifollicular granulomas with some giant cells (44,48). Other features include epidermal changes consisting of mild hyperkeratosis and spongiosis, as well as dermal inflammation, composed of lymphocytes and histiocytes, that is mild to moderate, perivascular, and perifollicular. The granulomatous component is variable; some biopsies lacked granuloma formation or follicular involvement altogether. Some cases showed focal follicular rupture with inflammation to the released contents (44). Special stains for fungi and mycobacteria have been negative (48).

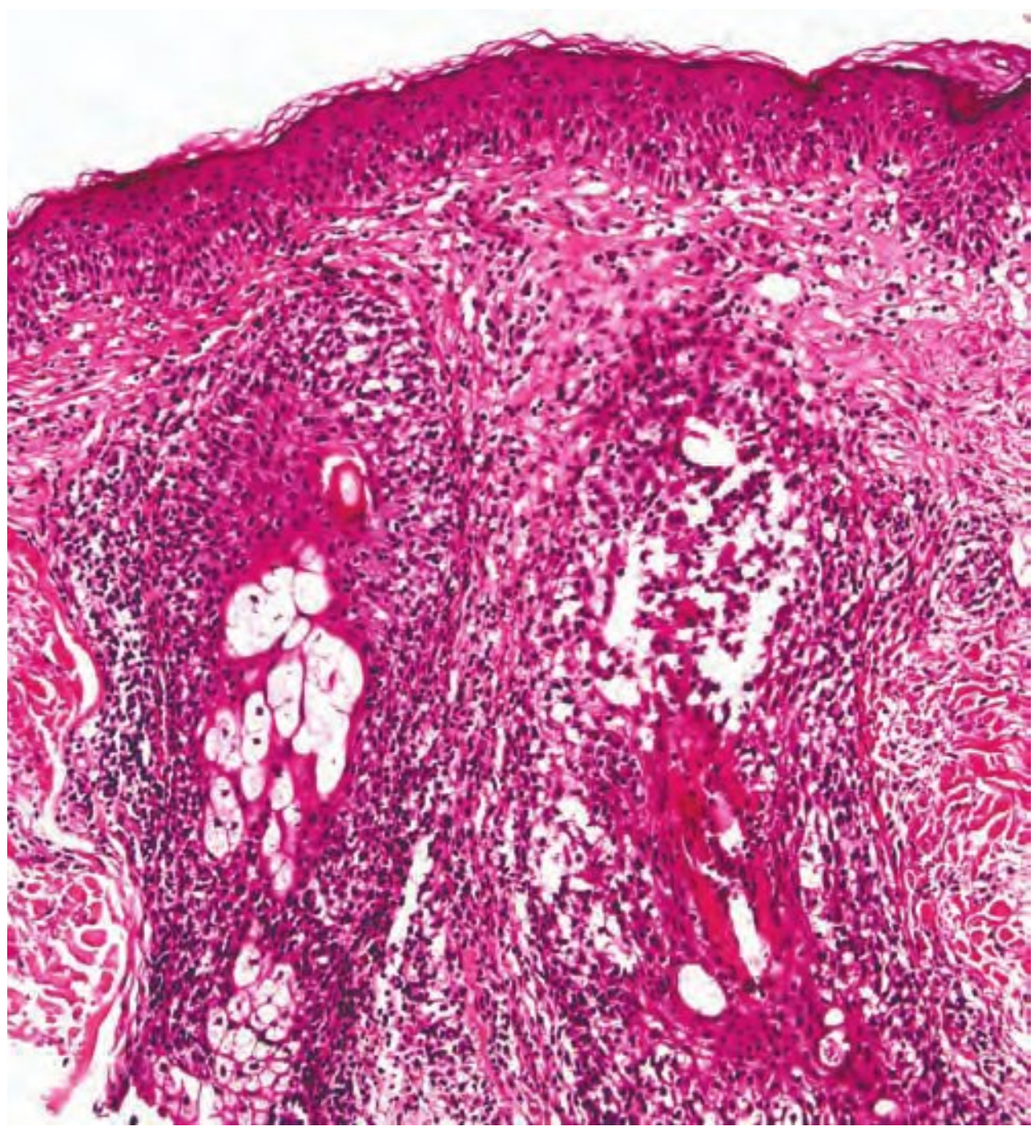


FIGURE 18-5. Perioral dermatitis. There is perifollicular mononuclear inflammation with infundibular spongiosis and exocytosis of lymphocytes.

Pathogenesis. Many possible etiologies for *perioral dermatitis* have been proposed, including *Candida* organisms, bacteria, particularly of the fusiform type, *Demodex* mites, a wide range of contactants, both irritant and allergic (including cosmetics and fluoride-containing toothpaste), hormones (including birth control pills), topical corticosteroids (particularly potent ones), and emotional as well as systemic conditions. An Australian survey found an increased risk of developing perioral dermatitis with use of foundation makeup along with moisturizer and night cream (52). Periocular dermatitis has been reported with the use of a steroid eye ointment (53).

The etiology of *childhood granulomatous periorificial dermatitis* is not known, but an external contactant has been implicated in some cases, with various agents, including topical fluorinated corticosteroids, reported (48).

Rosacea

Rosacea is an acneiform inflammatory condition that primarily affects the face and is more common after the age of 30 years. It is characterized by background erythema within which scattered telangiectasias, papules, and occasional pustules develop (Fig. 18-6). It typically affects the nose, cheeks, glabella, and chin, and it is usually bilateral but occasionally unilateral or focal. If it is severe, lesions may spread to the neck and, rarely, become disseminated. Rhinophyma, a bulbous swelling of the soft tissue of the nose, is a late complication that occurs almost exclusively in men. Eye changes—especially blepharitis and conjunctivitis—are quite common in rosacea, and in 5% of cases a painful keratitis can develop (54). Rosacea can precipitate persistent facial lymphedema.

A recently proposed clinical classification scheme for rosacea delineated four subtypes: (a) erythematotelangiectatic, (b) papulopustular, (c) phymatous, and (d) ocular (51,55). In this classification, a single rosacea variant was defined, *granulomatous rosacea*, that did not show morphology of one of the subtypes.



FIGURE 18-6. Rosacea. Scattered erythematous papules with background telangiectasias that give the face a "ruddy" appearance.

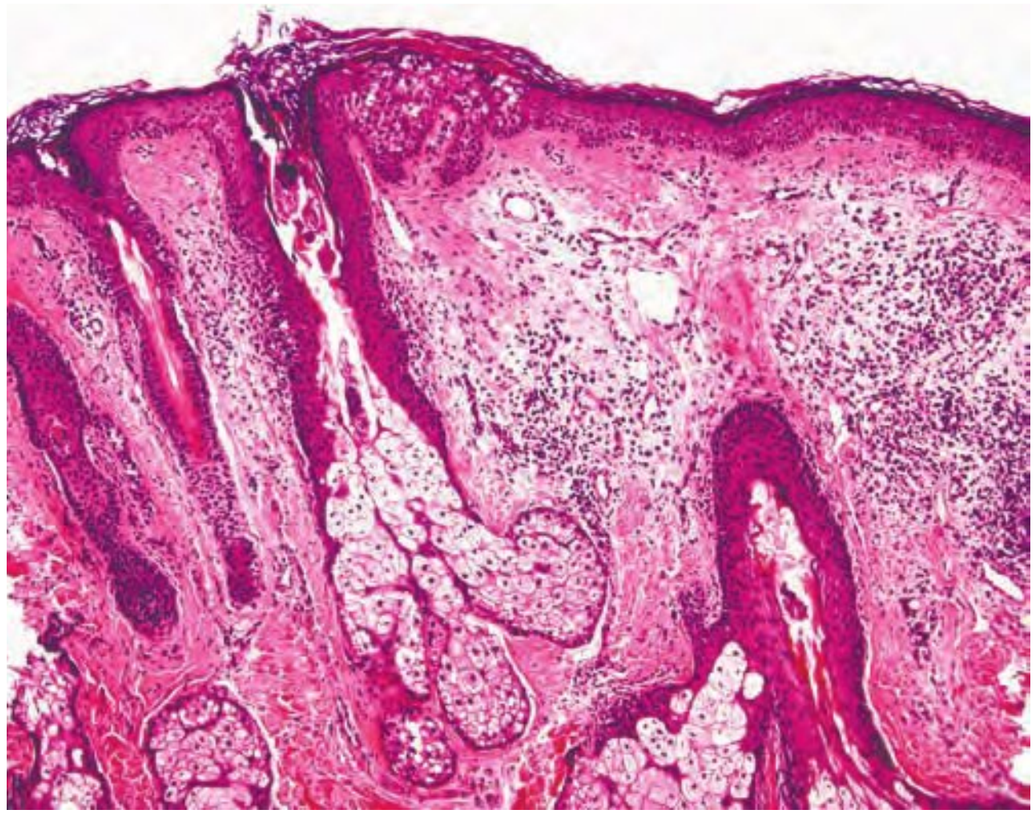


FIGURE 18-7. Rosacea. Patchy lymphocytic inflammation surrounds vellus hair follicles, which contain Demodex mites, as well as some blood vessels. Telangiectasias are present.

Histopathology. Vascular dilation of upper and middermal vessels with perivascular and perifollicular lymphohistiocytic inflammation (and occasional plasma cells) is generally present in all cases (Fig. 18-7). Lymphatic dilation is also common and may be prominent. With mild follicular involvement, there is infundibular spongiosis and lymphocyte exocytosis. With more extensive follicular involvement, neutrophils accumulate, resulting in a superficial pustule. Reflecting the clinical presentation, various other pathologic changes can be seen from case to case, including organization of dermal lymphocytes into small nodular aggregates (56).

Granulomatous infiltrates are reported to occur in about 10% of all cases of rosacea (56) (Fig. 18-8), and caseation necrosis has been identified in about 10% of these patients

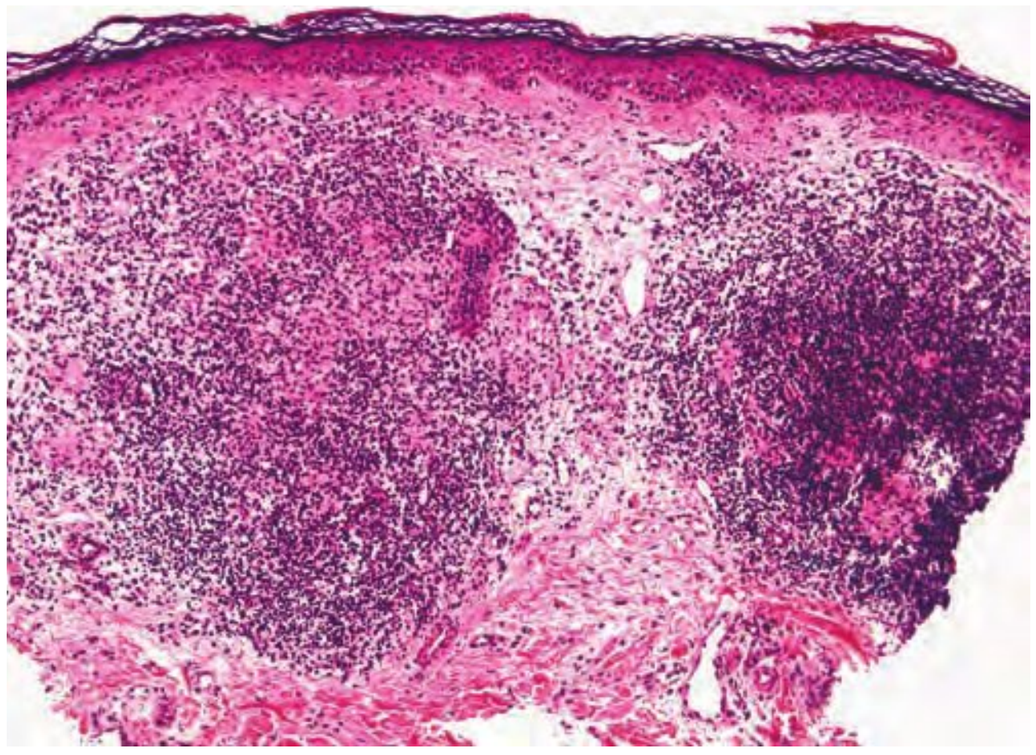


FIGURE 18-8. Granulomatous rosacea. The infiltrate is dense and has a prominent histiocytic component, clustered into granulomas. Telangiectatic blood vessels are present.

(57). *Granulomatous rosacea* can histologically mimic mycobacterial infections, with epithelioid histiocytes forming a tuberculoid pattern. In such cases, other investigative procedures, including tissue cultures, may be necessary. Less frequently, the changes resemble cutaneous sarcoidosis. Multinucleated giant cells of the foreign-body type may aggregate around follicular contents spilled from a ruptured follicle.

In a study of rhinophyma, the classic or common type showed histologic features of fully developed rosacea, except for sebaceous gland hyperplasia, which can be prominent (58). The sebaceous ducts become dilated and filled with keratin and sebum. The same study showed that in patients with the severe form of rhinophyma, there is marked dermal thickening with sclerotic collagen bundles and large amounts of mucin, an absence of pilosebaceous structures, sparse inflammation, and telangiectasias (58). Many spindle-shaped and "bizarre" cells staining for factor XIIIa were seen in the interstitium. It was noted that the microscopic findings in the severe form of rhinophyma demonstrate many similarities to elephantiasis nostras caused by chronic lower-extremity lymphedema.

Pathogenesis. Although triggers of rosacea are well known, the pathogenesis of the disease is unknown. It is probable that the etiology of rosacea is multifactorial (59), but sun damage appears to be a constant feature. Rosacea is not associated with an increase in sebum excretion. Dahl proposed that the vascular dilation leads to dermal edema, which in turn promotes the inflammation that is ultimately responsible for the sequelae of rosacea (60). In this model, warm facial skin from increased blood flow may modify the behavior of bacteria and/or *Demodex* or change the enzymatic activity of keratinocytes or other skin cells, leading to altered metabolism and inciting inflammation.

The role of *Demodex* organisms has been debated for decades. Some reports claimed a significant association of mites in rosacea biopsies (61–65), but other studies did not support this claim (66). Although a definitive causative role for *Demodex* in rosacea is uncertain, the mites may represent an important cofactor in heightening disease severity (65).

An association with gastrointestinal *Helicobacter pylori* infection has been the subject of investigation. In one study, a number of rosacea patients had gastrointestinal symptoms related to gastritis; the prevalence of *H. pylori* in those patients with rosacea was 88%, compared to 65% in the control group without rosacea (but with nonulcer dyspepsia) (67). Furthermore, eradication of *H. pylori* with 1 week of therapy that included oral metronidazole, omeprazole, clarithromycin, and topical intraoral metronidazole resulted in marked improvement or resolution of rosacea symptoms after 2 to 4 weeks. In another report, a man with intractable rosacea for 4 years was treated with a similar treatment regimen directed against *H. pylori*, which had been documented by gastroscopy and serologic testing. His skin began to improve with treatment and cleared completely 2 months later, remaining clear for at least 3 years thereafter (68). Attempts to find *H. pylori* in the skin have been unsuccessful. A proposed pathogenesis is increased flushing due to vasodilators such as nitric oxide and gastrin, and inflammatory cytokines such as tissue necrosis factor-α and interleukin-8 (IL-8), all produced by *H. pylori* (69). Nevertheless, definitive studies validating an association of *H. pylori* with rosacea have yet to be done (70).

Immunoglobulins and complement components have been identified at the dermal–epidermal junction in patients with rosacea (71), but others have disputed these findings (72). Immune deposits in the skin of rosacea patients may be a reflection of chronic actinic injury.

Demodicidosis

Demodicidosis is the term for cutaneous disease caused by mites of the genus *Demodex*. Despite more than 65 years of investigation into the role of *Demodex* mites in human skin disease, questions remain. Aside from their controversial role in rosacea, *Demodex* mites have been implicated in follicular-based skin eruptions resembling rosacea, albeit with some unique features that warrant consideration as distinct entities (73). There are at least three clinical forms of demodicidosis (73). The first, *pityriasis folliculorum*, is characterized by facial erythema with fine follicular plugs and scale producing a "nutmeg-grater" or "sandpaper-like" appearance. It usually affects women and may be associated with itching and burning. The second, *rosacea-like demodicidosis*, resembles rosacea, in that there are papules and pustules. In contrast to rosacea, however, there is follicular scaling, sudden onset, rapid progression, and no history of flushing. There may be eyelid involvement (demodectic blepharitis) and poor general health, such as diabetes mellitus (73). Lastly, "*demodicidosis gravis*" resembles severe granulomatous rosacea. These forms may represent a spectrum of disease in which the clinical expression depends on the degree and duration of *Demodex* infestation and the individual's age and overall health (73). *Demodex* may also be important in the pathogenesis of nonclassic presentations involving facial pruritus and erythema and nonspecific acneiform lesions (74).

Demodex are obligatory parasites frequently found in mammalian pilosebaceous units, and colonization is usually asymptomatic (64). The mites found in humans are of the species *D. folliculorum* and *D. brevis*. *D. folliculorum,* the predominant mite, has a longer body, inhabits the infundibulum of hair follicles, and is found almost exclusively on the face (75,76). *D. brevis* is smaller and lives exclusively within sebaceous glands on the face and trunk (75,76).

Demodicidosis has also been classified as *primary* or *secondary*, with the latter occurring on diseased skin (77). The primary form affects nondiseased skin, is caused by *D. folliculorum*, and causes an eruption in the T-zone of the face, involving 8% to 15% of the face. Secondary demodicidosis is characterized by a symmetric eruption of the malar region, covering 30% to 40% of the face, and is caused by *D. brevis*. There are other distinguishing features, such as onset of erythema, pruritus, and seasonality (77).

A study of consecutive biopsies submitted to one dermatopathology laboratory showed *Demodex* mites in 10% of all biopsies and 12% of all follicles (75). Their prevalence increased with age, and males were more heavily infested. In another study, there was a nonrandom association between histologic folliculitis and presence of *Demodex* in the follicles (76); mites were found in 42% of inflamed follicles but in only 10% of noninflamed follicles, whereas 83% of follicles containing *Demodex* showed inflammation. This demonstrated a strong association but not a cause-and-effect relation because the possibility that *Demodex* could preferentially select inflamed follicles was raised. Additional support for a pathogenic role was provided by reports of sudden facial eruptions in which numerous *Demodex* mites were identified and the eruption failed to respond to therapy for rosacea but cleared quickly with treatments directed against *Demodex*, such as crotamiton or ivermectin and permethrin (78).

Some believe that *Demodex* mites are pathogenic only in large numbers (78), but an individual's overall health also appears to be important, as demonstrated by reports in immunocompromised children (79–81) and multiple reports in patients with HIV and AIDS, in which the eruption may also involve the neck, upper trunk, and extremities (80,82,83). One study stated that demodicidosis is prevalent even in immunocompetent individuals (61), and it has been reported in immunocompetent children (84). Patients with HLA types Cw2 and Cw4 are more likely to develop clinical symptoms of demodicidosis, whereas HLA-A2 individuals appear to be more resistant (85). There is a coassociation with immune response, including subtypes and functional activity of lymphocytes, and circulating levels of immune complexes (86).

Human demodectic alopecia may be a real entity characterized by alopecia, erythema, and scale, with numerous *Demodex* mites in affected follicles (87). It resembles canine demodectic mange and has been successfully treated with permethrin. *Demodex* may also cause a refractory scalp folliculitis (88).

Histopathology. The diagnosis can be made in the clinical setting by examining scale with 40% KOH (89) or by standardized skin surface biopsy (SSSB), in which cyanoacrylate glue is used to sample the horny layer and follicular contents (90). The presence of five or more mites in a single low-power field by KOH or more than 5/cm^2 by SSSB is considered significant.

Biopsies of *pityriasis folliculorum* show a perivascular and diffuse dermal lymphocytic infiltrate without granuloma formation (73). *Demodex* mites are present within pilosebaceous units. Biopsies of *rosacea-like demodicidosis* (Fig. 18-9) show a primarily perifollicular infiltrate of mononuclear cells with possible granulomatous inflammation (73). The infiltrate is composed predominantly of CD4$^+$ T lymphocytes (65), and perifollicular Langerhans cells may be found. "*Demodicidosis gravis*" shows granulomas with central necrosis (caseation) and foreign-body-type multinucleated giant cells (91).

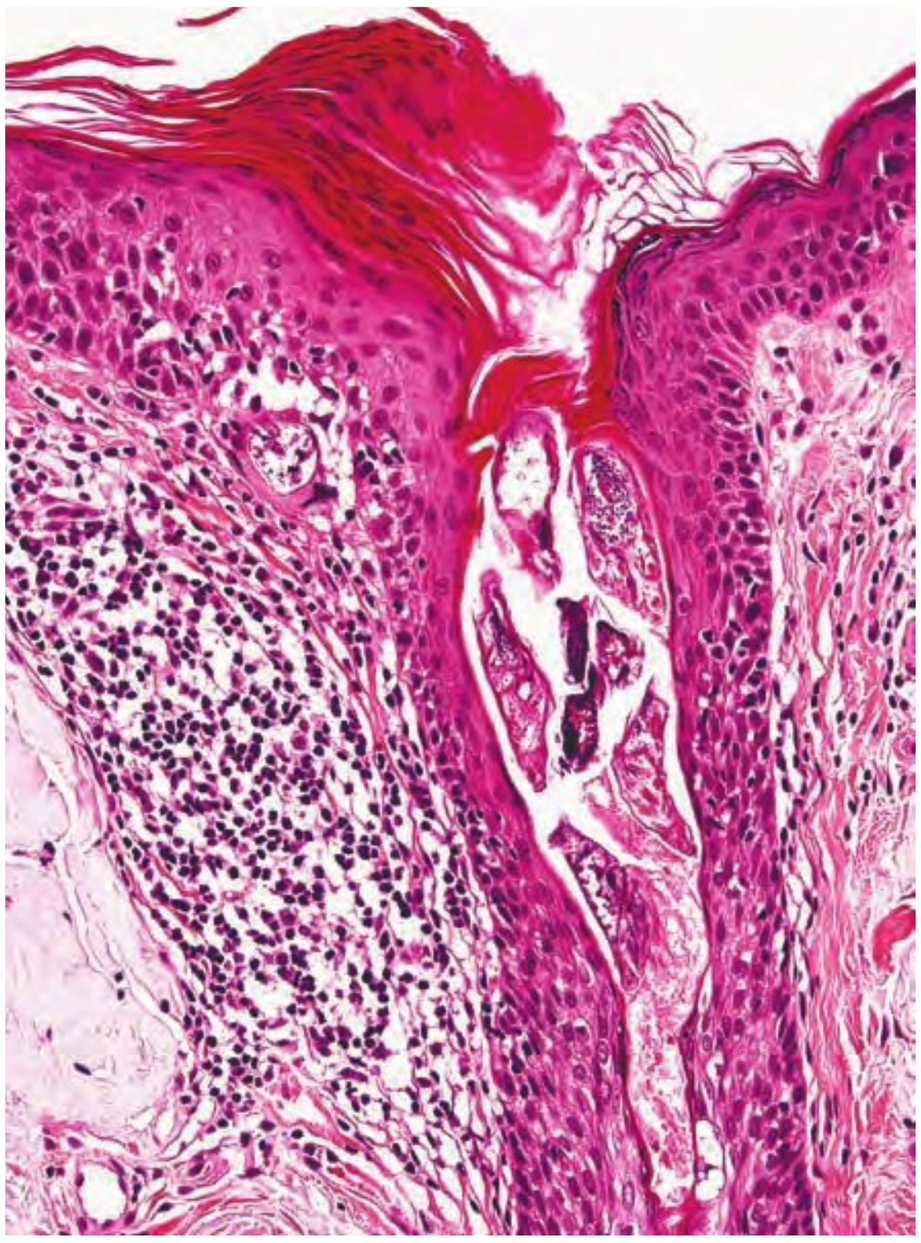


FIGURE 18-9. Demodicidosis. The follicular infundibulum contains multiple Demodex mites, and there is perifollicular lymphohistiocytic inflammation. Where the left side of the follicular epithelium meets the epidermis, an organism appears to be perforating through to the dermis.

Pathogenesis. The pathogenesis of *Demodex*-related disease may be linked to one of the following: (a) blockage of hair follicles and sebaceous ducts due to reactive epithelial hyperplasia and hyperkeratinization, (b) mites serving as vectors for bacteria, (c) a foreign-body reaction to the mite, or (d) induction of host immunity by the mites and their waste (64). Some mite antigens may also elicit a delayed hypersensitivity reaction (65). One paper suggested that a mite-derived lipase could potentially release fatty acids from serum triglycerides, producing an irritant reaction (92).

Lupus Miliaris Disseminatus Faciei

Lupus miliaris disseminatus faciei (acne agminata) is considered by some to be a granulomatous variant of rosacea, but other authors consider it to be a distinctive rosacea-like syndrome (93). The clinical presentation is distinctive, with discrete, flesh-colored or mildly erythematous papules—arranged singly or in small groups—involving the eyelids and upper lip, areas where rosacea lesions are not commonly found (94). The background erythema and telangiectasias of rosacea are lacking. Papules frequently persist for 12 to 24 months and are resistant to standard rosacea therapy, although spontaneous

healing can occur. Unusual presentations have included axillary lesions (95,96) and during pregnancy in a patient with cutaneous lupus erythematosus (97). One group proposed the use of equally cumbersome terminology, "facial idiopathic granulomas with regressive evolution" (F.I.GU.R.E.) (98). Clinically similar lesions due to metastatic silicone granulomas were reported in a patient with silicone breast implants (99).

Histopathology. Biopsy specimens sectioned through the central portion of a papular lesion demonstrate one of the most highly characteristic patterns of cutaneous histopathology. Surrounding a usually large area of caseous necrosis, aggregates of epithelioid histiocytes and occasional multinucleate giant cells form a "tubercle" with sparse lymphoid inflammation at the periphery (Fig. 18-10).

In one study, this characteristic histology was only found in a minority of patients in fully developed lesions, and an attempt was made to describe the histologic features of early, fully developed, and late lesions (100,101). Early, developing lesions show perivascular and perifollicular lymphocytes and some histiocytes. Fully developed lesions show a sarcoidal granuloma (first stage), sometimes accompanied by an abscess (second stage) or surrounding an area of caseation necrosis (third stage). The granuloma may be perifollicular and involve one or more hairs, and the follicle may be "ruptured" with a neutrophilic response. Granulomas may also be compact or loose and may occupy the upper or lower dermis, and some hug the epidermis. Late lesions demonstrate scattered lymphocytes, histiocytes, and neutrophils and perifollicular fibrosis. Additional findings include follicular dilation, hyperkeratosis, sometimes combined with follicular plugging, and pigment incontinence (100).

Despite the histologic picture, no direct relationship with tuberculosis has been documented, including testing using polymerase chain reaction with DNA fragments specific for *Mycobacterium tuberculosis* complex (102).

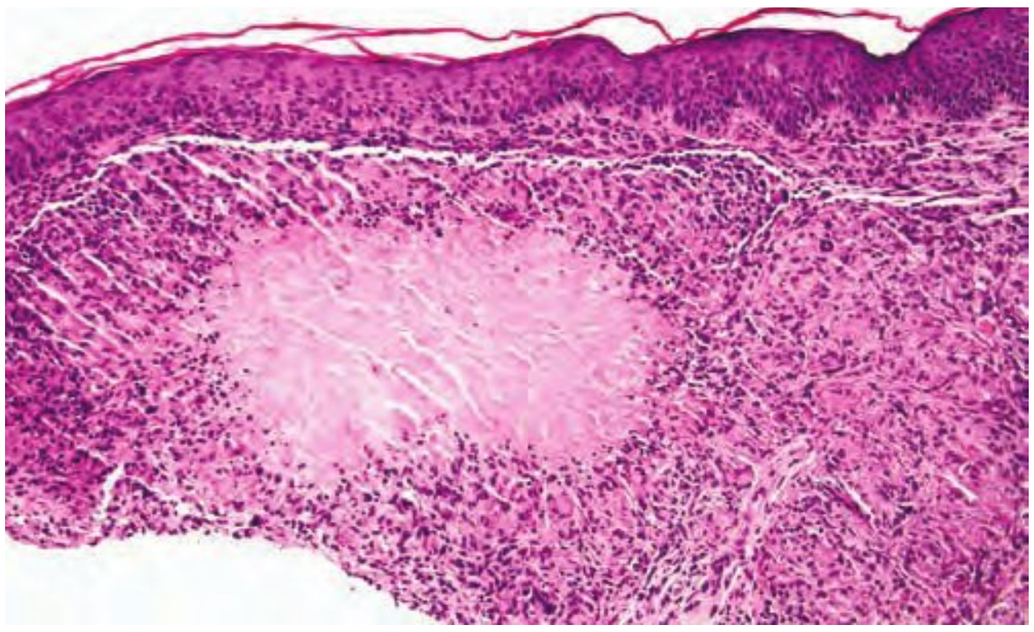


FIGURE 18-10. Lupus miliaris disseminatus faciei. Caseous necrosis is surrounded by epithelioid histiocytes and peripheral lymphocytes, forming a "tubercle" that mimics Mycobacterium tuberculosis infection.

Eosinophilic Pustular Folliculitis

Ofuji originally described *eosinophilic pustular folliculitis* (EPF) in immunocompetent Japanese patients as itchy follicular papules and pustules arranged in arcuate plaques with central healing and peripheral spread (103,104). Although most reported cases have been from Japan, the condition is now known to be geographically more widespread. Lesions typically involve seborrheic areas, including the face, trunk, and upper arms, with documented reports of extrafollicular lesions of the palms and soles (105,106). Moderate leukocytosis and eosinophilia in the peripheral blood may be present. There is usually spontaneous healing over months to years (107). There are reports of the eruption in children (108), including neonates (109), and in this subset lesions occur predominantly on the scalp. Scarring alopecia of the scalp in an adult has been reported (110). Although a cause has not been identified, rare medication-induced cases have been described due to carbamazepine (111) and allopurinol (112), after patch testing with minocycline (113) and indeloxazine hydrochloride (114), and after prolonged treatment with oral corticosteroids in a patient with pustulosis palmoplantaris (115). Cases have been associated with nevoid basal cell carcinoma syndrome (116), hepatitis C infection (117), and infestations (118).

Lesions with similar histology are well documented in patients with HIV infection (119), including children with HIV (120), and other immunocompromised conditions, such as myelodysplastic syndrome (121), non-Hodgkin's lymphoma (122), B-cell chronic lymphatic leukemia (123), polycythemia vera (124), after bone marrow transplantation (125), and after autologous peripheral blood stem-cell transplantation (126). There appear to be enough clinical dissimilarities from the disorder described by Ofuji to consider HIV-associated disease a distinct entity, and use of the terms *eosinophilic folliculitis* or *HIV-associated eosinophilic folliculitis* was recommended to reflect this (119). Another classification scheme proposed the designations classical, infancy associated, and immunosuppression associated (mostly HIV) (104,127). In HIV patients, lesions tend to be urticarial papules with less tendency to become pustular, and leukocytosis is less common (128). They are most commonly found on the face, scalp, and upper trunk and often are excoriated.

Histopathology. In Ofuji's disease, there is exocytosis of eosinophils into a spongiotic follicular infundibulum and accompanying sebaceous gland, eventually forming eosinophilic micropustules (Fig. 18-11) (110,129,130). The epidermis adjacent to the affected follicle may contain lymphocytes and eosinophils, with the latter aggregating into small eosinophilic pustules that are subcorneal or intraepidermal; these epidermal changes reflect the histologic picture seen in palmoplantar lesions, where follicles are absent (105). In more inflamed lesions neutrophils may be present (105). In the dermis, there are perivascular and interstitial infiltrates of lymphocytes and numerous eosinophils, which may surround sweat glands. Associated follicular mucinosis has been reported (131).



FIGURE 18-11. Eosinophilic pustular folliculitis. Eosinophils and lymphocytes surround and infiltrate the follicle, forming intrafollicular eosinophilic micropustules.

A study of 52 biopsies in 50 HIV-positive patients best described the histology of *HIV-associated eosinophilic folliculitis* (128). Perifollicular and intrafollicular lymphocytes and eosinophils are concentrated about the isthmus, and may involve the sebaceous duct. There is spongiosis of the follicular epithelium. Eosinophils and lymphocytes may be seen aggregating in the hair canal, but neutrophils are rare. In early lesions, lymphocytes may predominate and be distributed perifollicularly and interstitially. In more developed lesions, dermal inflammation diminishes and perifollicular/follicular inflammation increases. Less common findings include inflammation of the sebaceous gland, eosinophilic pustules, and follicular rupture (128). Dense eosinophilic infiltrates with degranulation and flame figures, resembling Well's syndrome, may sometimes be seen. A small number of macrophages can be present. Bacteria, yeast, or *Demodex* may be identified, albeit away from the areas of inflammation. Because the disorder is highly pruritic, excoriation is a common secondary finding.

Features that may help to distinguish suppurative folliculitis in HIV-positive patients from *HIV-associated eosinophilic folliculitis* have been described; suppurative folliculitis in HIV-positive patients more commonly shows an infiltrate dominated by neutrophils and macrophages, the presence of microorganisms amid the inflammation, and rupture of the involved follicle. The use of transverse histologic sections has been advocated over vertical sections for increasing diagnostic sensitivity and demonstrating the key pathologic findings in HIV-associated eosinophilic folliculitis (132).

Pathogenesis. The cause of Ofuji's disease (EPF) is not known. Although the prevalence in Japan could not be explained by HLA patterns (110), the occurrence in brothers in the neonatal period hints at some inherited predisposition or possibly an infectious etiology (133).

The perivascular infiltrating cells in EPF were found to be mostly T lymphocytes, with some $CD68^+$ myelomonocytic cells, and most of the eosinophils were positive for eosinophil cationic protein (134). A moderate increase in the number of tryptase-positive, chymase-negative mast cells, the type predominantly found in lung and small intestine, was noted around hair follicles and sebaceous glands (129). A study of Ofuji's disease found markers of sebaceous differentiation to be decreased or absent, whereas follicular differentiation markers were expressed normally (107).

In another study of three patients with EPF, serum levels of interferon-γ and IL-2, -4, and -6 were measured before and after successful treatment with indomethacin (135). Investigators found elevated IL-4 in the EPF patients, which remained unchanged after treatment, and increased interferon-γ with disease remission. Decreased expression of IL-5 mRNA in peripheral blood mononuclear cells was demonstrated after the disease was controlled in two EPF patients undergoing treatment with interferon-γ (136); IL-5 is responsible for the growth and differentiation of eosinophils.

Ultrastructurally, in EPF lesions characterized by an infundibular pustule, acantholytic outer root sheath keratinocytes showed desmosomal cleavage with microvilli formation, and some contained sebaceous lipid droplets (137). Apposition of T lymphocytes and Langerhans cells was seen.

In the differential diagnosis, eosinophilic follicular pustules may be seen in erythema toxicum neonatorum, and intraepidermal eosinophilic vesicles can be seen both in acropustulosis and the vesicular phase of incontinentia pigmenti. However, the clinical presentation of these conditions would generally be significantly different than that in EPF, although it has been suggested that EPF in infants and infantile acropustulosis may be variants of the same disorder (138). Identical eosinophilic pustular eruptions have been described in association with *Pseudomonas* infection (139) and in fungal infections due to dermatophytes (140).

Follicular Mucinosis and Alopecia Mucinosa

Follicular mucinosis is characterized clinically by grouped erythematous papules and/or plaques that may be markedly indurated or nodular (Fig. 18-12) and histologically by mucin accumulation in hair follicles (141). It can be classified into two types: a primary (idiopathic) type and a secondary variety. The *primary* form tends to have a shorter but benign course. The *secondary* type has been associated with numerous benign and malignant conditions, including lymphomas, of which the majority are mycosis fungoides. A distinct variant of mycosis



FIGURE 18-12. Follicular mucinosis/alopecia mucinosa. This round, slightly elevated pink plaque in an adolescent boy has resulted in clinically apparent alopecia because the hairs at this site are coarser.



FIGURE 18-13. Alopecia mucinosa. Diffuse thinning of the scalp associated with slightly elevated, scaly plaques. The scalp erythema and poorly defined areas of alopecia distinguish this example from alopecia areata.

fungoides—follicular mycosis fungoides—may or may not be associated with follicular mucinosis (142,143).

The *primary* form tends to affect children and young adults more frequently and resolves spontaneously in several months (acute benign type) or several years (chronic benign type) (144). It is often confined to the head and neck but may be disseminated. The *secondary* type tends to form more widespread plaques and is almost always a disorder of adults.

The secondary type has been found in association with other lymphoproliferative disorders, including Hodgkin's disease (145–147), cutaneous B-cell lymphoma (148), acute myeloblastic leukemia (149), chronic lymphocytic leukemia (147), and syringolymphoid hyperplasia with cutaneous T-cell lymphoma (150), as well as a number of inflammatory cutaneous disorders such as chronic discoid lupus erythematosus (151), angiolymphoid hyperplasia (152), alopecia areata (153), eosinophilic pustular folliculitis (131), spongiotic dermatitis, lichen striatus, arthropod bites, sarcoidosis, Goodpasture's syndrome (154), leprosy (155), and growths such as verrucae (154), melanocytic nevi, and squamous cell carcinoma of the tongue (156). The numerous associations with production of follicular mucin certainly suggest that this is a relatively nonspecific reaction pattern.

There has been controversy about whether the histopathology allows for distinction between the primary and secondary forms. Initially it was considered that the histopathology could be predictive (157). Later, some researchers claimed that transition from the benign form to a lymphomatous type could occur (158,159), whereas others disputed this finding (154). In 1989 a study of 59 cases concluded that there was no clinical or pathologic pattern by which the ultimate outcome of the condition could be predicted (145).

Others have reported that adults older than the age of 40 years with widespread follicular mucinosis are at increased risk for mycosis fungoides or Sézary's syndrome (154,158), although Cerroni et al. claimed that criteria purported to differentiate lymphoma-associated follicular mucinosis from the idiopathic type were not effective (159). A long-term follow-up study (median 10 years) of seven patients younger than 40 years of with primary follicular mucinosis failed to demonstrate progression to cutaneous T-cell lymphoma, despite the presence of a T-cell clone in five of the patients (160).

In 1957, Pinkus described *alopecia mucinosa,* the term used when follicular mucinosis affects terminal hair-bearing areas and is associated with hair loss (161) (Fig. 18-13). Papules and plaques may be present or inconspicuous in this form, which may show only alopecia. Scarring is seen more commonly when alopecia mucinosa is associated with cutaneous T-cell lymphoma. Others claim that alopecia mucinosa is simply one of the many morphologic variants of mycosis fungoides (162), whereas LeBoit and LeBoit acknowledged the paradoxes of alopecia mucinosa that have led to the debate over classification (163).

Histopathology. Within the outer root sheath and sebaceous gland epithelium, there is reticular epithelial degeneration that sometimes evolves into more extensive cavitation within which mucin is deposited (Fig. 18-14). Occasionally, little mucin can be detected, perhaps because of removal of this water-soluble material in the processing procedure. The deposited mucin is an acid mucopolysaccharide that stains metachromatically with toluidine blue at pH 3.0, as well as with Alcian blue at acid pH. The fact that it can be substantially removed by digestion with hyaluronidase demonstrates that the mucin is predominantly hyaluronic acid. Colloidal iron stain may also be used for its detection.

Inflammation is composed of lymphocytes and histiocytes, but there can also be eosinophils. There may be exocytosis into the outer root sheath epithelium of the infundibulum and the sebaceous gland epithelium. Although individual pathologic criteria are not absolutely diagnostic of the type of

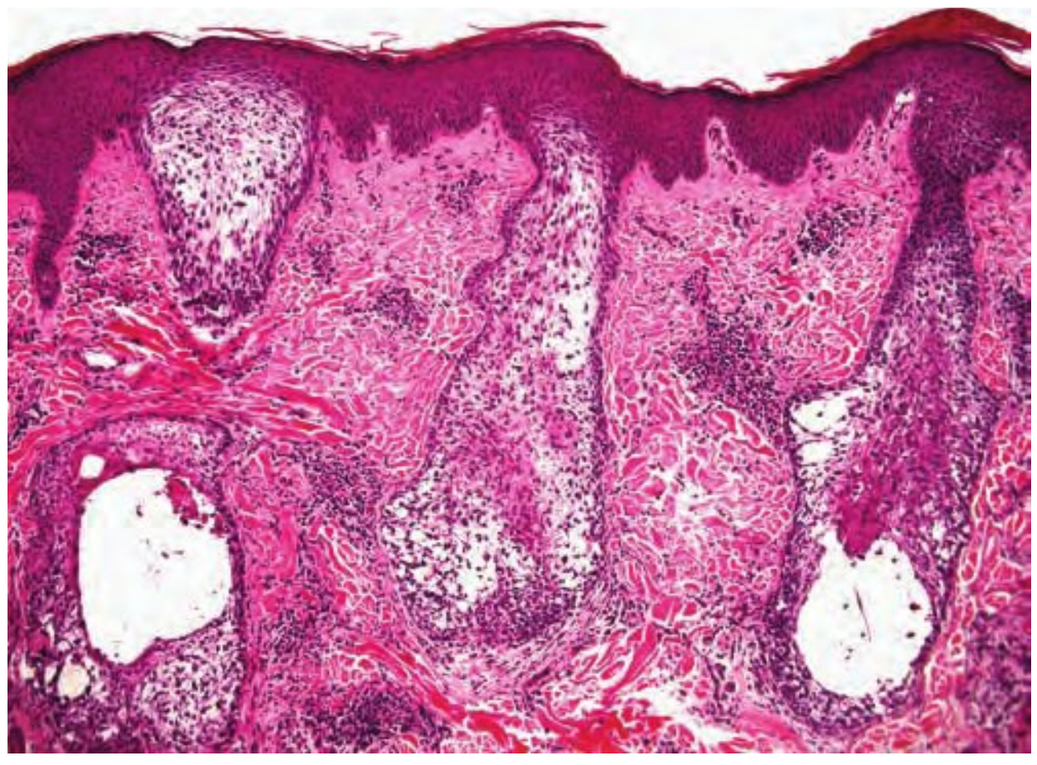


FIGURE 18-14. Follicular mucinosis. The outer root sheath epithelium of several follicles shows reticular degeneration with areas of cavitation. There are intercellular strands of bluish-staining mucin.

follicular mucinosis (primary or secondary), features that have been proposed as favoring a lymphoma-associated lesion include an atypical lymphocytic infiltrate or increased density of the perifollicular infiltrate with substantial folliculotropism (Fig. 18-15) (164). This study also suggested that a prominent eosinophilic infiltrate and more substantial mucin deposition tend to favor a benign process, but a subsequent study failed to substantiate these findings (145).

Pathogenesis. Electron microscopic studies have shown that the mucin is a product of the outer root sheath epithelial cells. The cytoplasm shows prominent, dilated, rough-surfaced endoplasmic reticulum containing fine, granular, filamentous material that is secreted into the intercellular spaces (165). In two of our patients with primary, idiopathic *alopecia mucinosa* with reversible alopecia, we found, using transverse sections, an increased number of resting-phase follicles, mostly catagen, ranging from 46% to 92% of all terminal follicles (unpublished observation).

Keratosis Pilaris

This common persistent condition characteristically affects the lateral aspect of the arms, thighs, and buttocks. Keratotic follicular papules, sometimes with surrounding erythema, are present. They are usually asymptomatic. Keratosis pilaris may be seen in association with ichthyosis vulgaris (166) and appears to be more common in patients with atopic dermatitis.

Similar lesions may form as part of a variety of more extensive erythematous keratinizing disorders. Keratosis pilaris rubra is a variant that shows more widespread skin involvement and more prominent erythema (167). Keratosis pilaris atrophicans represents a spectrum of clinical conditions, including keratosis follicularis spinulosa decalvans (168–170), in which the involved follicle becomes atrophic and destroyed, sometimes associated with scarring alopecia of the scalp.

Histopathology. An orthokeratotic keratin plug blocks and dilates the orifice and upper portion of the follicular infundibulum (Fig. 18-16). A twisted hair shaft may be trapped within this keratin material, and mild perivascular mononuclear cell infiltrates are usually present in the adjacent dermis.

A similar condition, lichen spinulosus (171), shows a very similar histologic picture except that the keratin plug may protrude more substantially above the skin surface and contain one or more hair shafts (172). Lesions similar to keratosis pilaris may also be seen in phrynoderma (vitamin A deficiency; see Chapter 16), but the follicular keratin plug is said to be parakeratotic (173).

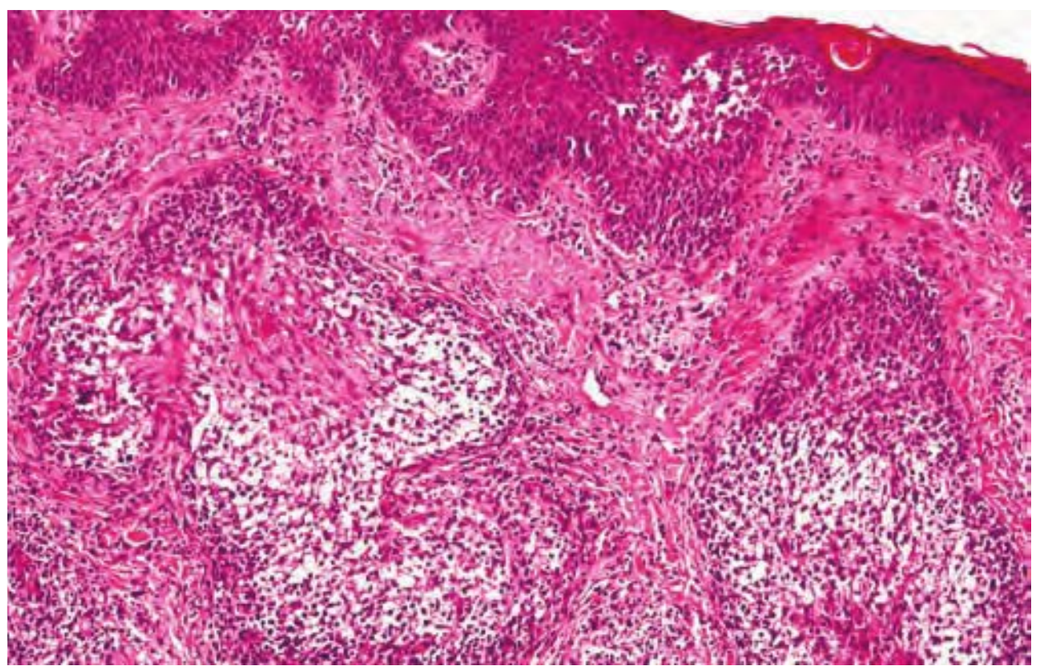


FIGURE 18-15. Follicular mucinosis associated with folliculotropic mycosis fungoides. In addition to changes of follicular mucinosis, there is extensive folliculotropism of lymphocytes. There is also epidermotropism of large lymphocytes.



FIGURE 18-16. Keratosis pilaris. The follicle is plugged with compact orthokeratin that protrudes above the skin surface.

Pathogenesis. Genetic factors may play a role in this condition. Patients with a generalized form of keratosis pilaris were found to have a chromosome 18p deletion, implicating a gene on the short arm of chromosome 18 (174).

Trichostasis Spinulosa

Trichostasis spinulosa is a fairly common condition that may present clinically as raised follicular spicules or as open comedones or be inapparent (175). It occurs predominantly on the face, nose, or cheeks of middle-aged and older individuals, but it has been reported in a pediatric patient (175). It may be pruritic. Generalized trichostasis spinulosa has been reported in a patient with chronic renal failure (176).

Histopathology. Affected hair follicles demonstrate retention of small hair shafts within a dilated infundibulum, sometimes enveloped in a keratinous sheath (Fig. 18-17). As many as 20 or more hair shafts may be trapped in this way, often projecting above the skin surface. A perifollicular mononuclear infiltrate may be present. In the clinical setting, the follicular plugs may be easily extracted with fine forceps or a comedone extractor and examined microscopically, demonstrating a cluster of vellus hairs within a keratinous plug.

Pathogenesis. The etiology of trichostasis spinulosa is not known for certain. The retained hairs are normal telogen hairs, which suggests a normally functioning follicle. Congenital dysplasia of the hair follicles and external factors such as dust, oils, ultraviolet light, heat, and irritants have been proposed (175). One hypothesis is that hair shaft entrapment is the result of hyperkeratosis in the follicular infundibulum, thus producing an obstruction to normal hair shedding (177).



FIGURE 18-17. Trichostasis spinulosa. A dilated follicular infundibulum with retention of multiple vellus hair shafts. The granular blue material represents resident bacteria of the follicle.

DISEASES OF HAIR FOLLICLES LEADING TO HAIR LOSS: ALOPECIA

A discussion of alopecia generally pertains to loss of hair on the scalp, although other body sites may be affected, as can be seen in alopecia areata, trichotillomania, telogen effluvium, and lichen planopilaris, to name a few. A useful way broadly to classify the alopecias is to divide them into nonscarring and scarring types depending on their (relative) propensity to culminate in permanent hair loss. An algorithmic approach to the alopecias was presented in an excellent paper by Solomon (178). Sometimes classification of an individual case of alopecia can be complicated by the coexistence of more than one process. For example, scarring alopecia can occur in a patient with underlying androgenetic alopecia.

Some types of alopecia are discussed elsewhere in this text, such as lichen planopilaris (see Chapter 7), lupus erythematosus (see Chapter 10), syphilitic alopecia (see Chapter 22), perifolliculitis capitis abscedens et suffodiens (see Chapter 21), folliculitis (*"acne"*) keloidalis nuchae (see Chapter 21), and alopecia neoplastica (see Chapter 36). Although hair shaft disorders result in alopecia, a diagnosis is often made on clinical grounds and based on examination of hair shafts rather than biopsy material; therefore, a discussion of hair shaft disorders is not included here but can be found in one of several review articles (179–181). Alopecia that is easily diagnosed in the clinical setting based on history, physical examination, and microscopic assessment of gently pulled hairs, thereby negating the need for a scalp biopsy, is also not discussed; these include postoperative pressure-induced alopecia, temporal triangular alopecia, and loose anagen syndrome.

General Considerations in Diagnosing Alopecia

The Scalp Biopsy

A punch biopsy or incisional biopsy extending into fat to include terminal hair bulbs is necessary for proper evaluation of alopecia. A punch biopsy is easier for the clinician to perform, and most scalp biopsies are submitted as such. It is generally accepted that at least a 4-mm punch be used to obtain a sufficient number of hairs for study. In addition, many of the published quantitative parameters for diagnosing different forms of alopecia are based on a 4-mm punch, so this is the one that is generally recommended (182).

Controversy exists regarding the manner in which the punch biopsy should be sectioned: vertically, where the cylinder of tissue is bisected longitudinally, which is the standard way of sectioning punched specimens procured for other

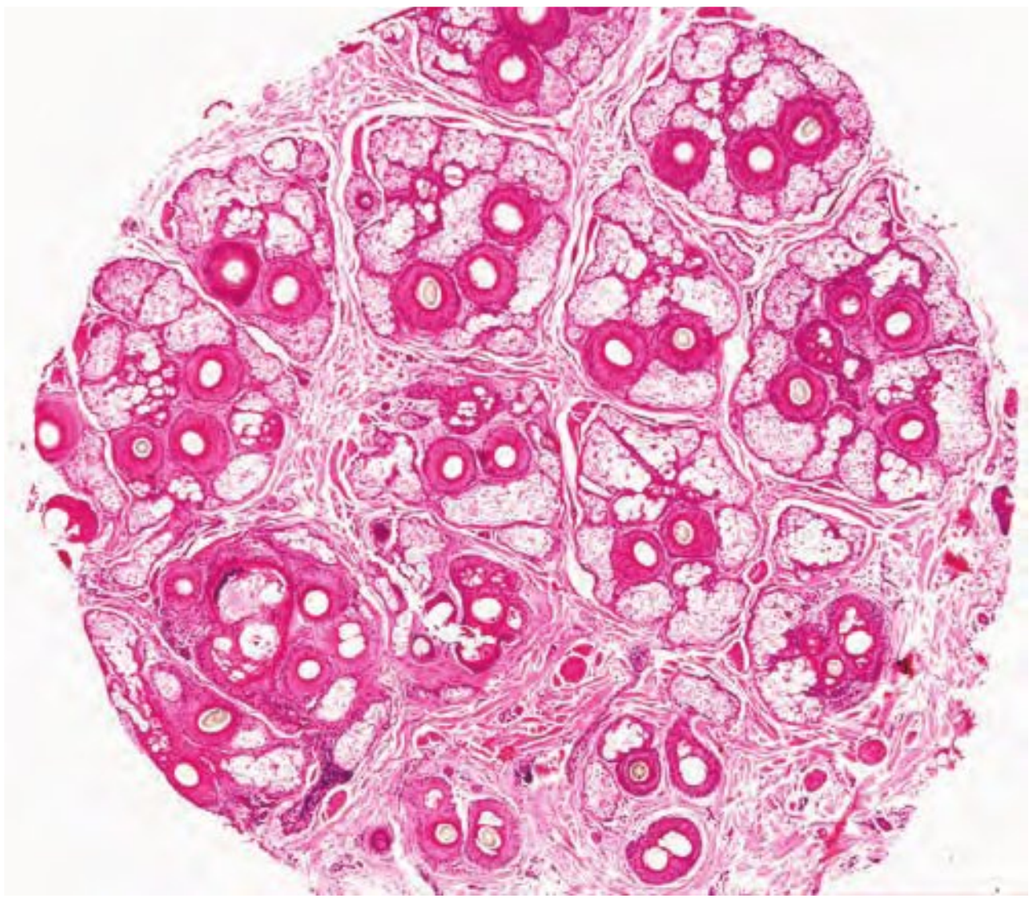


FIGURE 18-18. Horizontal section, scalp. This 4-mm punch biopsy was sectioned horizontally (a.k.a. transversely), enabling visualization of every follicle in the specimen. At this level, through the middermis near the isthmus, arrangement of pilosebaceous structures into "follicular units" is apparent.

cutaneous disorders, or horizontally (a.k.a. transversely), in which the skin cylinder is "bread-loafed," which is the method pioneered by Headington (183). Horizontal sectioning enables visualization of all the follicles in the specimen (Fig. 18-18), whereas it has been estimated that conventional vertical sections demonstrate only 10% to 15% of the follicles in the sample (183). Dermatopathologists appear to be polarized with regard to which method of sectioning is preferable. Of dermatopathologists who favor vertical sections, some feel that they can glean as much information if serial sections are obtained, and some feel uncomfortable interpreting hair follicle anatomy and pathology in a horizontal orientation. A notable disadvantage of transverse sections is the inability properly to evaluate the epidermis (178). However, when a transversely sectioned biopsy is cut through, a portion of the epidermis can usually be seen and evaluated, albeit tangentially.

Some authors have recommended that two 4-mm punch biopsies be performed from the area of disease activity, and that one biopsy be sectioned transversely and the other sectioned vertically. The latter is bisected at the time of the biopsy, with one half sent for routine histology (embedded with the two halves of the transversely sectioned specimen), and the other half processed for direct immunofluorescence (184). In some forms of nonscarring alopecia such as telogen effluvium or early androgenetic alopecia, in which the histologic findings may be subtle, it may be helpful to take one specimen from the involved vertex of the scalp and one specimen from the occiput; on comparing the two, one should find the occipital scalp to be relatively normal in androgenetic alopecia and equally involved in telogen effluvium. Certainly a single biopsy is preferable from a patient morbidity standpoint, and a single biopsy may be sufficient (185).

For diagnosing cicatricial alopecia, the recommendation is for one 4-mm punch biopsy specimen from the edge of an involved area where there is new hair loss, a positive hair pull test, or inflammation as evidenced by clinically apparent erythema (186). If the goal of the biopsy is to assess the potential for hair regrowth (prognosis), then the optimal area to sample is an older, more central area with a "burnt-out" appearance.

In the past, serial horizontal sections would result in numerous sections and multiple slides to review, typically 12 to 20 (185). A proposed method for improving the convenience of transverse processing recommended trisecting or quadrisecting the specimen, inking one side of each resultant disk of tissue in a consistent orientation, and then embedding them all in a single cassette so that several microanatomic levels can be viewed on a single slide (185). My experience with this technique is that, although convenient, it sometimes results in loss of tissue (sometimes critical tissue) because laboratory personnel significantly efface some of the tissue pieces to obtain a "good" slice of *all* of the tissue disks. This can occur particularly when the pieces of tissue are embedded at slightly different depths in the paraffin block.

I have found that a safer way to process the punch specimen to avoid loss of tissue is to bisect it once transversely, approximately 1 mm below the epidermal surface, ink the cut surfaces, and embed the two pieces so that the inked surfaces are cut first, a method previously advocated (178,183). Deeper levels from the block reveal sections that approach the epidermis for one piece of tissue and the subcutis for the other piece of tissue.

The ideal way to procure a punch biopsy for transverse processing is to orient the punch tool parallel to the direction of hair growth, decreasing the frequency that hairs are transected by the biopsy procedure. The result is a cylinder of scalp skin in which the sides of the cylinder are not exactly perpendicular to the epidermal surface. With this in mind, when the specimen is bisected 1 mm below the epidermis, the cut should be angled parallel to the epidermal surface (not perpendicular to the sides of the tissue cylinder), so that each histologic section will show all of the follicles at roughly the same microanatomic level, which facilitates their interpretation. As a consequence, however, follicles and hair shafts will appear ovoid in shape under the microscope rather than round.

I prefer to interpret transverse sections whenever possible, and this chapter emphasizes this method. Transversely sectioned scalp biopsies offer the following advantages (178): (a) *All* of the follicles in the biopsy specimen can be seen and studied, (b) it allows for rapid evaluation of hair density and follicular units, (c) it allows for accurate assessment of follicle size, (d) pathologic alterations at different levels of the follicle can easily be evaluated, and (e) it facilitates quantitative interpretation of the biopsy. In my experience, it is a more sensitive technique for detecting tinea capitis when only scattered follicles are involved. Horizontal sections are ideal for evaluating the

number of viable follicles and estimating prognosis for hair regrowth. As previously mentioned, interpretation of horizontal sections requires a thorough understanding of hair follicle microanatomy, as well as the normal hair cycle. These are superbly described in Chapter 3 and in other sources (178, 183,187) and are not reiterated here.

Recently introduced terms include *exogen*—a distinct phase of the hair cycle in which the hair shaft is actively shed, most likely by a proteolytic mechanism (188,189)—and *kenogen*—referring to the empty hair follicle after the telogen hair is shed (190). Kenogen is believed to represent a physiologic rest period for the follicle prior to initiation of a new growth phase.

Terminology Defined

Solomon and Templeton noted that "working definitions" are "important in the microscopic evaluation of alopecia," although "these definitions are arbitrary and therefore debatable" (191). Although authors differ in the definitions they use to characterize hair follicles, the following definitions are commonly employed. A terminal hair was designated by Headington as having a hair shaft diameter of 0.06 mm or greater and a vellus hair as having a hair shaft diameter of 0.03 mm or less (183). Between terminal and vellus hairs are intermediate hairs (a.k.a. indeterminate), whose shaft diameter, i, is defined as $0.06 > i > 0.03$ mm (Fig. 18-19). A micrometer is sometimes needed accurately to assess hair shaft diameter, although without actually measuring them, hair follicles can be classified by comparing the shaft size to the width of the inner root sheath; the diameter of a vellus hair shaft should be less than or equal to the thickness of the inner root sheath (Fig. 18-19). Qualitatively, terminal hairs have their bulbs anchored in the subcutaneous fat, whereas vellus hair bulbs are in the mid to upper dermis.

True vellus hairs lack melanin pigment and are small throughout their existence, whereas *miniaturized* vellus hairs are terminal hairs that have decreased in size. Because these are histologically identical, it is not necessary to distinguish them for the purpose of diagnosing alopecias; henceforth in this chapter, the term *vellus hairs* will encompass true vellus hairs *and* miniaturized terminal hairs. Although some authors group intermediate hairs with the terminal hair population for the purpose of quantification, I prefer to include them with the vellus group because more often they represent a transitional follicle undergoing the process of miniaturization to a vellus hair. Reversal of the process via therapy with minoxidil or finasteride can confuse the picture, however. A cross section at the lower infundibular level is optimal for visualizing vellus hairs, allowing one accurately to count terminal and vellus hair shafts to determine the terminal-to-vellus hair ratio.

In determining the telogen count or anagen-to-telogen ratio, the term "*telogen*" actually encompasses all phases of the nonanagen follicle, including telogen, catagen, and telogen germinal unit (Fig. 18-20), because they all represent stages in a continuum: the irreversible process of hair follicle regression and shedding. For instance, a catagen follicle, with an epithelial column in the subcutis and/or lower dermis, often shows a telogen hair near the isthmus. Although vellus hairs also cycle, only terminal-sized follicles in catagen and telogen are counted as part of the regressing/resting hair population. The telogen count derived histologically, using these definitions, reflects the count obtained in the clinical setting by forcible hair pluck (using a rubber-tipped hemostat) because this method is unsuccessful at dislodging the smaller, vellus hairs (187,192).

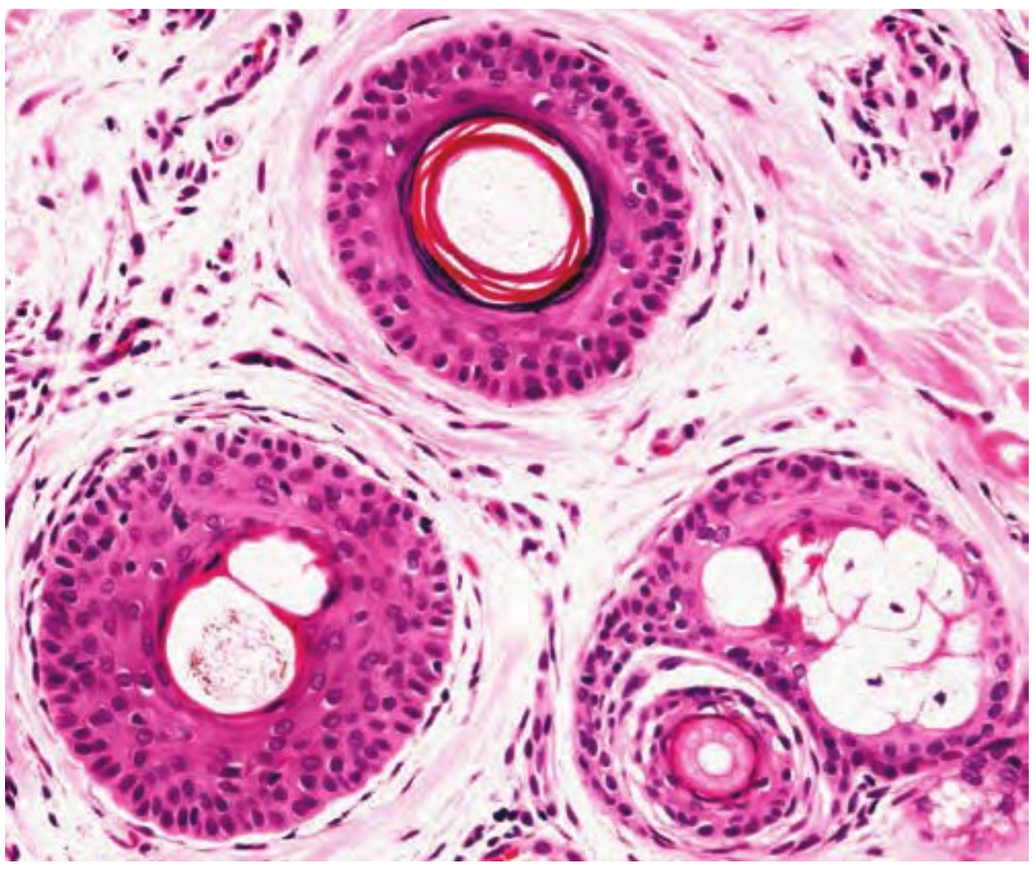


FIGURE 18-19. Normal variation in hair diameter (horizontal). This level is through the infundibulum of the terminal follicle, defined by a hair shaft diameter that is 0.06 mm or greater (top). The vellus hair (right) is readily identifiable by a shaft diameter that is equal to or less than the thickness of the inner root sheath (0.03 mm or less). An intermediate hair (lower left) has a shaft diameter that is between the other two.

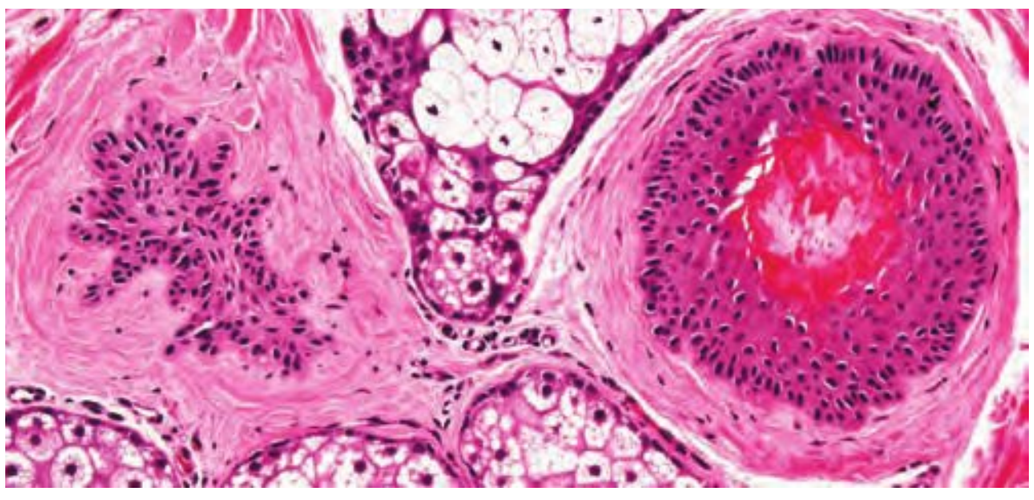


FIGURE 18-20. Normal resting follicles (horizontal). The follicle at right is a telogen follicle, identifiable by brightly eosinophilic trichilemmal keratinization of the proximal hair shaft. This structure is the histologic correlate of easily displaced telogen hairs viewed by microscopy in the clinical setting, so-called "club hairs." To the left is a telogen germinal unit, which represents the secondary hair germ. This structure is found in the mid to upper dermis and is characterized by follicular epithelium with radial projections. In vertical sections, it is sometimes visible just beneath the telogen hair.

A cross section through the isthmus is optimal for assessing the number of telogen and catagen hairs and telogen germinal units. This telogen count should be interpreted in the context of a second count at the infundibular level to assess terminal and vellus hairs because follicles in telogen or catagen according to their appearance near the isthmus show a shaft in the infundibulum that looks identical to that of a terminal anagen follicle; that is, a hair shaft with a diameter of 0.06 mm or greater situated in the infundibular hair canal. Often the infundibular portion of the hair shaft, untethered by the inner root sheath, is missing, presumably carried away by the microtome blade. In this situation, the pathologist must rely on the caliber of the follicular outer root sheath and the diameter of the empty hair canal to extrapolate the size of the hair shaft and obtain more accurate counts.

Miniaturization and conversion to catagen and telogen leave many collapsed fibrous root sheaths in the subcutis (Fig. 18-21). Also known as "stelae" and "fibrous streamers," they are found in conditions in which there is follicular miniaturization (i.e., androgenetic alopecia) or conditions with increased numbers of catagen and telogen hairs, such as telogen effluvium and trichotillomania.

Normal Parameters

Normal parameters as determined by examination of transversely sectioned scalp biopsies have been published in various sources and are typically based on a 4-mm punch biopsy. Most were from studies of white subjects, but ethnic differences in "normal" values have been demonstrated, and this must be taken into consideration when evaluating a scalp biopsy. Whites without alopecia should have approximately 40 total hairs in a 4-mm punch biopsy, with roughly 20 to 35 terminal hairs and 5 to 10 vellus hairs (182,183,192,193). The normal terminal-to-vellus hair ratio for adult scalp is 3:1 to 4:1 (183) but at least 2:1 (194). Another study found a value of 7:1 (193).

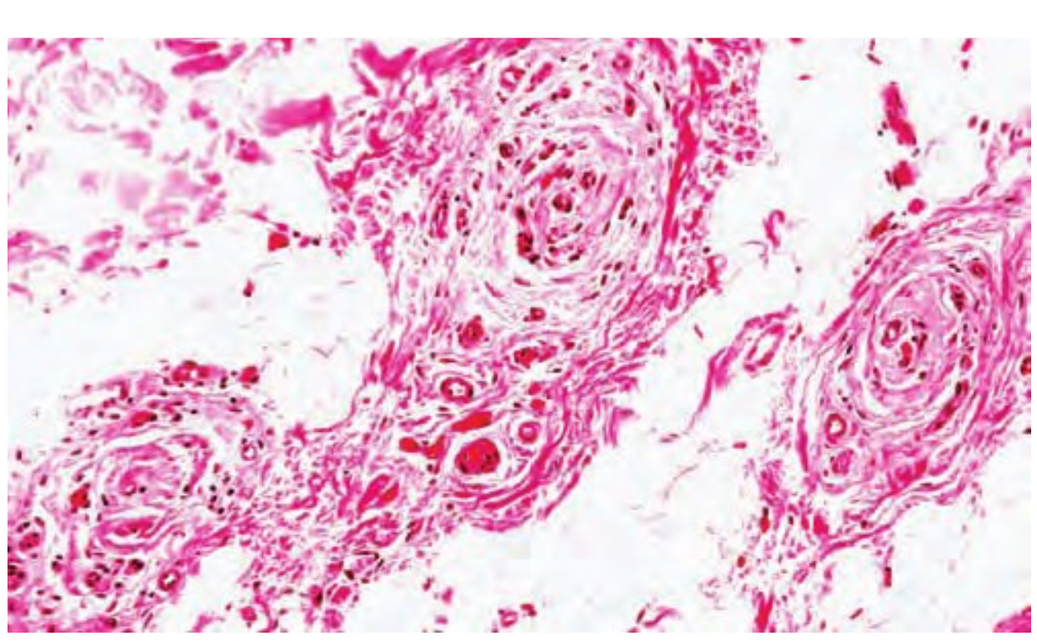


FIGURE 18-21. Fibrous streamers (horizontal). Also known as stelae, these collapsed fibrous sheaths are subcutaneous evidence of hairs that have moved upward through the process of miniaturization or conversion to telogen. They consist of concentrically arranged bands of collagen with numerous capillaries and an increased number of mast cells.

Hair density in African-Americans was found to be significantly lower than in whites, with an average of 18 terminal and 3 vellus hairs in a 4-mm punch biopsy (195). However, the follicles are typically larger (196). In Koreans, the follicular density was found to be significantly lower than in whites and blacks (197).

Hair follicles on the scalp are arranged in follicular units—bundles of hairs naturally found together. They form hexagonal modules separated from one another by intervening collagen and are best visualized by transverse sections through the upper dermis near the isthmus (Fig. 18-18) (198). There are typically 10 to 12 follicular units in a 4-mm punch (178). Each follicular unit normally contains 2 to 5 terminal hairs and 0 to 2 vellus hairs, along with sebaceous glands and arrector pili muscle (182).

Nonscarring Alopecia

Alopecia that is nonscarring clinically shows intact follicular ostia and histologically shows a normal density of hair follicles (199,200). Despite being categorized as "nonscarring," conditions such as androgenetic alopecia, longstanding alopecia areata, and traction alopecia can lead to irreversible loss of hair follicles. Transverse sections are particularly useful in the histologic diagnosis of nonscarring alopecias because the anagen-to-telogen ratio and terminal-to-vellus hair ratio may be crucial in making an accurate diagnosis. In particular, female patients with a fairly diffuse, nonscarring alopecia can be a diagnostic dilemma based on clinical grounds alone, and a biopsy can help. The main diagnostic possibilities in this setting are (a) female pattern hair loss, (b) acute and chronic telogen effluvium, (c) diffuse alopecia areata, and (d) loose anagen syndrome (201).

Alopecia Areata

Alopecia areata (AA) is characterized clinically by complete or nearly complete absence of hair in one or more circumscribed areas of the scalp (Figs. 18-22). Clinical inflammation, typically manifested by erythema, is not obvious, and the follicular openings are preserved, a clinical finding that allows the examiner to make the assessment of a nonscarring alopecia. In active areas of involvement, hair shedding is seen, as well as some short, fractured hair shafts, including the pathognomonic "exclamation point" hair. Complete scalp involvement (*alopecia totalis*) may occur suddenly or through prolonged, progressive disease. Complete or nearly complete loss of all body hair (*alopecia universalis*) can also occur. Involvement of the eyebrows and eyelashes and regularly spaced pits on the surface of the nails may be seen. The majority of patients with localized disease undergo spontaneous resolution, but others show persistent disease, and a few patients have permanent hair loss. "The only predictable thing about the progress of alopecia areata is that it is unpredictable" (202), which means essentially that one cannot reliably predict which patients will have limited disease with spontaneous resolution and which will have recurrent disease or chronic, severe disease.



FIGURE 18-22. Alopecia areata. A patch of alopecia with obvious follicular pores, indicating a nonscarring type of hair loss. Exclamation-point hairs are present at the edge of the patch to the right. Despite the microscopic lymphocytic infiltrate that is sometimes present, the areas lack clinical evidence of inflammation, namely erythema.

Histopathology: The diagnostic pathologic feature is peribulbar lymphocytic inflammation ("swarm of bees") affecting anagen follicles (Fig. 18-23) or follicles in early catagen. The inflammatory assault on anagen follicles induces a premature conversion to catagen (Fig. 18-24). Consequently, the number



FIGURE 18-23. Alopecia areata (horizontal). Classic peribulbar lymphocytic inflammation likened to a "swarm of bees."

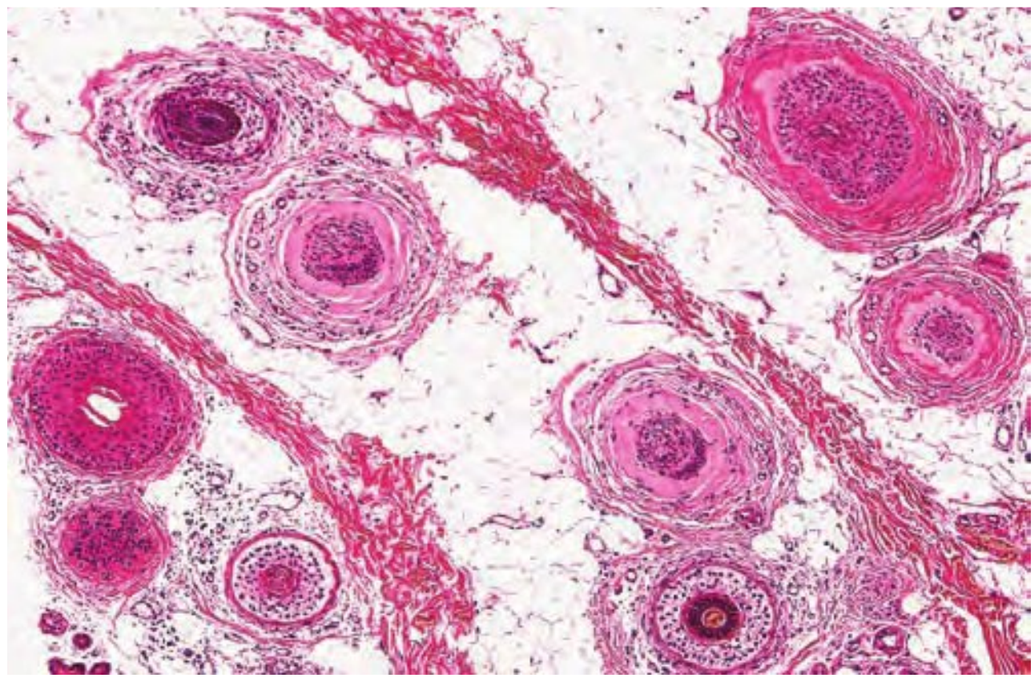


FIGURE 18-24. Alopecia areata (horizontal). Although peribulbar inflammation is not obvious here, the combination of an increased number of resting hairs and miniaturized hairs is characteristic of alopecia areata. Catagen follicles are notable by their eosinophilic "glassy" membrane and lack of a hair shaft.

of catagen and telogen follicles found may be marked, approaching 100% (203,204). Follicles may enter a persistent phase of telogen in which the hair shaft has already been shed, manifested by the *telogen germinal unit* (Fig. 18-20) (204). As follicles enter catagen, the lymphocytic infiltrate may persist around the epithelial remnant of the receding follicle and also within and surrounding the collapsed follicular sheaths. Telogen hairs show little to no perifollicular inflammation.

Lymphocytes may also be seen sparsely infiltrating the matrix epithelium of anagen follicles, inducing damage to the matrical cells that includes intra- and intercellular edema, cellular necrosis, and microvesicle formation. One of the earliest findings was shown to be a loss of structural integrity of bulbar keratinocytes in the central part of the supramatrical bulb and shrinkage of hair bulbs toward a club shape (205). As a result of injury to bulbar melanocytes and keratinocytes, pigment casts, which are clumps of melanin pigment, may be found within the dermal papilla, the sheath of miniaturizing or regressing follicles, or the follicular epithelium (194). Pigment casts are more often found in trichotillomania; one interpretation of their presence in the context of AA is that here too they represent external manipulation of the hair (49). Pigment casts have also been found in postoperative pressure-induced alopecia, leading those authors to postulate that they resulted from the sudden conversion of follicles from anagen to catagen, as occurs in trichotillomania and AA (206).

The inflammatory assault may produce dysmorphic follicles and shafts. Anagen hairs not sufficiently damaged so as to enter prematurely into catagen may continue to manufacture a hair shaft, one that may be small, distorted, and often nonpigmented (termed *trichomalacia*). The hair shaft may taper to a point so tiny and fragile that it fractures. Small, abnormal follicles called *nanogen* hairs are a distinctive finding in longstanding cases (Fig. 18-25) (196). They are difficult to categorize as anagen,

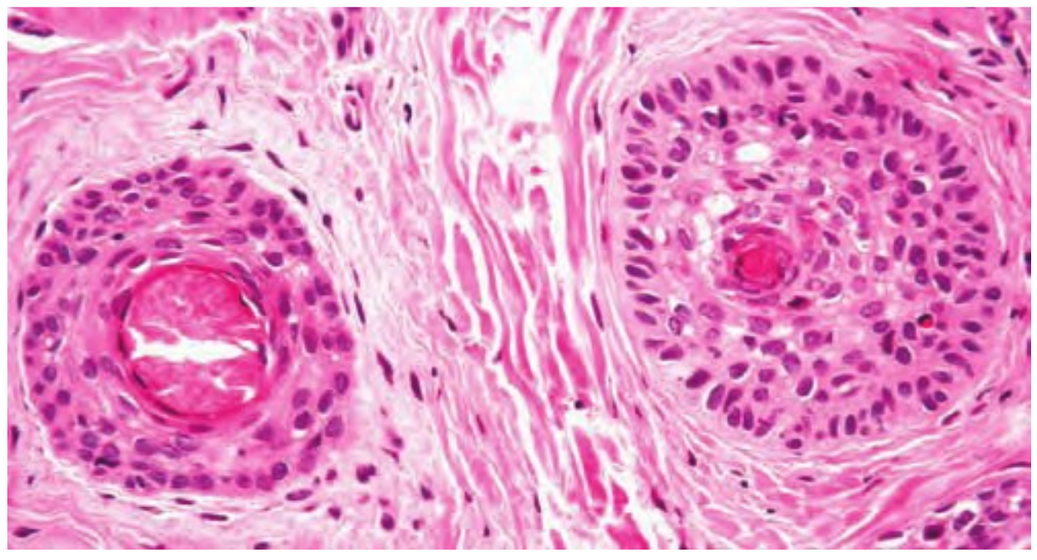


FIGURE 18-25. Alopecia areata (horizontal). Dystrophic hairs. The follicle at left has no shaft at all; the inner root sheath completely fills the canal. The follicle to the right is producing only a minute, "pencil-point" hair shaft that will break easily.

catagen, or telogen hairs, and in transverse sections they show only a minute, incompletely keratinized hair shaft or no shaft at all.

As telogen follicles reenter anagen, they again come under attack from pathogenic lymphocytes, which precipitate premature conversion to catagen once again, so that anagen duration becomes shorter and shorter and the follicles begin to miniaturize (Fig. 18-24). As the follicles decrease in size they become situated more superficially, although often deeper than normal vellus hairs, with their bulbs situated in the mid to lower dermis (194). With disease chronicity, most of the hairs become miniaturized. Miniaturization and conversion to catagen and telogen leave many collapsed fibrous root sheaths in the subcutis.

Whiting found that transversely sectioned scalp biopsies showed the diagnostic features of alopecia areata more often than vertically sectioned biopsies (207). He also published mean quantitative hair counts for horizontally sectioned scalp biopsies of alopecia areata. The mean terminal-to-vellus hair ratio was similar to that seen in androgenetic alopecia (1.1:1), reflecting extensive miniaturization. The mean anagen-to-telogen ratio was 73%:27%, and the total hair count (mean of 27 hairs) was 33% less than in the control group, with more severely affected patients (alopecia universalis) at the lower end of the spectrum. Others have also found that the follicular density can decrease in severe alopecia totalis and universalis of long duration (a decade or more), with scars replacing some of the follicular sheaths (208).

Whiting and others have emphasized the use of follicular counts to aid in the diagnosis of AA when the characteristic peribulbar inflammation is missing, with a high percentage of catagen or telogen hairs and miniaturized hairs as a strong sign of AA (Fig. 18-24) (209). In one study, the presence of eosinophils around the bulb and within fibrous tracts was found to be a helpful diagnostic feature of AA, identifying it in 38 of 71 patients. In biopsies lacking peribulbar lymphocytic inflammation, eosinophils were found approximately 50% of the time (210). Some plasma cells may also be present.

Some authors claim that in longstanding AA, the inflammatory infiltrates appear to diminish (203), whereas others believe that the degree of inflammation found on biopsy does not depend on disease duration, citing cases of longstanding AA that showed a great deal of inflammation (194). In a reappraisal of the histopathology of AA, Whiting suggested that the key factor in the histologic picture was the duration of the attack, with lymphocytes surrounding mainly terminal hair bulbs in acute episodes and involving mainly miniaturized hair bulbs in chronic, recurrent disease (211).

In the histologic differential diagnosis, alopecia syphilitica may closely mimic active AA (212). Features that help to distinguish syphilitic alopecia include lymphocytes situated near the isthmus, the presence of plasma cells, an endothelial reaction, interface dermatitis, and neutrophils in the stratum corneum (212,213). Alopecia areata may also look identical to the patchy, nonscarring alopecia that occurs in the setting of systemic lupus erythematosus, which shows mononuclear cell inflammation around terminal and miniaturized anagen hair bulbs, as well as an increased percentage of resting hairs, sometimes approaching 100% (196). Features favoring lupus erythematosus include increased dermal mucin, focal basal vacuolization of infundibular epithelium, and inflammation around blood vessels and eccrine glands, particularly when the infiltrate is dense. Although androgenetic alopecia shows diminution of follicular size, dermal infiltrates that are present in this condition are usually superficial, perivascular, and periinfundibular. Using a comparison of clinical and histologic features, one paper discussed problematic differential diagnoses with respect to AA (214).

Pathogenesis. The exact pathogenesis of AA is not known, but substantial evidence exists to support a role for genetic factors, nonspecific immune- and organ-specific autoimmune reactions, and environmental triggers (202,215–217). The antigenic stimulus for autoimmune attack may be the follicular keratinocyte, melanocyte, or dermal papilla. Advances in the understanding of alopecia areata in the last decade have benefited from animal models of the disease (218), including the C3H/HeJ mouse (219,220), the Dundee experimental bald rat (221), and the Smyth chicken (222). Quantitative and qualitative investigational guidelines for the study of AA were proposed in 1999 to facilitate collaboration among researchers, data comparison, and sharing of tissue specimens (223).

Familial cases of AA are well recognized, suggesting a genetic predisposition (224). A family history of AA reportedly ranges between 10% and 42% (225), with higher incidences in patients with disease onset early in life and in identical twins (226). Alopecia areata has been associated with both HLA class I and class II antigens, with different forms and severity of AA found to be associated with certain HLA types (202,227,228). AA has been associated with many conditions, including Down's syndrome, atopy, vitiligo, thyroid disease, pernicious anemia, diabetes, myasthenia gravis, lupus erythematosus, rheumatoid arthritis, ulcerative colitis, lichen planus, polymyalgia rheumatica, *Candida* endocrinopathy syndrome, and idiopathic thrombocytopenia purpura (202,229).

In a study using indirect immunofluorescence, autoantibodies to various parts of the anagen hair follicle were found in AA patients (230). Most commonly targeted were the outer root sheath, then the matrix, inner root sheath, and hair shaft. Tobin et al. also found serum autoantibodies to pigmented hair follicles in 100% of AA patients but in only 44% of control patients (231).

Earlier experiments showed the peribulbar infiltrate to be composed predominantly of $CD4^+$ cells (helper T lymphocytes) (232). Subsequently, $CD8^+$ cells (suppressor-cytotoxic T lymphocytes) were implicated in the pathogenesis of AA (233,234), with experiments supporting a cooperative role between $CD8^+$ and $CD4^+$ T cells (235). Expression of cell adhesion molecules in the matrix epithelium, dermal papilla, and adjacent vessels has been demonstrated, suggesting a mechanism for leukocyte binding (236,237).

The immune system of the hair follicle is unique and differs from that of the surrounding skin (238). The epithelial portion of the proximal anagen hair is immune privileged; the inner root sheath and hair matrix do not express major histocompatibility class (MHC) class I antigens (238–241). A theory put forth by Paus, an "immune privilege collapse model," suggests that in AA, the body's immune system may begin to recognize immune-privileged hair follicle antigens as a result of upregulated MHC molecules or downregulation of local immunosuppressive factors (238,242).

Cytokines may play an important role in AA. When serum cytokine levels were measured, it was found that IL-1α and IL-4 (Th2 cytokines) were elevated in patients with localized AA, whereas interferon-γ and IL-2 (Th1 cytokines) were significantly increased in AA patients with severe disease (alopecia universalis) (243). IL-1α, IL-1β, and tissue necrosis factor-α have been shown *in vitro* to produce changes in hair follicle morphology that resemble those in AA (244–246). In addition, a role for the peripheral nervous system has been postulated in AA, via neuropeptides with pro- and antiinflammatory properties released in the vicinity of critical areas of the hair follicle (247–250).

Trichotillomania

Trichotillomania is a condition in which patients pull or manipulate hair from the scalp or other body sites (251). For example, persistent rubbing of an area of the scalp that may be pruritic or compulsive avulsion of hair shafts can lead to zones of alopecia characterized by sparse, ragged, broken stubble. Hair shaft breakage and loss may be associated with damage to the scalp, as evidenced by erosions or crusts. Trichotillomania occurs most often in children and adolescent girls. In children under the age of 6 years, the disorder may be more benign and self-limited (252). In teens and adults, trichotillomania is more likely to be associated with psychopathology. It has features in common with obsessive-compulsive disorder (253,254), and in one study a large proportion of patients with trichotillomania also had comorbid self-injurious habits (255). Trichotillomania is part of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, classification of psychiatric disorders (255). Treatment of this form is often difficult; conventional modalities that may be tried include antidepressant or psychotropic medications, topical adjunctive therapies, and psychotherapy (252). Concomitant alopecia areata has been reported (256).



FIGURE 18-26. Trichotillomania (vertical). The hair canal is distorted in a spiral configuration, most likely secondary to twisting of the hair. Pigment casts, derived from bulbar or hair shaft melanin, are present.

Histopathology. In horizontally sectioned biopsies of trichotillomania uncomplicated by the coexistence of other types of alopecia, the density of hair follicles is normal, as is the terminal-to-vellus hair ratio. The diagnostic finding, when seen, is distorted hair follicle anatomy, without inflammation (Fig. 18-26) (194). Specifically, the pulling of hairs can leave behind empty anagen follicles and "torn-away" follicles, the result of plucked hair shafts that retain parts of the hair matrix and root sheaths (Fig. 18-27) (194). Additional microscopic evidence of traumatic injury was published by Royer et al. as the "hamburger sign," describing a vertically oriented split in the hair shaft containing proteinaceous material and erythrocytes, resembling a hamburger within a bun (257). Damaged follicles enter the resting phase, leading to an increase in the percentage of catagen and telogen hairs, as high as 75% (Fig. 18-28) (258). Often the hairs do not become normal catagen hairs and appear distorted and abnormal (194).

Pigment casts, which are clumps of melanin pigment, may be seen in the hair papilla and peribulbar connective tissue. They are also commonly seen in the upper portion of the hair follicle (Fig. 18-26) as a result of pigmented matrical cells

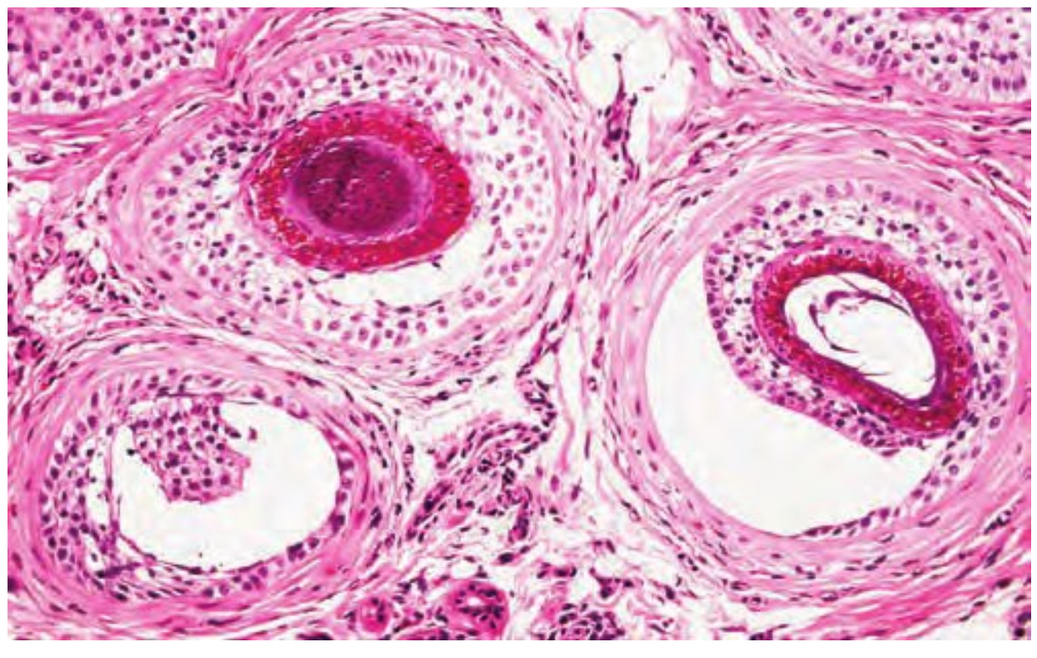


FIGURE 18-27. Trichotillomania (horizontal). At left is an empty anagen follicle, where a rim of outer root sheath epithelium remains after the hair was forcefully pulled, taking with it the inner root sheath and part of the outer sheath. At right, the follicle is partially avulsed and the shaft that is normally tightly anchored to the inner root sheath at this level is gone.

being deposited distally as the hair is plucked (194). Pigment casts are due to injury to the hair matrix, although some authors have theorized that they result from the sudden conversion of anagen to catagen (206). Hair shaft changes, termed *trichomalacia*, may be seen. Characterized by diminished size, distorted and odd shape, and irregular pigmentation of the shaft, trichomalacia is additional evidence of trauma to the matrix (194,258). Traumatized follicles can also show considerable distortion of the bulbar epithelium and conspicuous hemorrhage (258).

Because not all follicles in a given area are affected, transversely sectioned scalp biopsies may increase the yield of finding the diagnostic histologic features of trichotillomania, including increased numbers of catagen and telogen hairs (most cases) and empty or distorted follicles (greater than 50% of cases) (194). The same study found pigment casts and trichomalacia in less than 50% of cases. When the scalp is also rubbed persistently, epidermal changes of lichen simplex chronicus may be seen in vertical sections.

The histologic differential diagnosis of increased numbers of catagen and telogen hairs, characteristic of trichotillomania, includes alopecia areata and telogen effluvium. Trichotillomania also shares with early alopecia areata the features of normal hair density and occasional trichomalacia, but trichotillomania lacks the follicular miniaturization and peribulbar infiltrates. In telogen effluvium, evidence of trauma to follicles, as discussed earlier, is not seen. The histologic findings in early traction alopecia are said to be identical with those of trichotillomania, but fewer follicles are involved and the features are less prominent (see later discussion) (194).

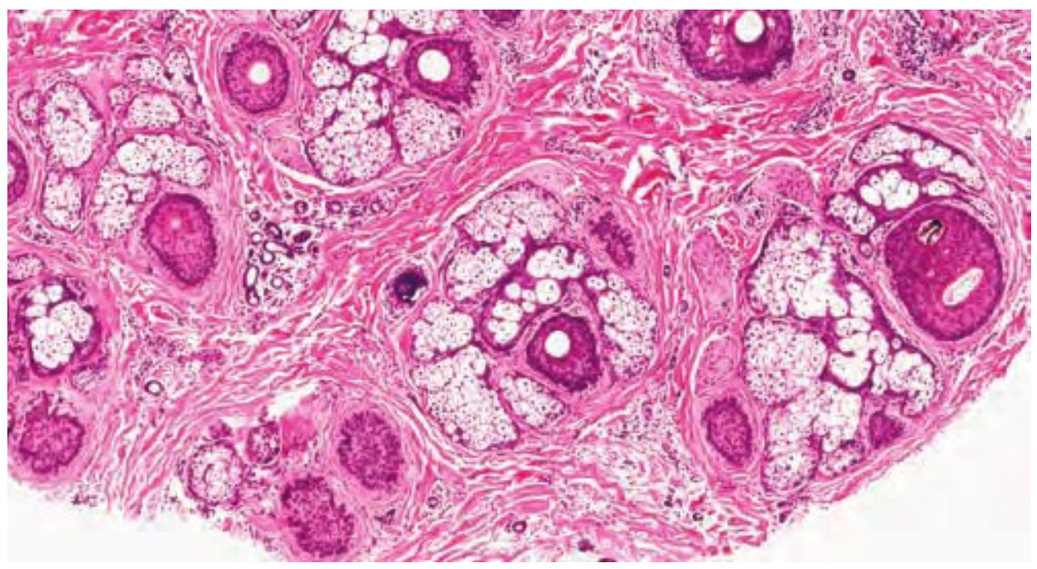


FIGURE 18-28. Trichotillomania (horizontal). Low-power view reveals an increased number of "resting" follicles, with catagen and telogen hairs, and telogen germinal units. A follicle to the far right contains a black pigment cast.

Traction Alopecia

Traction alopecia is another type of mechanical alopecia, usually resulting from a variety of hair-styling practices, particularly in African-Americans, that includes tight braids, corn rows, straightening, and the use of sponge rollers (259). Hair follicle injury is similar to that produced in trichotillomania, but in traction alopecia there are differences that relate to the use of less force over a greater period of time (194). Traction alopecia is often classified clinically and histologically as "early" and "late" disease (194). In early disease, tension on hair follicles exists over the course of months to a few years, sometimes presenting as a traction folliculitis with perifollicular erythema and pustules (260). In late disease, hair is subject to traction over many years. In early disease, discontinuation of the abnormal forces on the hair leads to regrowth of hair, but in late disease, follicles are lost, producing a permanent alopecia. Early and late disease are commonly found together in the same patient; as permanently scarred areas develop (late disease), terminal hairs at the periphery are used in styling, becoming the new target of traction (early disease) (194). Occupationally related traction alopecia has been reported due to wearing of a nurse's cap, occurring at the site of pin placement used to secure the cap (261).

Histopathology. In early traction alopecia, the histologic findings are similar to those of trichotillomania, albeit more subtle (194). For instance, the density of follicles is normal, with a normal number of vellus hairs. Premature conversion of anagen hairs to catagen occurs, resulting in an increased number of catagen and telogen follicles. Pigment casts and trichomalacia are sometimes found, although less often than in trichotillomania. Inflammation is absent.

In late disease, permanent loss of terminal follicles occurs, with replacement of follicular tracts by scar tissue (194) (Fig. 18-29). These "follicular scars" resemble columns of fibrous tissue; interfollicular areas are uninvolved. Because vellus hairs are not sufficiently large to be included in the method of styling and be affected by tractional forces, these hairs are preserved, and this is reflected in a normal absolute number of vellus follicles, often outnumbering terminal follicles. In late disease, the pathology shows an "end-stage" scarring alopecia, a

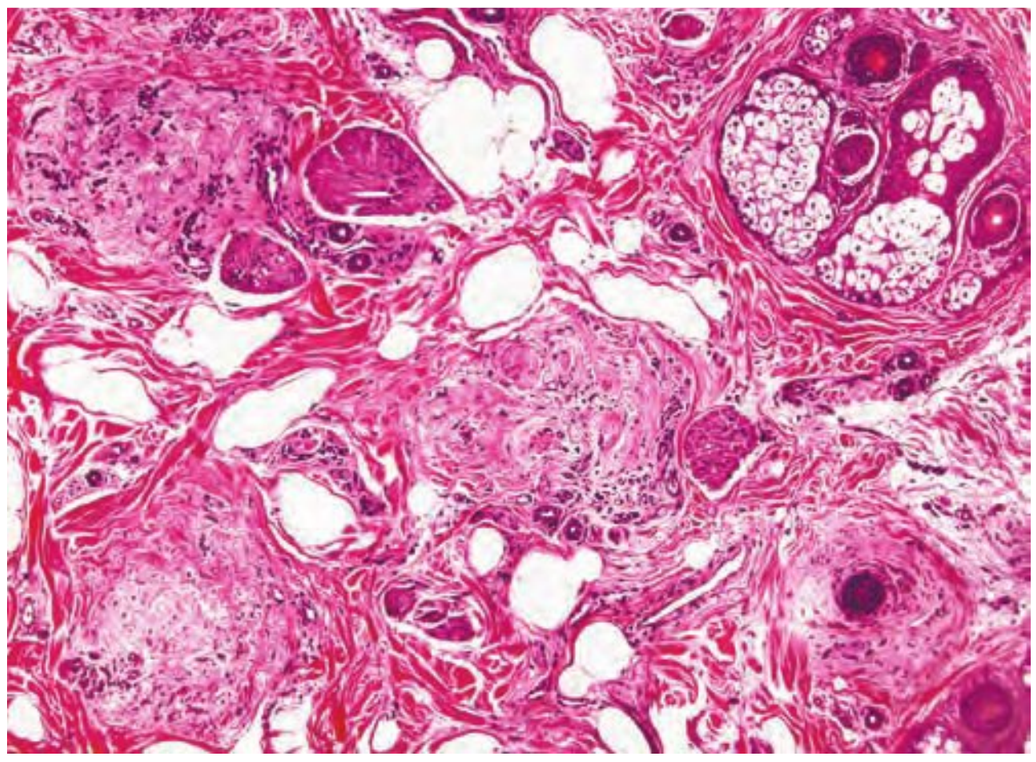


FIGURE 18-29. Traction alopecia, late stage (horizontal). The histologic picture is that of a burnt-out scarring alopecia. Several follicular scars are seen along with stranded arrector pili muscles and absent sebaceous glands. A few vellus follicles remain, at right. Their small size makes them immune to the mechanical forces that lead to hair follicle destruction.

histologic picture shared by many forms of permanent alopecia at an advanced stage. Pigment casts and trichomalacia are not seen in late traction alopecia.

Anagen Effluvium

Acute loss of actively growing (anagen) hairs occurs as a result of a severe insult that disrupts the mitotic activity of dividing cells in the hair matrix (262), with hair shaft production suffering greatly. The shaft becomes tapered proximally, breaks at the narrowest point, and is shed. The most commonly encountered forms of anagen effluvium are from chemotherapeutic agents and radiation therapy (192), although heavy metal poisoning and other toxins should be considered (262). Rapidly progressing alopecia totalis may present as anagen effluvium.

Microscopic Examination of Hairs. Diagnosis of anagen effluvium is usually made on clinical grounds with the aid of a trichogram or gentle hair pull, so that scalp biopsies are seldom done. Resting (telogen) hairs are immune to the metabolic insult, so that when sufficient anagen hairs are lost through shedding, a forcible hair pluck performed late in the course of disease will show almost all telogen hairs; a telogen count that approaches 100% on trichogram is a clue that a type of anagen effluvium is to blame. Early, a gentle hair pull demonstrates "pencil-point" tapered hairs with a pointed or frayed end (192).

In contrast, in loose anagen syndrome, the proximal portion of pulled anagen hairs shows a ruffled hair shaft cuticle because the inner and outer root sheaths are lost during extraction (192). One report described the loss of normal-appearing anagen hairs with an intact inner root sheath and partially intact outer root sheath in the setting of pemphigus vulgaris, in which the cleavage plane is in the outer root sheath (263).

Telogen Effluvium

Effluvium is a Latin term meaning "a flowing out" (264). Telogen effluvium results from "outflowing," or shedding, of hair shafts in the telogen phase of the hair growth cycle. The concept was originally delineated by Kligman (265). This condition has many precipitating causes or associated conditions, including childbirth, serious illness, including HIV infection, high fever, life-threatening trauma, major surgery, restrictive dieting and nutritional deficiencies, hypothyroidism, iron-deficiency anemia, medications, especially hormonal drugs, allergic contact dermatitis, the onset of androgenetic alopecia, and psychological stress (178,194,265–269). The shedding tends to occur diffusely throughout the scalp and may involve hair over the rest of the body.

Telogen hairs are recognizable by the club shape of their proximal end when visualized microscopically (*club hairs*). In conjunction with the history, physical examination of the scalp, and sometimes a *trichogram* (microscopic examination of shed, pulled, or plucked hairs), a diagnosis of telogen effluvium can often be made in the clinical setting. However, in difficult cases in which the differential diagnosis includes androgenetic alopecia and diffuse alopecia areata, a biopsy may be done.

Chronic telogen effluvium was a concept put forth by Whiting in 1996 after studying 355 patients with the disorder (270,271). Patients are usually middle-aged women 30 to 60 years of age with variable shedding that persists for years. Because hairs are replaced as fast as they are shed, patients do not become bald. An obvious cause is not identified (although an initiating factor may exist), hence the designation "idiopathic." In one long-term study, chronic telogen effluvium continued for 7 years in four of five women, and only one developed female pattern hair loss (272). Chronic telogen effluvium has rarely been reported in men (270,273). A scalp biopsy for horizontal sections is particularly helpful in distinguishing chronic telogen effluvium from androgenetic alopecia (274).

Histopathology. Only a subjective assessment of the proportion of follicles in telogen can be obtained with vertical sectioning of scalp punch biopsy specimens. More objective analysis can be obtained by examining horizontal sections (Fig. 18-30) (183). There is a normal number of hair follicles and an absence of follicular miniaturization, unless telogen effluvium occurs in patients with established androgenetic or another form of involutional alopecia. Inflammation is generally not seen.

Telogen follicles, characterized histologically by trichilemmal keratinization of the most proximal portion of the hair shaft, are increased. The number of catagen follicles or telogen germinal units also may be increased (Fig. 18-30). According to published data, the telogen count in normal scalp may range from 0% to 25% (265), with averages of 6% (193) and 13% (265) cited. Telogen follicles in excess of 15% are considered to be abnormal and suggest a diagnosis of telogen effluvium in the absence of significant inflammation and miniaturization (193,266). Others have suggested that a level of 25% is necessary for a definitive diagnosis of telogen effluvium (194,265),

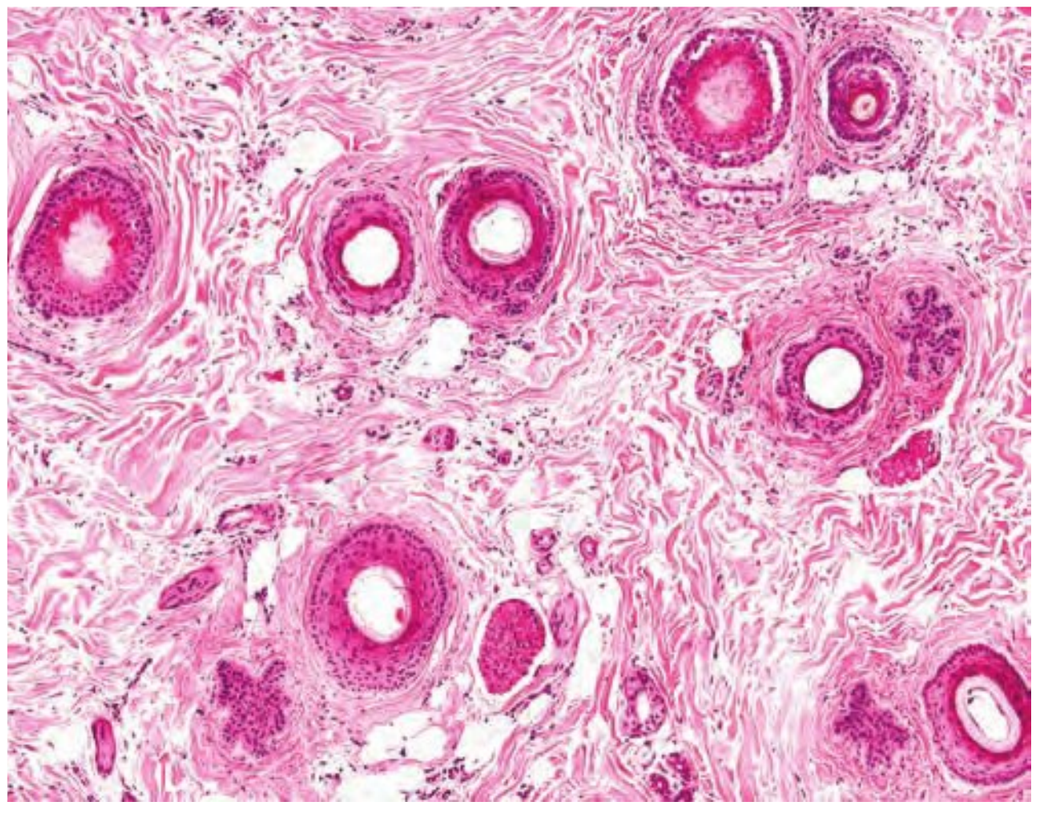


FIGURE 18-30. Telogen effluvium (horizontal). An increased number of telogen hairs is present. Forty-five percent of the 11 follicles in this field are in a stage of telogen; there are 2 typical telogen hairs and 3 telogen germinal units.

whereas a telogen count of 20% is "presumptive" evidence (265). Kligman also stated that telogen counts greater than 60% in telogen effluvium are rare. With a telogen count approaching 100% one should consider anagen effluvium or alopecia areata (192,194,204).

Biopsies from the crown/vertex and occiput yield similar findings because the process is diffuse. Timing of the biopsy clearly affects the pathologic changes observed. Should a biopsy be obtained in the very early stages of recovery, follicles in early anagen will be present in addition to elevated resting follicles, but if recovery is substantial, the histopathologic assessment may be entirely normal.

In a study of *chronic telogen effluvium* the average number of hairs in a 4-mm punch biopsy was normal at 39, the terminal-to-vellus hair ratio was normal, and the average telogen count was 11% (270). In comparison, the average telogen count was 16.8% in androgenetic alopecia and 6.5% in normal controls. Significant inflammation and fibrosis were present in only 10% to 12% of chronic telogen effluvium and control cases, as compared to 37% of androgenetic alopecia biopsies. Sinclair et al. found that when three horizontally sectioned, 4-mm punch biopsies from the scalp were performed instead of one, diagnostic distinction between chronic telogen effluvium and female pattern hair loss could be made more frequently (275).

Pathogenesis. In the acute form, increased shedding is noted approximately 3 months after the precipitating factor; this is the timetable for regressing anagen follicles to pass through catagen into telogen. Headington described five processes by which excessive telogen shedding may occur (266). Briefly, these processes depend on changes in the length of the anagen (growth) period and on the active release of hair shafts in telogen. Teloptosis is the termination of telogen with shedding of the hair, believed to be due to loss of adhesion between the club hair and cells of the surrounding epithelium (276). These authors distinguished two kinds of telogen hairs on trichogram—those with an epithelial sheath, suggesting early telogen, and those devoid of an epithelial sheath, indicating telogen termination or teloptosis. A transcription factor that is involved in physiologic cell death via apoptosis, p53, has been implicated in normal hair follicle regression in mice and may be important in disorders characterized by premature anagen-to-telogen conversion, such as telogen effluvium (277).

Androgenetic Alopecia

The hallmark of androgenetic alopecia (AGA) is follicular miniaturization, the process by which hair shafts become progressively finer and shorter. AGA results from an androgenic influence on hair follicles in certain areas of the scalp, and the pattern of involvement in the different sexes has led to use of the preferred terminology *male-pattern* or *female-pattern hair loss*. Some prefer this terminology over AGA because the etiologic role of androgens in women is not fully determined (278–280). AGA is the most common type of hair loss in males, affecting 50% of men by the age of 50 years and almost as many women, according to some reports (281,282), leading some to espouse that it is a physiologic process, not a pathologic one (283). AGA frequently shows a familial tendency, but inheritance does not follow simple Mendelian genetics and is most likely a polygenic trait (284,285).

In male patients, the process usually begins with bifrontal thinning, often with similar changes over the vertex. In full expression of the condition, there may be almost total baldness of the entire frontal/parietal scalp. The most common pattern seen in women is one of diffuse thinning over the crown and frontal scalp with preservation of the frontal hairline. The process occurs with less severity in women, so that significant balding is unusual.

Histopathology. Satisfactory evaluation of AGA can only be achieved from transverse sectioning of punch biopsy material (183,193,286), allowing for quantitative evaluation. Furthermore, samples smaller than 4 mm in diameter show an insufficient number of follicles for meaningful results.

Diminution of follicular size, or miniaturization, is the histologic hallmark of AGA. To fully appreciate the number of miniaturized follicles, horizontal sections at the level of the lower infundibulum of terminal hair follicles should be examined because sections below this may miss the vellus hairs whose bulbs are situated in the upper dermis (Fig. 18-31). Cursory inspection at low power reveals random variation in the caliber of hair follicles, consistent with a progressive miniaturization (Fig. 18-32) (287) , and absence of well-defined follicular units (286). Although vellus hairs can be quickly identified by the fact that their shaft diameter is equal to or greater than the thickness of their inner root sheath, they are quantitatively defined as having a shaft diameter of 0.03 mm or less (183). In his 1984 paper that laid the groundwork for horizontal

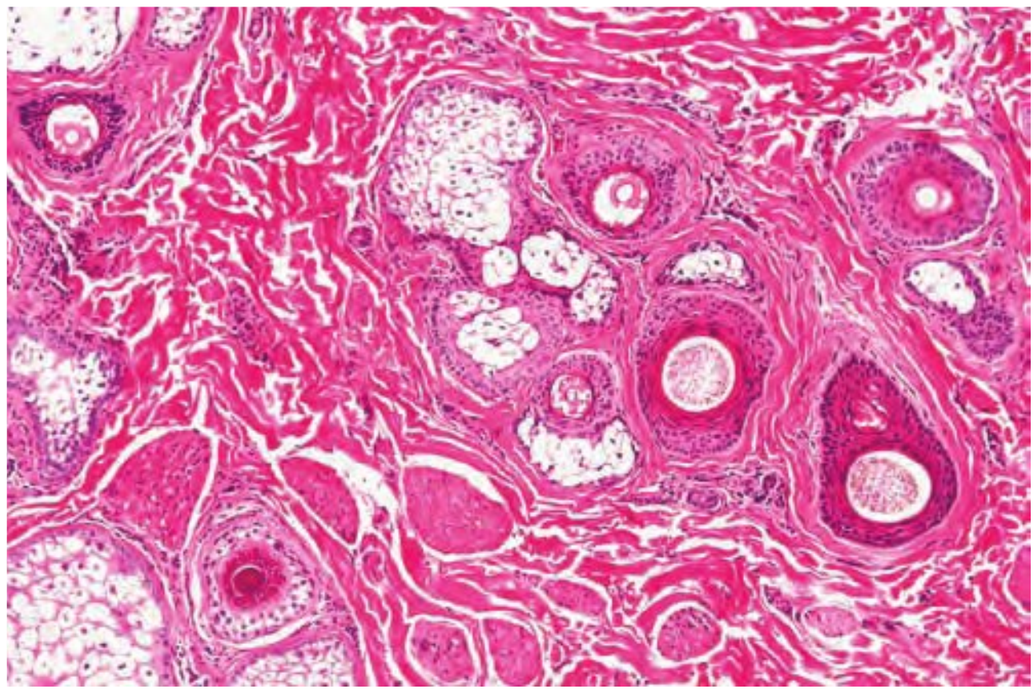


FIGURE 18-31. Androgenetic alopecia (horizontal). At a level through the lower infundibulum of terminal hairs, many vellus hairs become apparent, outnumbering the terminal follicles in this field.

interpretation of scalp biopsies, Headington also defined terminal hairs as having a shaft diameter of 0.06 mm or greater, thus recognizing an intermediate/indeterminate category in which the shaft diameter, i, measures $0.06 > i > 0.03$ mm, between terminal and vellus hairs (see Fig. 18-19) (183). An optical micrometer may be used to measure hair shaft diameter, if necessary.

However, slightly different definitions were used in subsequent articles on AGA, specifically with regard to the intermediate category. For example, Whiting classified terminal hairs as having a "shaft diameter exceeding 0.03 mm . . . . thicker than its inner root sheath," thereby grouping intermediate hairs with the terminal hair population (193). He then used a 3:1 (or less) terminal-to-vellus hair ratio as being diagnostic of male pattern AGA, although at other times he and others quoted a terminal-to-vellus hair ratio of less than or equal to 2:1 to diagnose AGA (193,194,288). Whiting found the *average* terminal-to-vellus ratio in AGA to be 1.7:1 (193). Using similar definitions of terminal and vellus hairs, Sperling and Winton reported finding an *average* terminal-to-vellus ratio of 1:6.1 (286), illustrating how, in advanced cases, miniaturized hairs outnumber terminal hairs (194). In my opinion, intermediate hairs should be grouped with the vellus hair population because more often they represent a transitional follicle undergoing miniaturization to a vellus hair (unless the patient is using agents such as minoxidil or finasteride to reverse the process); unfortunately, ratios for normal scalp and in AGA in which vellus and intermediate hairs are lumped together are not available in the literature and remain to be determined.

It is easy to undercount the number of vellus hairs, even with horizontal sections (286). Some vellus hairs may be so small as to be mistaken for keratinous debris. The use of toluidine blue stain was reported to be superior to the use of hematoxylin and eosin in identifying the tiniest of hairs because it stains the inner root sheath intensely blue (286).

The onset of AGA may be manifested by a telogen effluvium (289). Whiting found the telogen count in AGA to be 16.8%, as compared to 6.5% in controls (193), with telogen counts as high as 30% reported (286). Because the reduction in follicular size is associated with a shorter anagen phase (the smaller hairs do not grow as long), at a given point in time (for a histologic specimen this is the moment of biopsy harvest) a greater proportion of follicles will be found in telogen. There may be typical telogen hairs or, with increasing severity, telogen germinal units. A telogen germinal unit is the follicular epithelium that remains after the telogen hair shaft has been shed; it represents the secondary hair germ (Fig. 18-20) (183). Although vellus hairs continue to cycle through anagen and telogen in the papillary dermis, they are not considered to be part of the telogen count (198). Both miniaturization and increased conversion to telogen are associated with the finding of fewer terminal hair bulbs and more fibrous streamers in the deep dermis and subcutis (198). The fibrous streamers in AGA are thicker, more cellular, and possibly more fibrotic than those of normal follicles (194,290,291).

In advanced AGA there may be a reduced hair density with permanent loss of follicles, termed *cicatricial pattern hair loss* by Olsen and Olsen (193,286,292). Periinfundibular fibroplasia, ultimately leading to focal follicular scarring, may be responsible (193,293). In subtle cases, a second biopsy, taken from the occipital scalp, may be helpful for comparison because the occiput is typically uninvolved.

Lymphocytic infiltrates, defined as activated T cells in one study, are found around superficial vessels and in the vicinity of the lower infundibulum, sebaceous glands, and bulge in follicles transitioning to full miniaturization (294). The presence of inflammation has been reported in as many as 50% to 75% of cases (293) and has been linked to peripilar signs seen clinically (295). However, mild perifollicular and upper dermal inflammation can be observed in normal scalp with a similar frequency to AGA (287) and therefore is of no value in diagnosing AGA (194). Moderate inflammation, however, was

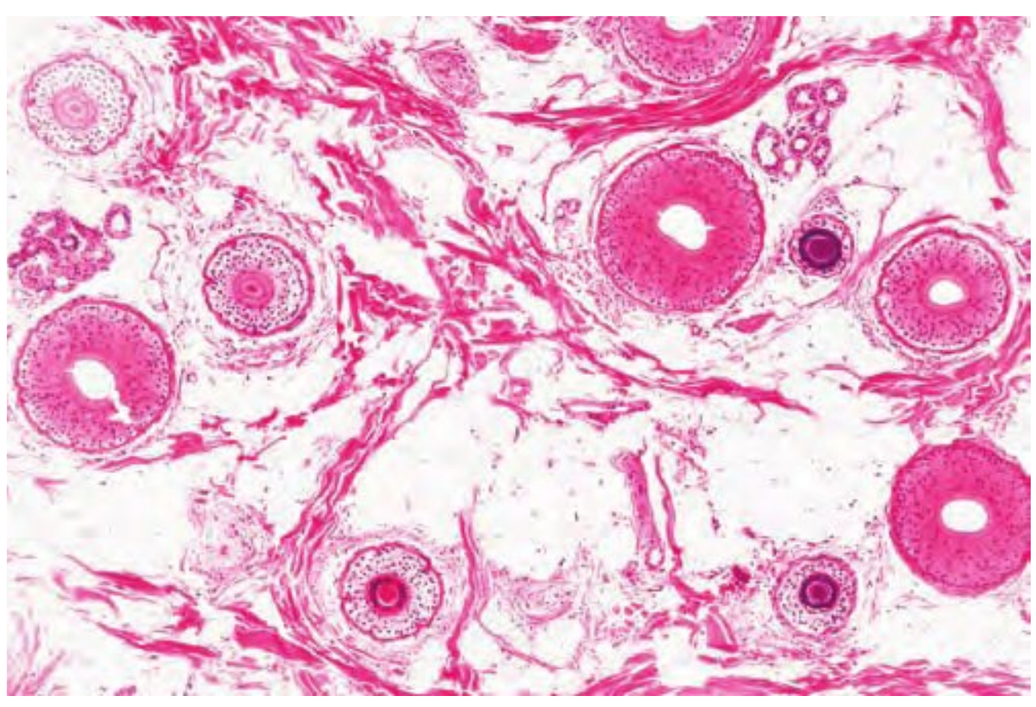


FIGURE 18-32. Androgenetic alopecia (horizontal). Even in the superficial subcutis, variability in the caliber of hair follicles, with an increased number of miniaturizing hairs, can be seen. Several fibrous streamers are also present.

seen more often in AGA than in normal individuals (193); the infiltrate was composed primarily of lymphocytes and histiocytes, with rare neutrophils, plasma cells, and giant cells. It has been suggested that inflammation in AGA may result from *Demodex*, seborrheic dermatitis, actinic damage, cosmetics, and grooming agents (193) and therefore should not be considered pathogenic (283). Nevertheless, its presence may have a bearing on the potential to respond to treatment; one study found that AGA patients with histologic inflammation or fibrosis showed less frequent regrowth on treatment with 2% minoxidil than AGA patients without inflammation (193), although the figures did not prove to be statistically significant. In conclusion, upper dermal inflammation can be seen in AGA, but it does not support or discount this diagnosis.

Pathogenesis. Androgens are the primary regulators of normal human hair growth. With the arrival of puberty, they transform vellus hairs in many sites, such as the axilla, to terminal hairs, while at the same time mediating the opposite effect on certain scalp follicles in predisposed individuals (296). The effects of androgens on the hair follicle are mediated via androgen receptors in the hair papilla (297). The primary androgen responsible for these effects is dihydrotestosterone (DHT), via androgen-receptor binding (298). Within the follicle, the enzyme 5α-reductase produces DHT from serum testosterone. Predisposed scalp displayed high levels of DHT and increased androgen-receptor expression in one study (298). In another study, frontal scalp follicles showed higher levels of androgen receptor and 5α-reductase than occipital scalp follicles, and men exhibited higher levels than women (299).

A group of investigators found that the predominant form of 5α-reductase in human scalp is type 1, concentrated in sebaceous glands (300). These same investigators found 5α-reductase type 2 to be present in the inner layer of the outer root sheath, the proximal inner root sheath, and the infundibulum and some in sebaceous ducts. The type 2 isozyme is responsible for AGA. It is preferentially inhibited by finasteride, which decreases scalp production of DHT and promotes hair growth in males with AGA (300).

Other serum hormones, such as adrenal-derived dehydroepiandrosterone, may also be converted to DHT by some hair follicles, and steroid sulfatase found in the dermal papilla may be the responsible enzyme (301). This may explain why males affected by X-linked recessive ichthyosis due to a defect in steroid sulfatase do not develop AGA or do so only mildly (302).

Apoptosis is an important part of hair follicle regression, and therefore factors that affect apoptosis may play a role in regulating the hair cycle (303). One study of apoptotic mechanisms in AGA suggested that levels of caspases, regulators of programmed cell death, and inhibitors of apoptosis may control hair follicle homeostasis (304,305). Another study found similar expression of bcl-2, p53, and other heat shock proteins in follicles from normal (occipital) scalp and follicles from scalp affected by AGA (frontal), whereas follicular expression of the proliferation marker Ki-67 was decreased in AGA (306). The authors concluded that abnormal regulation of apoptosis was not involved in AGA, but a lower proliferation rate may be. This contradicts an analysis of bcl-2 and TUNEL (terminal deoxynucleotidyltransferase–mediated deoxyuridine triphosphate-biotin nick end-labeling) staining—markers of apoptotic activity—in scalp of cadaveric males with AGA, in which significant differences were noted between normal and alopecic scalp follicles (307); the apoptotic "hot spot" was identified in the bulge-isthmus region.

Whiting postulated that the process of miniaturization cannot be explained simply by shortening of the anagen phase with repeated hair cycles (198). He suggested that miniaturization of some follicles occurred rapidly, over the course of a single hair cycle, possibly mediated by a change in the size of the dermal papilla, because vellus follicles have a smaller papilla than terminal follicles (289,308). In cell cultures of dermal papillae derived from balding scalp follicles, the cells were smaller and did not grow as well as those derived from nonbalding scalp follicles (309).

There is evidence that fibroplasia of the adventitial sheath surrounding the hair follicle is important to the pathogenesis of AGA (291,310). As previously noted, fibrous streamers in AGA may be more fibrotic than those of normal follicles (194,291). One study found *Demodex* to be present more frequently in patients with AGA and postulated that *Demodex*-induced inflammation could contribute to the process and possibly play a role in permanence (scarring) (311).

There exists a physiologic rest period during which the posttelogen follicle remains empty. This recently recognized phase of the hair cycle was termed *kenogen* (190). It may last longer and occur with greater frequency in AGA (312).

Scarring Alopecia

Various definitions exist for scarring (cicatricial) alopecia. A clinically relevant definition is the permanent loss of hair follicles, usually manifested on physical examination by absence of follicular ostia, sometimes with a porcelain-white appearance (313). Histology may or may not reveal true scar formation or inflammation, although most processes leading to permanent hair loss are inflammatory, at least initially. With this definition we can include disorders typically classified as "nonscarring" that in late stages lead to irreversible loss of hair follicles; this biphasic pattern can be seen in androgenetic alopecia, longstanding alopecia areata, and traction alopecia.

Processes that specifically target the hair follicle early in the course of the disease are *primary* scarring alopecias (314,315). *Secondary* scarring alopecias result from inflammatory or neoplastic processes that secondarily involve hair follicles. Secondary scarring alopecias are not discussed here, nor are primary scarring alopecias whose cutaneous manifestations are predominantly nonfollicular, such as lichen planopilaris and chronic cutaneous lupus erythematosus. The discussion of scarring alopecias that follows refers to *primary scarring alopecias*, as defined earlier in this paragraph.

There have been various classification schemes proposed for primary scarring alopecias, including inflammatory versus

noninflammatory, and neutrophil mediated versus lymphocyte mediated (316). The usefulness of these schemes is hampered by clinical and histologic overlap between the various types of scarring alopecia, as well as a lack of uniformity in the terminology used by clinicians and dermatopathologists (317). This is why clinical–pathologic correlation is so important in the interpretation of scarring alopecias. Future proposals for the definitive classification of scarring alopecias will require insight into pathogenic mechanisms or biological markers of disease, possibly provided by molecular research (182). A unifying concept of *central centrifugal scarring alopecia*, discussed later, was proposed in 2000 (318). In addition, based on a Workshop on Cicatricial Alopecia sponsored by the North American Hair Research Society, a working classification of scarring alopecia based on clinical and pathologic features was published with hopes for an improved classification scheme pending additional, collaborative investigation (186). More important, however, this workshop laid the groundwork for meaningful clinical–pathologic correlation by setting guidelines for the study of scarring alopecias to uncover etiologic factors, ultimately aiding in treatment, and facilitated collaboration between investigators. Needless to say, the problem of classifying scarring alopecias will not be solved in this chapter. The intent here is to present "classic" features of more commonly encountered disorders and some rarer, more recently described conditions.

In one published algorithm for classifying alopecia, emphasis was placed on the pattern of fibrosis (scarring), with a branch point separating follicular fibrosis from diffuse dermal fibrosis (319). The *pattern* of scarring is important in the permanent alopecias. For example, when a condition produces enough damage to completely destroy the follicle, there is replacement of the pilosebaceous structure by scar tissue (Fig. 18-33) (320). These "follicular scars" may occur without interfollicular fibrosis. Histologically the follicular epithelium is replaced by a column of thickened collagen, sometimes surrounded by a rim of connective tissue that stains faintly blue on hematoxylin and eosin–stained sections (Fig. 18-33).

The end stage of many forms of scarring alopecia may look similar, with the "final common pathway" characterized by decreased follicular density, absence of sebaceous glands, replacement of follicles by follicular scars that may extend into the subcutis, and sometimes tufting (see later discussion of *tufted folliculitis*). A study of elastic tissue in various forms of permanent alopecia showed distinctive staining patterns using Verhoeff-van Gieson stain (321). Fibrous tracts of normal follicles show an elastic tissue sheath, which may be destroyed or altered by scarring and inflammation (Fig. 18-34). Cases of end-stage lichen planopilaris showed a wedge-shaped scar involving the upper one third of the follicle where the elastic sheath was destroyed (Figs. 18-35). In addition, in well-developed lesions of lupus erythematosus, a broad pattern of scarring throughout the dermis was characteristic, with destruction of perifollicular elastic sheaths. In cases of "central progressive alopecia in black females" (*follicular degeneration syndrome*), the fibrous tracts were broad ("tree trunk") and out-

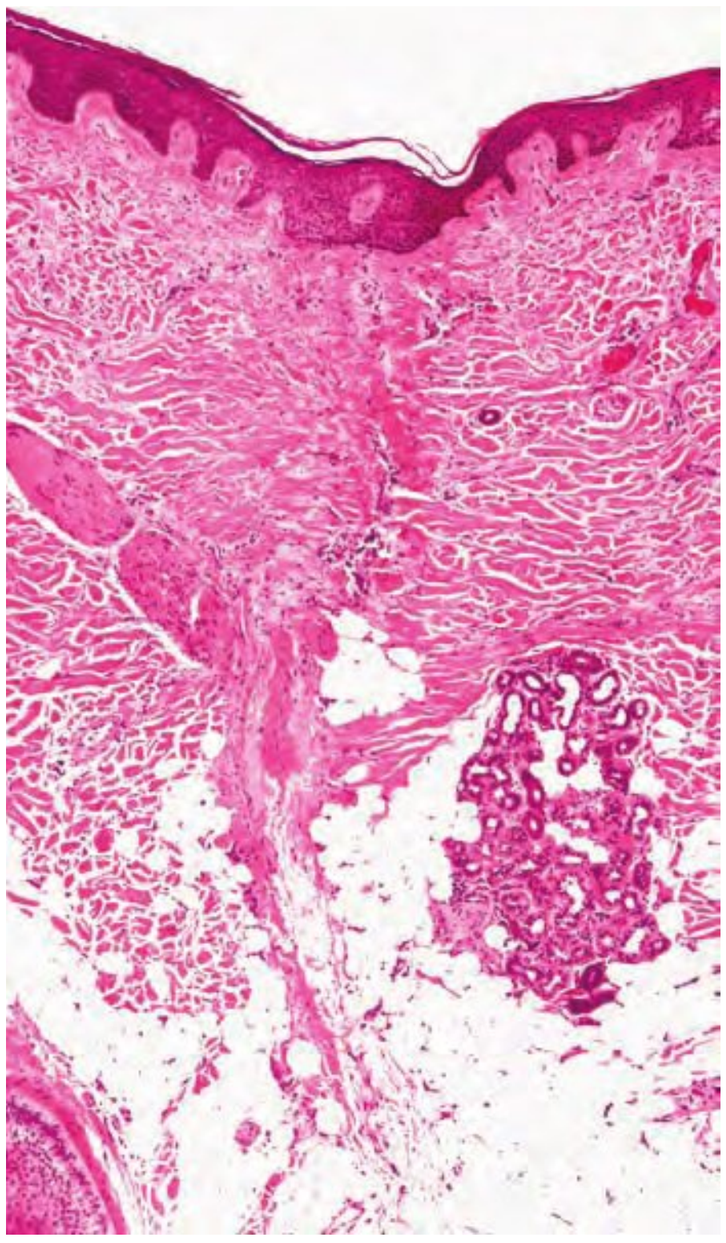


FIGURE 18-33. Follicular scar (vertical). A column of fibrosis replaces the hair follicle and extends into the subcutaneous fat. Note the stranded arrector pili muscle.

lined by an intact elastic sheath. Thickened elastic fibers were also found throughout the dermis, interpreted to be the result of "recoil" as the dermis became shrunken and hyalinized. "Idiopathic 'ivory white' pseudopelade" showed findings that were identical to this. In morphea, dermal elastic fibers were

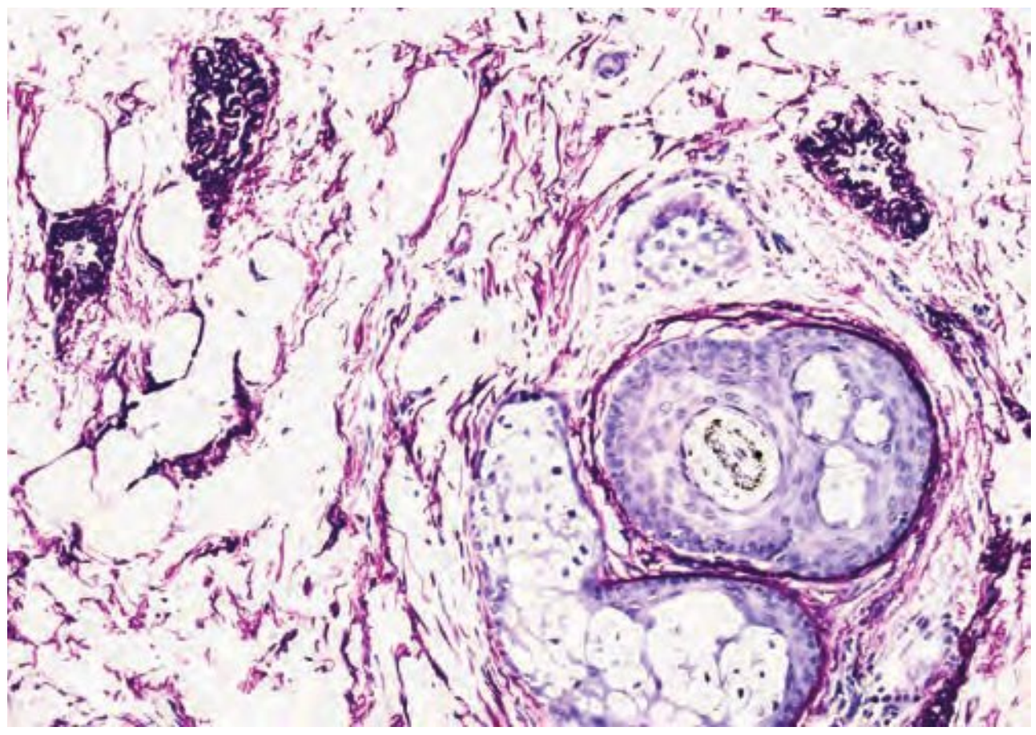


FIGURE 18-34. End-stage scarring alopecia, elastic stain (horizontal). Elastic fibers that encircle normal follicles stain purple with the Luna stain. Three destroyed follicles have left behind their elastic sheath, identifiable as purple rings with a corrugated appearance.

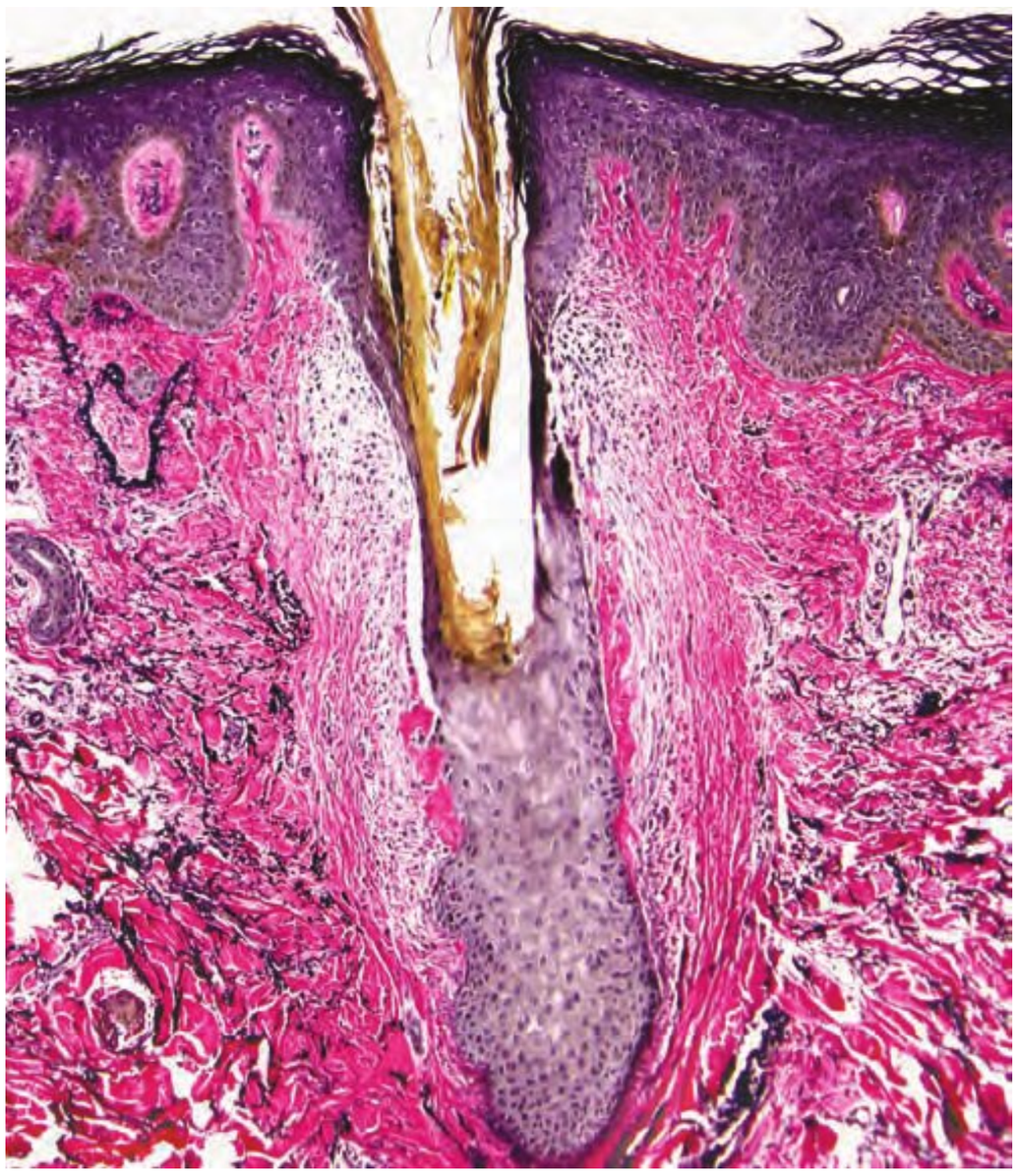


FIGURE 18-35. Scar in lichen planopilaris (vertical). Verhoeff-van Gieson elastic tissue stain shows a wedge-shaped perifollicular scar devoid of elastic fibers.

normal, and the fibrous tracts (with an intact elastic sheath) were narrow.

The value of transverse sections in the interpretation of nonscarring alopecias is well documented, but their value in scarring alopecias is less clear. This may be a matter of personal preference for the dermatopathologist, but one study found that when only one biopsy was available, the diagnosis made with vertical sections alone had a higher concordance rate with the original diagnosis than did transverse sections alone, although biopsies studied using vertical and transverse sections together had the highest concordance (322). A blinded, prospective study of primary cicatricial alopecia could only discriminate neutrophilic types from lymphocytic types on histology but could not further differentiate clinically distinct forms of primary cicatricial alopecia (323).

Although the exact pathogenesis of each type of permanent alopecia may be different, some general pathogenic mechanisms have been proposed. For instance, Headington believed that the basic pathogenesis common to cicatricial alopecias was hair follicle stem cell failure (324). Massive synchronous apoptosis was suggested in one study (325). In a commentary on scarring alopecias, the role of the sebaceous gland was emphasized, particularly its importance in the dissociation of the hair shaft from the inner root sheath (326); the asebia mouse is an animal model for scarring alopecia that is based on a sebaceous gland defect (327,328).

Pseudopelade of Brocq

This uncommon condition has arguably generated more controversy and confusion than any other type of alopecia. Many articles have been written about pseudopelade of Brocq (PPB), with some classifying it as a distinct clinical–pathologic entity ("classic" or "idiopathic" PPB) (329) and others defining it as an end-stage of scarring alopecia resulting from disorders such as lichen planopilaris, discoid lupus erythematosus, scleroderma, folliculitis decalvans, or chronic traction (330,331). Therefore, the term must be defined each time it is used anew. The salient clinical features that follow are similarly reported by both sides of the debate.

PPB in the classic definition is characterized by asymptomatic, discrete, scattered or clustered, irregularly shaped, ivory- or porcelain-white patches of alopecia predominantly over the parietal scalp and vertex (316) (Fig. 18-36) and rarely on nonscalp sites such as the beard (332). The patches are sometimes atrophic, producing an appearance often likened to "footprints in the snow" (324). Late-stage lesions of lichen planopilaris, lupus erythematosus, or scleroderma can produce this same clinical picture (333). Idiopathic PPB is found mostly in whites and in women more than men and occasionally in children (334). Disease progression occurs in "spurts," ultimately running its course and leaving areas of permanent alopecia. The key feature that supposedly makes idiopathic PPB distinctive is the lack of clinical inflammation throughout

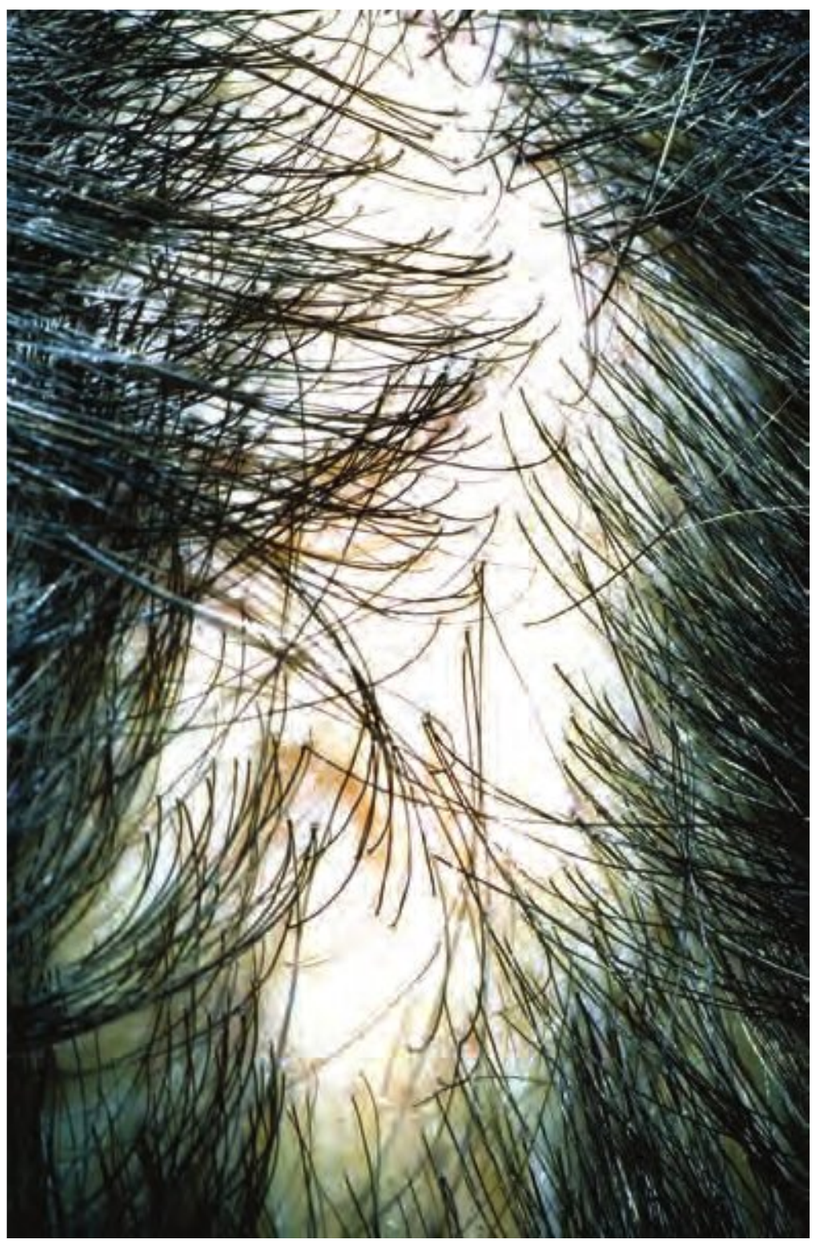


FIGURE 18-36. Pseudopelade of Brocq. "Ivory white," macular areas of hair loss without evidence of inflammation (erythema). This is distinguished from alopecia areata by the lack of follicular ostia.

its course, although some theorize that an inflammatory phase exists but is fleeting (335).

In 1885, Brocq first used the term pseudopelade, which literally means "pseudo alopecia areata" in French (336). Later, in 1905, Brocq characterized "pseudopelade" as a distinct entity (337). How the concept of PPB changed over the twentieth century was chronicled in an article by Dawber entitled "What is pseudopelade?" (338).

A major publication often cited in support of PPB as a separate disorder came from Pinkus in 1978 in which he noted a distinctive pattern of perifollicular and interfollicular elastic tissue in PPB and other forms of scarring alopecia, using acid orcein stain (339). In 180 cases that satisfied the histologic criteria for idiopathic PPB established by Brocq and others, Pinkus found that the site of destroyed hair follicles (above the level of the bulge) was marked by broad cords of collagenous and elastic fibers (Fig. 18-37). He further subdivided these 180 cases into classic PPB and fibrosing alopecia, the latter characterized by less perifollicular inflammation and, more important, the presence of prominent elastic fibers around the lower, cycling portion of the preexistent hair follicle. The major criticism of Pinkus' work is that his histologic criteria for PPB were not correlated with clinical findings (182).

Subsequently, elastic tissue staining patterns in various forms of permanent alopecia were examined using Verhoeff-van Gieson stain (321). Two cases of "idiopathic 'ivory white' pseudopelade" showed a hyalinized dermis with thickened elastic fibers and broad fibrous tracts with an intact elastic sheath, findings indistinguishable from "central progressive alopecia in black females" (*central centrifugal cicatricial alopecia*), and similar to the findings of Pinkus.

Braun-Falco et al. subsequently studied 26 cases believed to represent PPB (330) (cases of scarring alopecia due to known, identifiable causes were excluded) and concluded that the clinical and histologic criteria they proposed were distinctive enough to warrant designation as a separate disease (333).

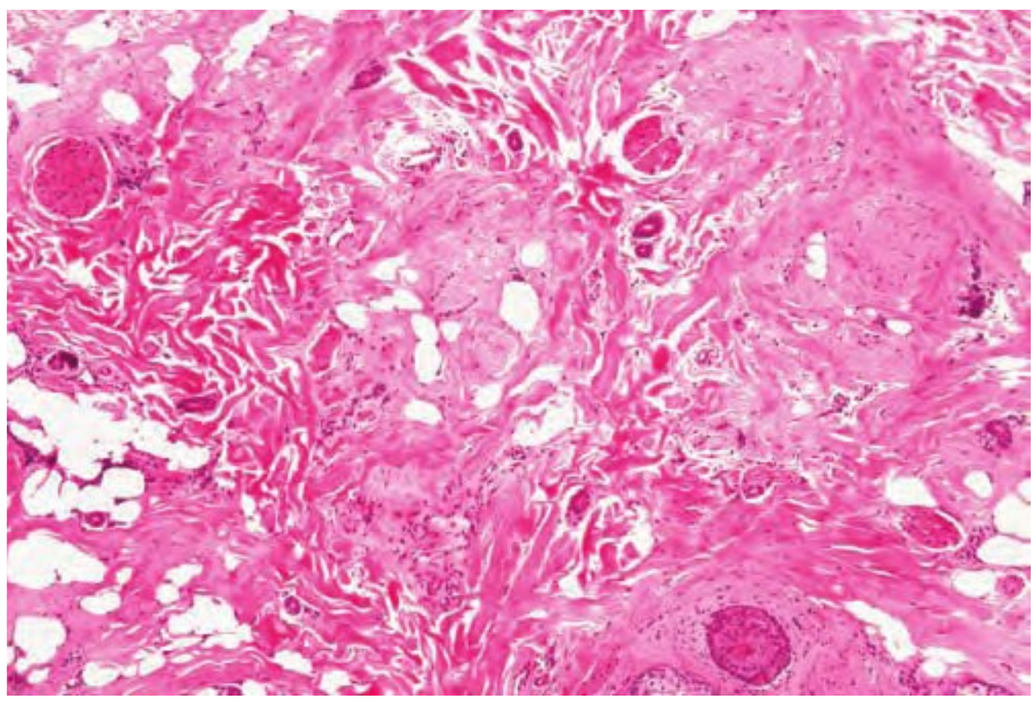


FIGURE 18-37. Pseudopelade of Brocq (horizontal). Viable pilosebaceous follicles are notably absent, replaced by follicular scars. Several unaffected arrector pili muscles remain.

On the other hand, many reports support idiopathic PPB as an end-stage scarring alopecia. In the 1950s, Degos noted that 70% of the time, a preceding or underlying disease could be found, so he called the typically described findings a "pseudopeladic" state (340). One study used criteria established by Braun-Falco to diagnose PPB in 33 patients. Because two thirds of these patients showed features of discoid lupus or lichen planopilaris, the authors concluded that PPB could not be considered a distinct entity (341). Some groups have published evidence that lichen planopilaris and PPB may be variants of the same disease. One of these groups presented 4 alopecic patients with clinical and histologic features of PPB who also had cutaneous and mucosal findings of lichen planus (342). The authors believed that PPB represented a less inflammatory stage in the disease spectrum of lichen planopilaris. In another study of 10 patients who underwent 28 biopsies, the histologic features were not distinctive enough to differentiate PPB from lichen planopilaris (343).

In summary, the diagnosis of idiopathic PPB is one of exclusion. The terminology has become so confusing that for cases in which an underlying disorder is not identifiable, Sperling et al. proposed an alternate, more descriptive term, "patchy, scarring alopecia of unknown etiology" (318).

Histopathology. Because the histologic findings of a typical lesion of PPB are those of a "burnt-out" scarring alopecia (182), clinical correlation is always necessary for accurate interpretation. The classic description of PPB is one of predominantly follicular scarring characterized by columns of fibrosis replacing hair follicles (Figs. 18-33 and 18-37), sometimes extending into the subcutaneous fat. This is accompanied by a loss or decrease of sebaceous glands and absence of widespread (interfollicular) scarring (192,330). Normal arrector pili muscles remain, isolated in the middermis or inserting on the vertically oriented fibrotic streams (Figs. 18-33 and 18-37). The epidermis may be normal or, rarely, atrophic, and sweat glands are normal. Marked inflammation is absent.

The apparent lack of inflammation in this disorder may be the result of a short, often missed, inflammatory phase. Such lesions were the target of one study that found massive folliculocentric lymphocytic infiltration associated with pronounced apoptosis (325). The fact that histologic inflammation exists in some cases has lead some authors to further subdivide PPB into inflammatory and noninflammatory subtypes based on histology (335).

In two sources, the findings of early inflammatory and more developed lesions of PPB are well described (178,324). Early lesions of PPB show variable lymphocytic inflammation in the superficial dermis that is perivascular or perifollicular, centered about the infundibulum or midpoint of the follicle. The infiltrates may extend into the follicular epithelium and occasionally into sebaceous glands, but deep perifollicular inflammation or interface alteration is not detected. With disease progression there is early loss of sebaceous glands. In later, well-developed lesions, inflammation becomes patchy, mild, and perivascular, and it eventually disappears. There may be

premature disintegration of the inner root sheath, and the infundibular epithelium may become eccentrically thinned. Concentric lamellar fibrosis may be present. Fusion of infundibular outer root sheaths ("tufting") may be seen (see *tufted folliculitis*). In time, follicles are destroyed, with naked hair shafts remaining and inciting a granulomatous response. Fibrous tracts mark the site of obliterated follicles. Even features of this often-missed inflammatory phase of PPB are shared by other forms of scarring alopecia (318).

Direct immunofluorescence in PPB is negative, with occasional immunoglobulin M at the basement membrane zone of the follicular infundibulum (330). Immunofluorescence changes of lupus erythematosus and lichen planopilaris should be absent (344).

Pathogenesis. As a theoretical basis for PPB, Sullivan and Kossard speculated that there could occur a noninflammatory focal loss of follicles, possibly due to premature exhaustion or inhibition of the stem cell compartment to recycle (331). Headington postulated that the pathogenesis of PPB is probably related to a T-cell–mediated inflammatory process involving the bulge region (324). An autoimmune etiology has also been hypothesized (345).

An ultrastructural study of hairs and follicles from scalp affected by pseudopelade found pili torti–like hairs with oblique or longitudinal grooves and ridges, a deformed hair cuticle and cortex, and an asymmetric inner root sheath (346).

Central Centrifugal Cicatricial Alopecia

Because many forms of scarring alopecia share clinical and histologic features that make them difficult to distinguish with certainty, a unifying concept of *central centrifugal cicatricial alopecia* was proposed to reflect the overlap (318). Central centrifugal cicatricial alopecia (CCCA) is a category that includes several types of cicatricial hair loss that have in common the following features (Fig. 18-38): (a) alopecia centered on the crown or vertex of the scalp, (b) progressive, chronic disease with eventual "burnout," the affected scalp becoming shiny and smooth, without follicular ostia, (c) fairly symmetric expansion, with the most active areas at the periphery, and (d) clinical evidence of inflammation (i.e., erythematous papules or pustules) in these active sites, corresponding to microscopic inflammation (182,318). Clinically, inflammatory lesions may be sparse to absent. CCCA encompasses three *patterns* of disease: follicular degeneration syndrome, pseudopelade pattern (a "modern" use of the term, *not* pseudopelade of Brocq), and folliculitis decalvans.

Histopathology. The earliest and most characteristic histologic finding of CCCA is premature desquamation of the inner root sheath (Fig. 18-39) (196), typically seen in only a few follicles. The inner root sheath normally degenerates at the isthmus, which is delimited below by the attachment point of the arrector pili muscle and above by the insertion of the sebaceous duct. "Crumbling" or absence of the inner root sheath below the isthmus, at a level through the deep dermis near the eccrine



FIGURE 18-38. Central centrifugal cicatricial alopecia. An area of permanent alopecia on the crown of the scalp characterized by absent follicular ostia.

coils or in the subcutis, characterizes this finding. This may the primary event in the pathophysiology of this condition, although some consider it to be a secondary phenomenon (347). Headington did not consider it to be specific, noting

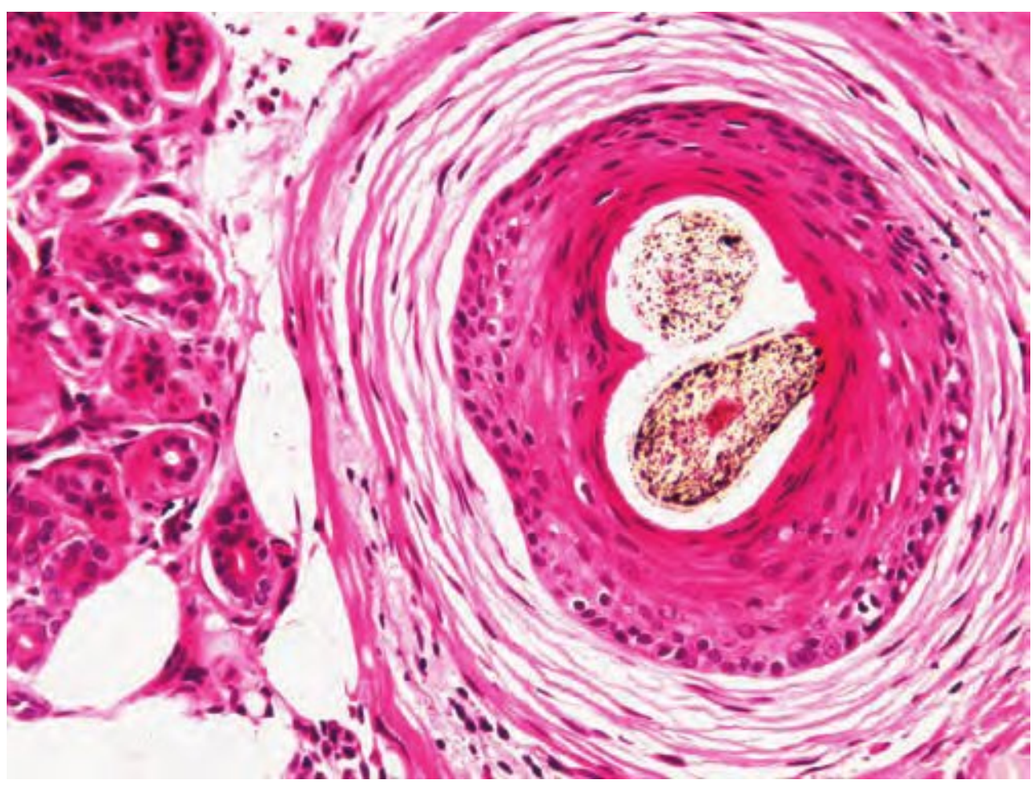


FIGURE 18-39. Central centrifugal cicatricial alopecia (horizontal). At a level through the superficial subcutis, the inner root sheath is missing. The outer root sheath is thinned, and there is already perifollicular fibrosis and polytrichia.

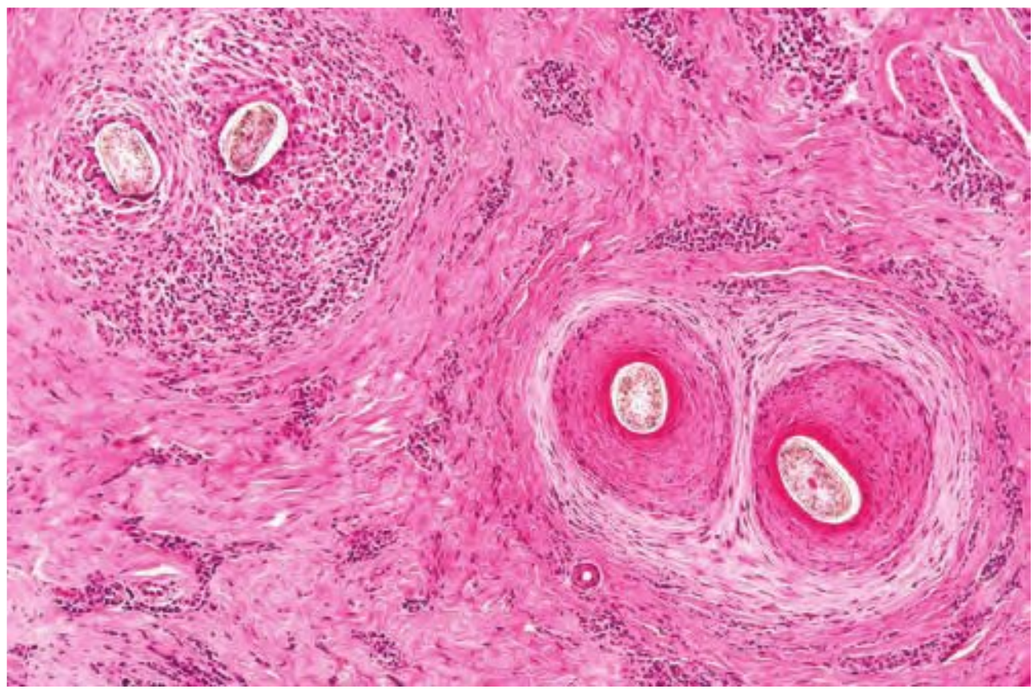


FIGURE 18-40. Central centrifugal cicatricial alopecia (horizontal). The following features are demonstrated: eccentric thinning of the follicular epithelium, concentric lamellar fibroplasia, lymphoplasmacytic inflammation, dermal fibrosis, and naked hair shafts inciting a granulomatous response.

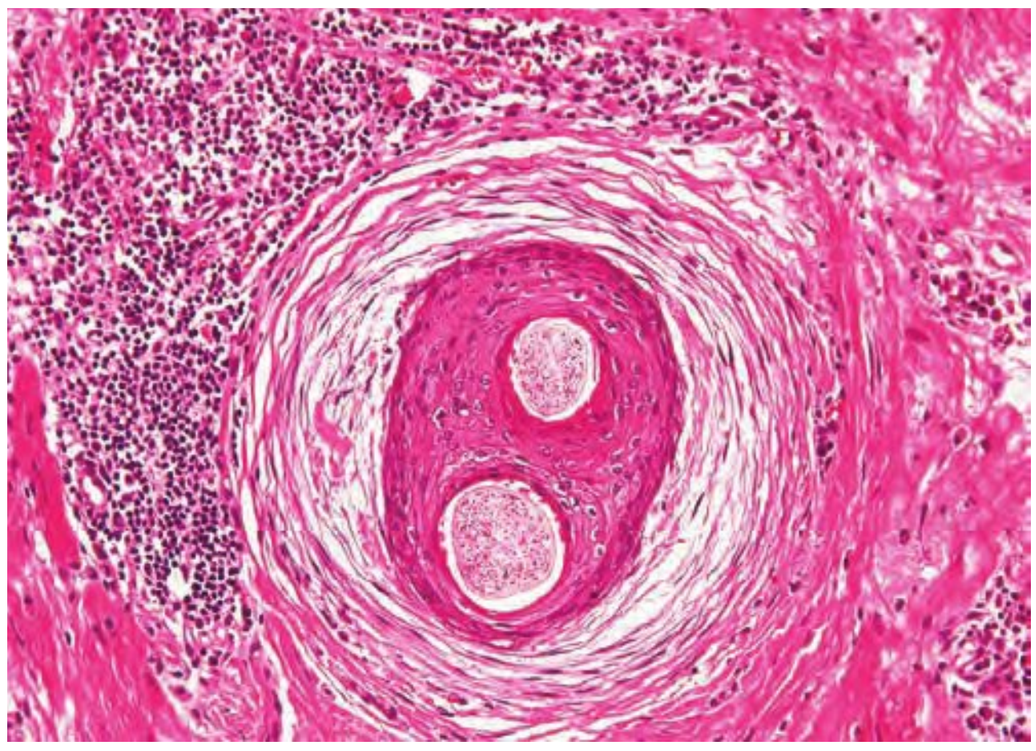


FIGURE 18-41. Central centrifugal cicatricial alopecia (horizontal). In the upper dermis, two follicles exhibit fusion of their outer root sheaths along with concentric fibrosis, focal thinning of the follicular epithelium, and perifollicular lymphocytic inflammation.

that premature desquamation of the inner root sheath could also be seen in chronic cutaneous lupus erythematosus and pseudopelade of Brocq (324). What is unique to CCCA, however, is its occurrence *early* in the disease process.

Most likely as a consequence of premature loss of the inner root sheath, CCCA exhibits some or all of the following histologic features in clinically involved scalp (Fig. 18-40) (182,318): (a) eccentric thinning of the outer root sheath follicular epithelium, most prominent at the level of the isthmus and lower infundibulum, associated with (b) close apposition of the hair shaft and follicular contents to the dermis, (c) concentric lamellar fibroplasia (resembling "onion skin"), and (d) chronic inflammation composed of lymphocytes and plasma cells surrounding the zone of fibroplasia. In addition, there is (e) eventual migration of the hair shaft into the dermis, inciting granulomatous inflammation and additional epithelial damage, and (f) replacement of the destroyed follicle by a vertical band of connective tissue, resulting in a "follicular scar." The lymphoplasmacytic inflammation is usually concentrated on the side opposite penetration of the shaft through the follicular epithelium. Singly, these six histologic features may be found in other types of scarring alopecia. As with all scarring alopecias, sebaceous glands are lost. There may also be polytrichia, whereby damaged follicles fuse their outer root sheaths at the infundibular level (Fig. 18-41).

If a clinical pustule from the expanding margin is biopsied (Fig. 18-42), there may be folliculocentric neutrophilic inflammation (Fig. 18-43), allowing for subclassification as the folliculitis decalvans pattern. Those cases classified as the pseudopelade pattern showed the histologic features described but typically were white patients with a clinical picture of indolent disease characterized by perifollicular scale and some papules (196).

I would like to make special mention of the *follicular degeneration syndrome* subtype of CCCA from a historical perspective, when it was considered a distinct clinicopathologic entity. This subtype of CCCA occurs almost exclusively in African-American patients, usually women, between the second and fourth decades (348,349). It was originally described as "hot comb" alopecia (350), but it was subsequently shown that use of a hot comb to straighten the hair was not requisite (348,349). Although the precise etiology is unknown, hair care practices that include heat, bleaching, pomades, and traction, as well as the predominance in African-Americans, suggest that environmental, cultural, and genetic factors, as well as possible



FIGURE 18-42. Folliculitis decalvans. The advancing edge of a scarred alopecic plaque shows the earliest lesions of folliculitis decalvans, follicular-based pustules with crusting.

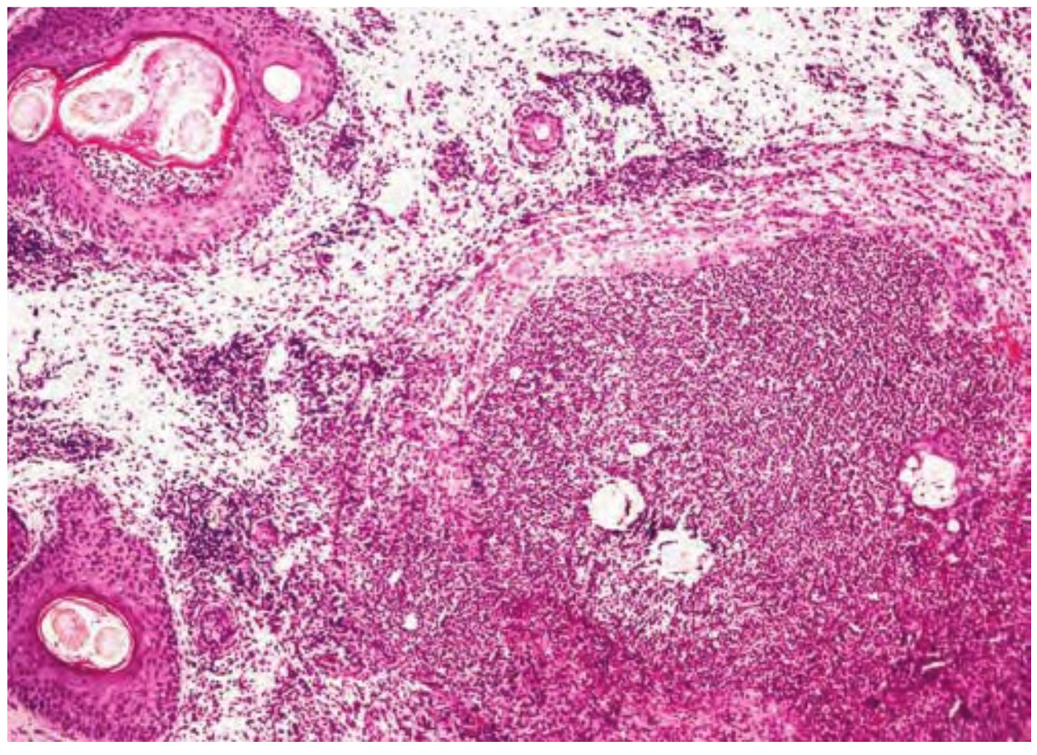


FIGURE 18-43. Folliculitis decalvans (horizontal). A dilated infundibulum containing several hairs is filled with neutrophils (follicular-based pustule). The follicular epithelium is partially destroyed by the inflammation. Other hairs in the left of this field exhibit polytrichia.

structural factors unique to hair follicles in blacks, may play a role (348).

Folliculitis Decalvans

Although some authors have equated folliculitis decalvans (FD) with erosive pustular dermatosis (351), since the last decade it has been considered to represent a highly inflammatory subtype of central centrifugal cicatricial alopecia (318). From a historical perspective, FD as a distinct entity has been described as a patchy pustular alopecia with recurrences (324) (Fig. 18-42). Later lesions show areas of scarring with pustules at the periphery (324). Cultures from the pustules usually reveal *Staphylococcus aureus*. Although some believe that the bacteria are pathogenic, others hold that they are the result of superinfection (318). When pustules are absent, the clinical picture resembles pseudopelade of Brocq (352). The finding of tufted hairs is common (353). FD has been reported in a patient with Darier's disease (354), in other areas besides the scalp, including the beard, face, and nape (355), and in 32-year-old identical twins, suggesting a possible genetic component (356).

Histopathology. Early, pustular lesions show an abscess centered about the affected follicle at the level of the lower to upper infundibulum (Fig. 18-43) (324), which may show comedonal dilation (352). Later lesions typically show perifollicular inflammation composed predominantly of lymphocytes, with fewer plasma cells, neutrophils, eosinophils, and giant cells (351,357). There may be hyperkeratosis, follicular plugging, and evidence of tufting. Late-stage lesions show follicular destruction secondary to diffuse dermal scarring (324). In such lesions the inflammation is less pronounced and is composed of lymphocytes, macrophages, and some giant cells in response to follicular remnants (357).

Pathogenesis. A number of authors believe that *S. aureus* is involved in the pathogenesis of FD (357), perhaps via bacterial superantigens that stimulate the immune system without intracellular processing (358) or an abnormal host response to *S. aureus* toxins in an otherwise straightforward infection (357). There have been reports of alterations in cell-mediated and humoral immunity, neutrophil chemotaxis, and low serum complement levels (359). Other investigators believe the presence of pustules is due to secondary infection with *S. aureus* or an immune response to disrupted follicles and their contents (318,360).

Tufted Hair Folliculitis

"Tufted folliculitis" is a finding that may be present in various forms of scarring alopecia and should not be considered a distinct entity, although some authors believe that it is, specifically characterizing it as a subset of folliculitis decalvans (353,361). Believing that it is a pattern that occurs in many forms of scarring alopecia and therefore is nonspecific, Sperling held that "the term tufted folliculitis should be purged from the lexicon of scarring alopecia" (182). It can be seen as a late process in several conditions, including central centrifugal scarring alopecia, folliculitis decalvans, inflammatory tinea capitis, *S. aureus* folliculitis, lichen planopilaris, dissecting cellulitis, follicular degeneration syndrome, and acne keloidalis nuchae (347,362,363). It has also been reported after traumatic scalp laceration (364) and after years of pemphigus vulgaris involvement of the scalp (365).

"Tufting" corresponds to the clinical finding of "doll's hair deformity," resembling the clustered hairs that are characteristic of a child's doll (Fig. 18-44). Another name for this finding is "polytrichia" (350). It has been reported in a 10-year old child (366). It should be distinguished from compound hairs, where two or three hairs exit from a single infundibulum, a normal finding on the occipital scalp.



FIGURE 18-44. Tufted folliculitis. Groups of hairs exit the scalp through a single opening (polytrichia), producing a clinical appearance that has been likened to "doll's hair." There is interfollicular scarring and erythema.

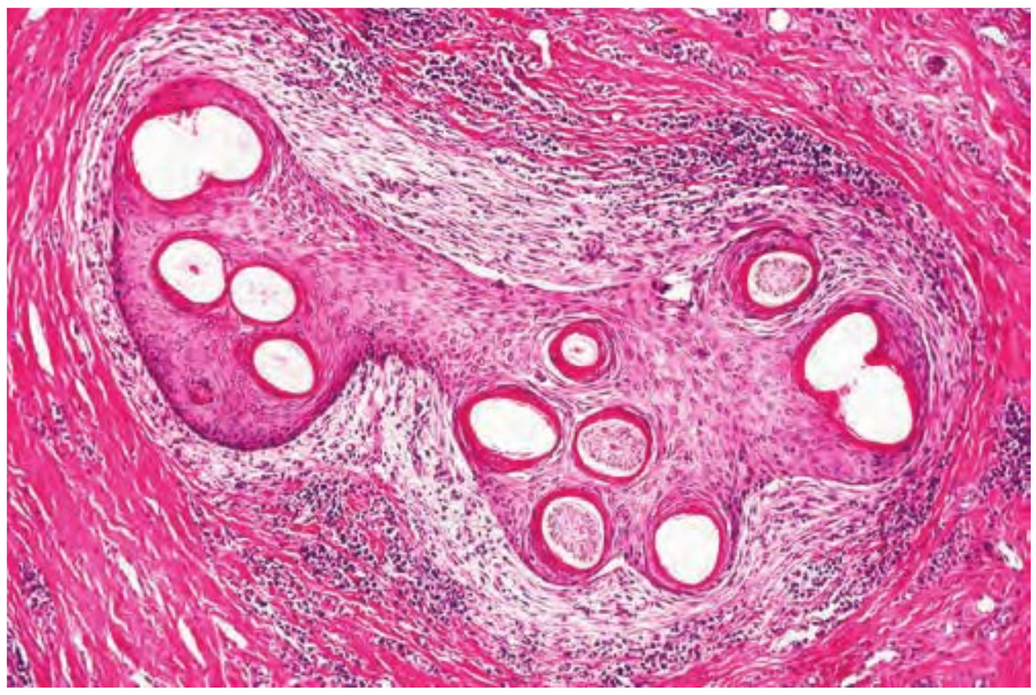


FIGURE 18-45. Tufted folliculitis (horizontal). In this extreme example, multiple hairs share a common outer root sheath and ultimately exit the scalp through a single opening. Perifollicular fibrosis and inflammation are present.

Histopathology. Histology shows a single group of three to five follicles, or several (two to four) such groups of follicles, in which the infundibular epithelium of the affected hair follicles is fused together (Fig. 18-45) so that the multiple hair shafts are situated in the infundibular hair canal and exit the skin through a shared ostium, which may show hyperkeratosis and parakeratosis (353). There is perifollicular fibroplasia superficially, as well as interfollicular fibrosis. The lower segments of the hairs are unaffected. The epidermis may be depressed from contraction of the fibrous tissue, forming a dell from which the hairs emerge. There may be variable infiltrates around the follicles and perivascularly that are composed of lymphocytes, histiocytes, and plasma cells, in addition to neutrophils when pustular lesions are biopsied. The hair tufts may eventually be destroyed by the process itself, and a foreign-body giant-cell reaction to free hair shafts may be seen. In one report, hairs were plucked from the tufts, revealing more than one-third telogen hairs (353).

Pathogenesis. Tufting results from injury to the outer root sheath epithelium of hairs in a single follicular unit or in several adjacent follicular units, possibly from a superficial suppurative folliculitis (353). There is accompanying perifollicular and interfollicular fibroplasia, leading to contraction of the involved skin and clustering of the follicular units. In healing, the outer root sheaths of the follicles grow together at the infundibular level. Other mechanistic theories include retention of telogen hairs (367), infection by *S. aureus* (361), and a congenital lesion, possibly a hair nevus, that became secondarily infected and scarred.

Postmenopausal Frontal Fibrosing Alopecia

This form of scarring alopecia is now considered a frontal variant of lichen planopilaris (368,369). It occurs in older women (mean age, 66.8 years), predominantly postmenopausal, with progressive recession of the frontal hairline (369,370). Other distinguishing features from typical lichen planopilaris include a marked decrease or complete loss of the eyebrows in most patients, a focal rather than multifocal pattern of alopecia, and lack of signs of lichen planus at other sites (369). There are rare exceptions, including one case with oral lichen planus (371) and another with cutaneous lichen planus in a premenopausal woman (372). Clinically the involved areas are pale, without sclerosis or induration, and show loss of follicular orifices (369). At the transition zone, follicles show perifollicular erythema and keratinization. Although frontotemporal recession can occur in postmenopausal women, mostly as a consequence of androgenetic alopecia, the follicular destruction in frontal fibrosing alopecia makes this condition unique (368,369).

Histopathology. Biopsies show histologic features of lichen planopilaris (Fig. 18-46), including perifollicular lymphocytic inflammation affecting the lower infundibulum and isthmus area near the bulge, hydropic degeneration of basal follicular keratinocytes with necrotic cells, concentric fibroplasia around the upper follicle, and absence of interfollicular changes (368,369). Naked hair shafts surrounded by granulomatous inflammation may be seen. Late lesions resemble burnt-out scarring alopecia, with noninflammatory fibrotic tracts replacing follicles and extending into the subcutis (373).

Pathogenesis. The infiltrate is predominantly composed of activated T-helper lymphocytes (368). The possibility that this

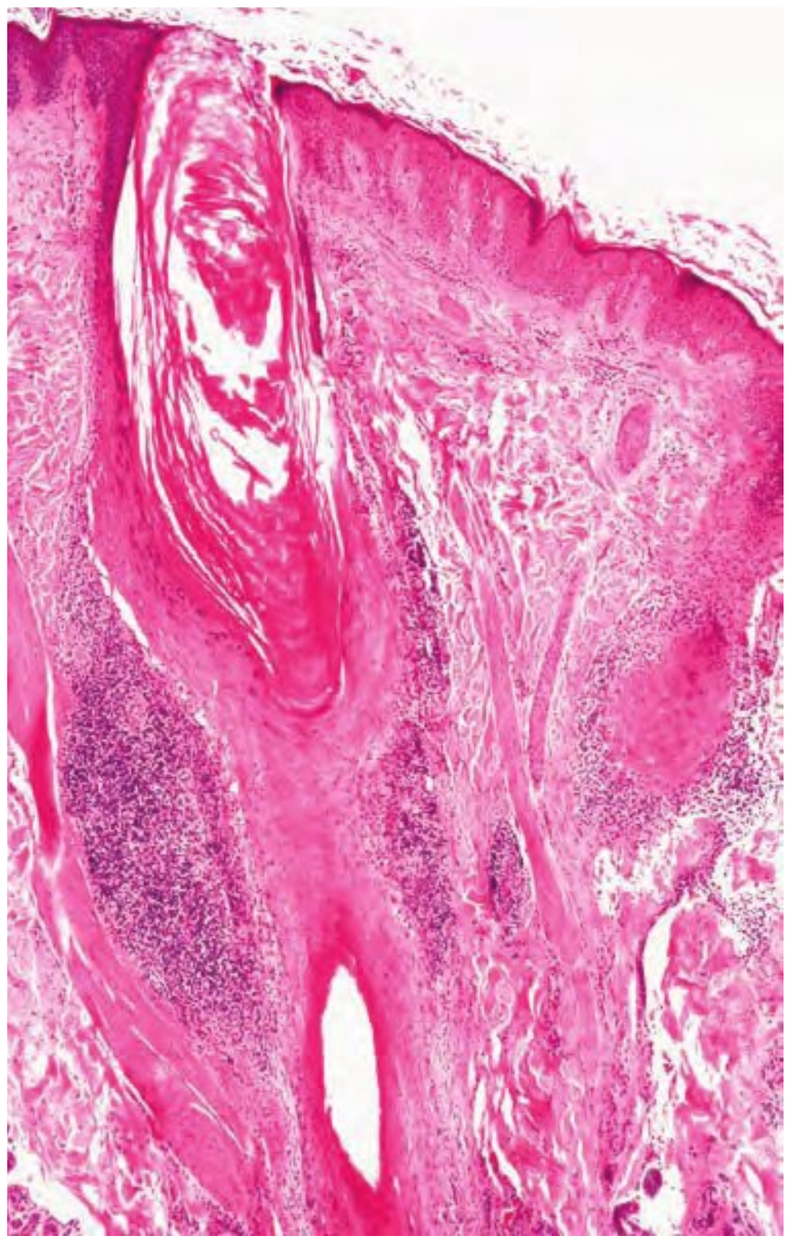


FIGURE 18-46. Postmenopausal frontal fibrosing alopecia (vertical). The changes are identical to those seen in lichen planopilaris, with lichenoid lymphocytic inflammation around the isthmus and lower infundibulum.

condition is triggered by androgenetic alopecia was considered, but some patients also displayed androgenetic alopecia over the central scalp that was unaffected by the fibrosing process (368,369). Despite the fact that most patients were postmenopausal, evidence to support a role for hormonal factors has not been demonstrated.

Fibrosing Alopecia in a Pattern Distribution

Fibrosing alopecia in a pattern distribution was described as another lichen planopilaris variant in which the clinically involved areas occur in a distribution characteristic of androgenetic alopecia (374). Both women and men were involved, but women outnumbered men with roughly a 4:1 ratio, and the mean age of affected patients was 59 years. Patients showed progressive fibrosing alopecia of the central scalp in the area of androgenetic alopecia. Affected follicles displayed perifollicular erythema and follicular keratinization. Multifocal lesions typical of lichen planopilaris or other mucocutaneous signs of lichen planus were not seen.

Histopathology. The histology of early and late lesions shows findings identical to those of early and end-stage lichen planopilaris (see the discussion of histopathology for postmenopausal frontal fibrosing alopecia), in conjunction with follicular miniaturization (374). Although both terminal and vellus hairs are affected by the inflammation, the miniaturized follicles appear to be preferentially targeted (318).

Miscellaneous Alopecia

Senescent Alopecia

Senescent or senile alopecia refers to the normal hair loss that occurs as a consequence of the aging process, with scalp hair becoming progressively and diffusely thinned starting at age 50 years but more typically by the seventh or eighth decade (294,331). Both sexes are affected. All elderly individuals exhibit thinning to some degree, but in severe cases, an individual may seek medical advice (192).

Histopathology. A 4-mm punch biopsy demonstrates the following: a decrease in the total number of hairs, from a normal of 35 to 45, to 25 to 35, a normal telogen count (less than 20%), a terminal-to-vellus hair ratio of at least 2:1, and a lack of deep inflammation (192,194). Horizontal sections are well suited to assess these parameters. The diameter of hairs may be diminished, and fibrous tracts may be seen (331). The occiput should show similar findings to those of other areas of the scalp (192).

Pathogenesis. Presumably follicles are lost forever; it is tempting to speculate that the regenerative capacity of follicular stem cells is restricted to a finite number of hair cycles.

Lipedematous Alopecia

Lipedematous scalp is localized or diffuse thickening of the scalp without hair loss, a result of thickening of the subcutaneous fat layer (375). This finding, in association with usually diffuse or patchy alopecia, has been termed *lipedematous alopecia* (376–378). It is a rare chronic condition, with relatively few cases being reported, that occurs most often in African-American females, although it has been reported in white women (379,380), as well as in men (381,382). The alopecia is characterized by short hairs that fail to grow longer than 2 cm in length. The scalp feels thick and boggy or spongy on palpation (378). It is smooth, without furrows, contrary to cutis verticis gyrata. Patients may complain of scalp pruritus, pain, or parasthesias. It was found in one patient with discoid lupus erythematosus (383).

Scalp thickness ranges from 10 to 15 mm, whereas normal scalp thickness averages 5.8 ± 0.12 mm, according to a study in which measurements were made at the bregma using skull x-rays (384). Scalp thickness may also be measured using computed tomography (375), magnetic resonance imaging (382), or ultrasound (377) or by introducing a sterile needle into the scalp (376).

Histopathology. The defining abnormality is increased thickness of the subcutaneous fat layer (385). To appreciate this on biopsy, the specimen must extend to the galea, and vertical sections are required. Superficial biopsies will not show the diagnostic finding. There is no evidence of adipose tissue hypertrophy or hyperplasia; instead, there is edema, with disruption of the normal subcutaneous architecture of lobules separated by collagenous septae (386). Degeneration of the adipose tissue into loosely associated collagenous strands, vessels, and aggregates of fat cells is also seen (386). Excess mucin deposition is not generally characteristic but was seen in some cases (377,379). There may be mild hyperkeratosis and acanthosis, as well as a sparse, superficial perivascular, interstitial, and perifollicular mononuclear infiltrate with occasional eosinophils (386).

A good explanation for the associated alopecia has not been found, although some researchers have noted a decrease in the number of follicles and focal bulbar atrophy (386). The hairs are in anagen and appear normal. In a study of lipedematous scalp and lipedematous alopecia, only the two cases with hair loss showed ectactic lymphatic vessels, believed to be potentially pathogenic (379). Scarring in the dermis or subcutis is generally absent, but perifollicular fibrosis has been noted (376,377). Follicular plugging and atrophic follicles have also been reported (376). Microscopic examination of hairs pulled in the clinical setting may show distal loss of the hair cuticle and changes of trichorrhexis nodosa, with hairs that break easily.

Pathogenesis. The etiology is unknown. The approximate doubling in scalp thickness is due entirely to thickening of the adipose layer. Free-floating lipid droplets along with adipocytes in various stages of degeneration were seen using electron microscopy (386). In addition to reduced follicular density, it is postulated that alopecia from aberrant hair shaft production may occur secondary to increased tissue oncotic pressure on hair bulbs (386).

Atrichia with Papular Lesions

Atrichia with papular lesions is a rare autosomal recessive condition characterized by total alopecia involving the scalp and body and usually the eyebrows (387), although eyelashes may be spared (388). Normal hair is present at birth but is shed within the ensuing months to years of life, never to be replaced (389). At around age 2 years, individuals start to develop generalized cystic papules. Unlike other forms of ectodermal dysplasia, defects in nails, sweat glands, or teeth are not seen (387).

Histopathology. A biopsy from affected scalp will demonstrate an absence of developed hair follicles (Fig. 18-47). Intact sebaceous glands may sometimes be seen (388). Follicular infundibula are present without the lower two thirds of hair follicles, which are often replaced by irregular epithelial structures or cysts (390). Consequently, hair shafts are not manufactured. Cysts develop from these abnormal follicles, producing clinical papules on the scalp and elsewhere that, when biopsied, reveal keratinous cysts with differentiation toward the follicular infundibulum (epidermoid, found in the upper dermis) and isthmus (trichilemmal, found in the middle and lower dermis) (388,390). The cysts may rupture, leading to foreign-body granulomas. Eccrine glands are normal in appearance.

Pathogenesis. Mutations in the human hairless (*HR*) gene on chromosome 8p12 produce the described clinical phenotype (391–393), although a patient with mutations in the vitamin D receptor gene has been reported (394). The hairless gene in humans is a homolog of the murine hairless gene (391,395). The human *HR* gene encodes a zinc-finger transcription factor protein that is expressed in the brain and skin (391).

Atrichia with papular lesions is recessively inherited, requiring two defective alleles; although most of the identified mutations have been homozygous within consanguineous families, compound heterozygous mutations have also been found (389). Possession of one allele with a *HR* gene mutation (heterozygous carrier) did not alter the expression of androgenetic alopecia in one study (396), and a significant association was not found in a group of men with androgenetic alopecia screened for *HR* gene mutations (397).

INFLAMMATORY DISEASES OF SWEAT GLANDS—ECCRINE

Syringolymphoid Hyperplasia with Alopecia

Originally described in 1969 (150,398), this rare dermatosis presents with localized or scattered, erythematous to red-brown patches, plaques, and hyperkeratotic follicular papules, sometimes producing anhidrosis (399). There may be an associated alopecia, most noticeable on the scalp, when there is follicular involvement (400). Most cases involve adult men.

Whereas some cases are considered idiopathic, others are associated with cutaneous T-cell lymphoma (CTCL) (400–402). "Idiopathic" cases should be followed closely to monitor for progression to clear-cut CTCL.

Histopathology. There are dense lymphocytic infiltrates surrounding superficial and deep vessels, hair follicles, and eccrine sweat glands. The sweat glands show epithelial hyperplasia, lymphocyte exocytosis, and sometimes obliteration of ductal lumina (Fig. 18-48) (401). Follicular mucinosis may be seen in some cases.

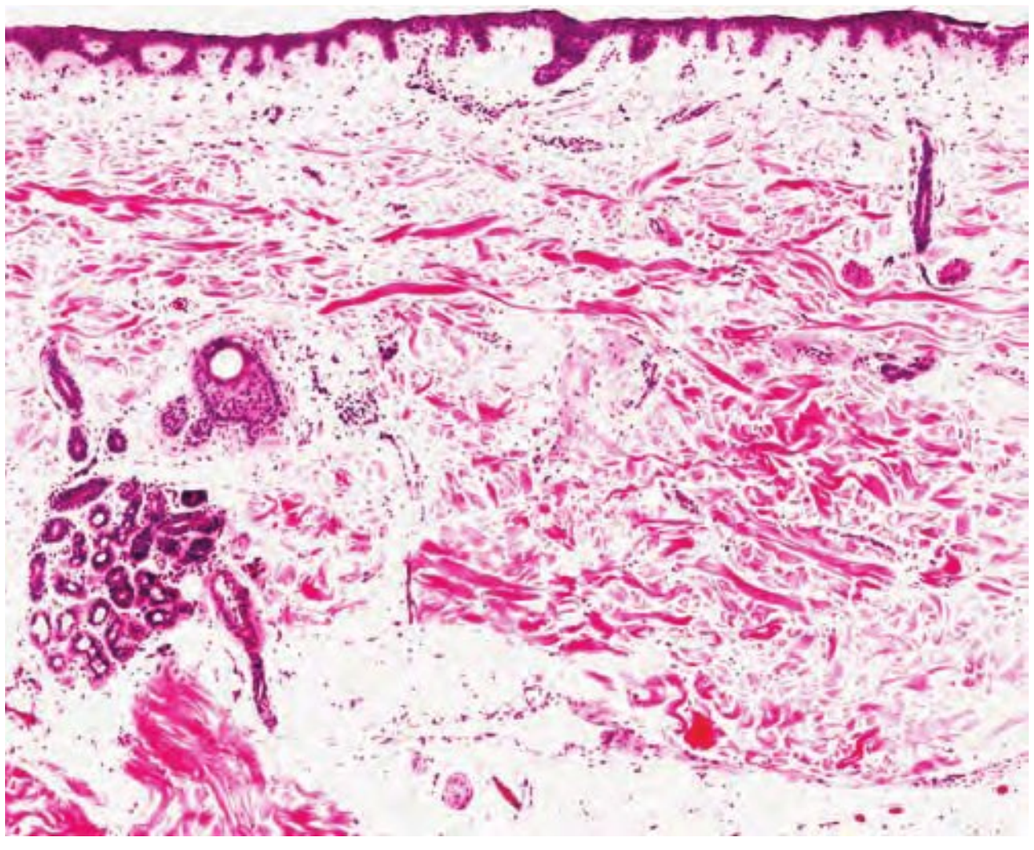


FIGURE 18-47. Atrichia with papular lesions (vertical). In this biopsy from the scalp, functional follicles are absent. Only a rudimentary follicle without a hair shaft is seen, near the eccrine gland, which is normal.

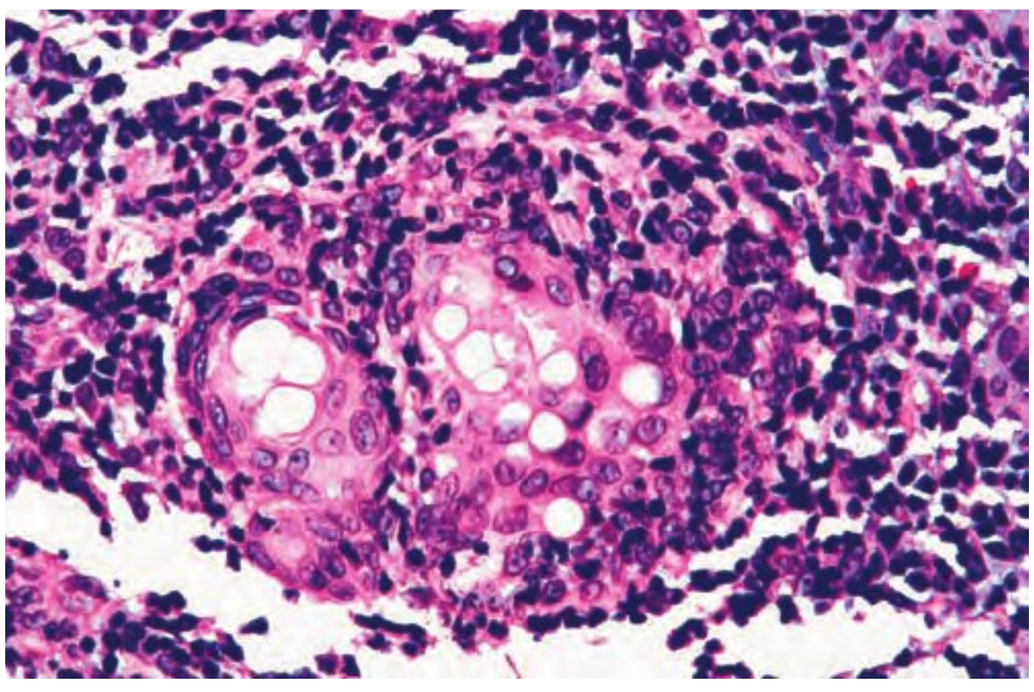


FIGURE 18-48. Syringolymphoid hyperplasia with alopecia. A mildly hyperplastic eccrine sweat gland shows partial obliteration of ductal lumina, a dense surrounding lymphocytic infiltrate, and lymphocyte exocytosis (syringotropism), findings that should prompt consideration of mycosis fungoides.

In cases associated with CTCL, early lesions may show features more akin to a "precursor" lesion, with psoriasiform epidermal hyperplasia, spongiosis, papillary dermal fibrosis, scattered eosinophils, and a lichenoid infiltrate composed of small lymphocytes and some larger ones with convoluted nuclei, without significant epidermotropism (150). Late lesions show epidermotropism with Pautrier's collections and denser perivascular and periadnexal infiltrates. Atypical lymphocytes infiltrate the eccrine gland epithelium (syringotropism) and also the follicular outer root sheath. The eccrine glands demonstrate hyperplasia with formation of complex, sometimes cribriform, structures (150). "Syringotropic variant of mycosis fungoides" was proposed as the preferred term for those cases associated with CTCL (403).

Neutrophilic Eccrine Hidradenitis

Neutrophilic eccrine hidradenitis (NEH) occurs in varied clinical settings (404). *Chemotherapy-associated NEH* is discussed in Chapter 11. NEH has been described in conjunction with infectious agents, including *Serratia marcescens* (405), *Enterobacter cloacae* (406), *Staphylococcus aureus* (407), streptococcal endocarditis (408), *Nocardia* (409), and HIV-1 (410–413), as well as miscellaneous associations that include granulocyte colony-stimulating factor (414), actinic reticuloid syndrome (415), Behçet's disease (416), acute myelogenous leukemia in the absence of chemotherapy (417), and one case in an otherwise healthy adult (418).

A subset of NEH that occurs in healthy children and young adults, *palmoplantar hidradenitis*, has been reported under many names, including "idiopathic palmoplantar eccrine hidradenitis," "juvenile neutrophilic eccrine hidradenitis," "recurrent eccrine hidradenitis," "idiopathic plantar hidradenitis," "traumatic plantar urticaria," and "plantar erythema nodosum" (419–426). Painful erythematous papules and nodules occur on the palms and soles. Constitutional symptoms are usually absent. In one study of 22 patients, occurrences were most frequent in the spring and fall, and almost half of the patients experienced more than one episode (427). The condition is benign and self-limited. Although the pathogenesis is unclear, temporal association with intense physical activity and exposure to cold, damp footwear have been reported (420,423).

A related condition has been described, the *Pseudomonas hot-foot syndrome* (428). Painful red-to-purple nodules developed on weight-bearing sites on the soles of 40 children within 1 to 2 days of using a community wading pool where the floor was covered with an abrasive grit (believed to be important to the pathogenesis). Lesions were cultured from some patients, yielding a strain of *Pseudomonas aeruginosa* identical to that found in the pool, and some of the children had associated *Pseudomonas* folliculitis. Previous reports of hot-tub folliculitis had noted similar plantar lesions (429) . Nevertheless, one group denied the existence of the *Pseudomonas* hot-foot syndrome, stating that the findings were consistent with idiopathic palmoplantar hidradenitis (430).

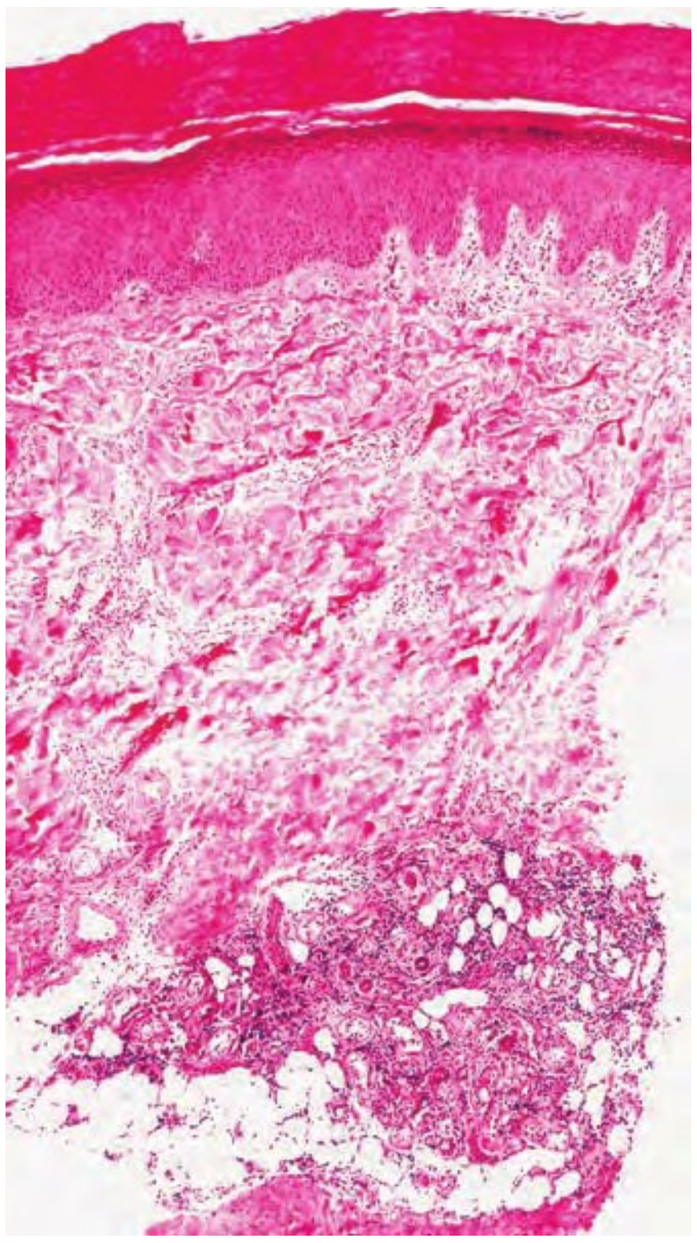


FIGURE 18-49. Palmoplantar hidradenitis. This biopsy from the plantar surface demonstrates an infiltrate around the eccrine gland coil.

Histopathology. The histology of *palmoplantar hidradenitis* occurring in children is similar to that of NEH induced by certain forms of chemotherapy (see Chapter 11), except that syringosquamous metaplasia is missing (431). A neutrophilic infiltrate is centered on the eccrine gland coils (Figs. 18-49 and 18-50). There may be mild mixed inflammation surrounding vessels in the mid and deep dermis, without leukocytoclastic

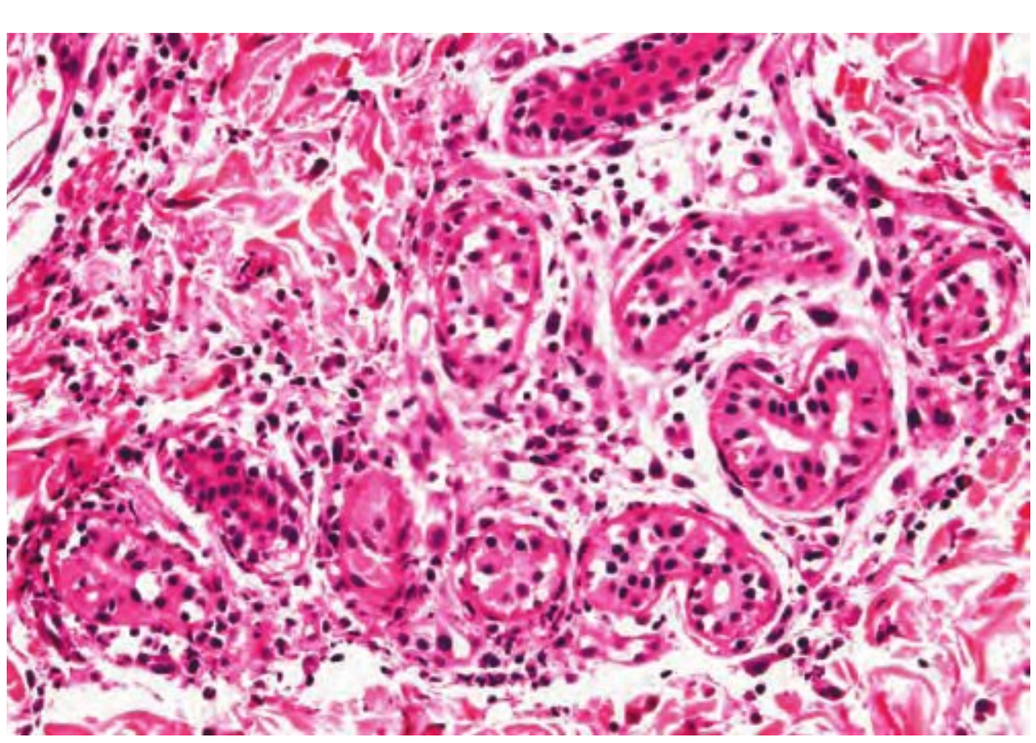


FIGURE 18-50. Palmoplantar hidradenitis. Neutrophils and neutrophilic debris surround an eccrine gland, constituting a pattern of neutrophilic eccrine hidradenitis.

vasculitis. Neutrophilic inflammation may involve the acrosyringium or assume a nodular pattern in the reticular dermis with abscess formation (422,426). Stains for fungi and bacteria are negative, even in those cases in which cultures of lesions are positive for bacteria (404).

In the *Pseudomonas* hot-foot syndrome, biopsies from two of the patients showed superficial and deep perivascular, interstitial, and perieccrine inflammation composed of neutrophils and lymphocytes that extended into subcutaneous fat lobules. One of the cases showed a dermal microabscess with extension into the fat and focal vasculitis with an intravascular thrombus (428). The authors noted that extension into subcutaneous fat lobules was a distinguishing feature from idiopathic NEH in children, a point that others have refuted (430).

INFLAMMATORY DISEASES OF SWEAT GLANDS—APOCRINE

Fox-Fordyce Disease

Fox-Fordyce disease (apocrine miliaria) is a disorder of apocrine sweat glands characterized by firm, itchy, follicular papules in anatomic sites where apocrine glands occur, namely the axillae (Fig. 18-51), areolae, and genitalia (432). It occurs almost exclusively in women after adolescence.

Histopathology. Step sections of a vertically oriented biopsy specimen are usually needed adequately to show the characteristic changes. There is hyperkeratosis of the follicular infundibulum and excretory duct of the apocrine sweat gland at the point where the latter inserts into the hair follicle. The apocrine duct behind the obstructing keratin plug becomes dilated (433). A spongiotic vesicle occurs in the follicular infundibulum, possibly representing an apocrine sweat-retention vesicle, with potential to rupture. Lymphocyte exocytosis is seen in the area of spongiosis. There may also be infundibular acanthosis and mild perivascular and periadnexal lymphocytic inflammation in the adjacent upper dermis (434,435). A comprehensive review of the histopathology noted other possible microscopic findings, including vacuolar alteration at the dermoepithelial junction of infundibula, dyskeratotic cells in infundibula, cornoid lamella–like parakeratosis within an orthokeratotic plug filling a dilated infundibulum, and foamy macrophages surrounding follicular infundibula and apocrine ducts (436). Transverse histologic sections facilitated identification of the diagnostic histologic features in one case, and this technique was touted as the most effective way to diagnose Fox-Fordyce disease on biopsy (437).



FIGURE 18-51. Fox-Fordyce disease. The uniform spacing of these discrete papules in the axilla is a clue to their adnexal origin.

A third type of sweat gland has been identified in the axillae; it is intermediate in size between the larger apocrine gland and smaller eccrine gland (438). Called the apoeccrine gland, it has a secretory coil like an apocrine gland but opens directly to the epidermal surface like an eccrine gland. A recent article details a case of Fox-Fordyce disease characterized by nonfollicular papules that histologically showed blockage of the intraepidermal portion of the apoeccrine sweat duct by cells that were released from the secretory portion via a holocrine mechanism (439).

Pathogenesis. The pathogenesis appears to be related to blockage of the apocrine sweat duct. Apocrine anhidrosis results, as demonstrated by the lack of apocrine secretion following intradermal injections of an epinephrine solution into the affected area (432). There are, however, reports suggesting that mechanical obstruction alone may not explain Fox-Fordyce disease (434).

INFLAMMATORY DISEASES OF CARTILAGE

Chondrodermatitis Nodularis Helicis

Chondrodermatitis nodularis helicis (CNH) usually presents as a single, small, exquisitely tender, erythematous nodule on the superior rim of the helix of the ear (Fig. 18-52) and less frequently on the antihelix or posterior ear (440). The lesion develops a crust and ulceration in the center, producing elevated margins that may mimic basal cell carcinoma. CNH occurs mostly in white men older than 40 years of age (441). The lesion tends to persist indefinitely without treatment.

Histopathology. Epidermal ulceration or a wedge-shaped epidermal defect is usually present. The intact adjacent epidermis is hyperplastic and may contain some dyskeratotic keratinocytes. A crust of exudate, parakeratosis, and dermal debris covers the surface of the epidermal defect (442). The dermis directly below shows fibrinoid collagen degeneration that stains more deeply eosinophilic than reticular dermal collagen, is homogeneous, and is acellular; it may reach the perichondrial tissue beneath (Fig. 18-53). The stroma adjacent to the zone of degeneration shows vascular proliferation with lymphohistiocytic inflammatory cells. There may also be some fibroplasia and occasional plasma cells and neutrophils. Glomus cell aggregates have been described in these vascularized granulation tissue–like areas (443). Peripheral solar elastosis is



FIGURE 18-52. Chondrodermatitis nodularis helicis. Papule on the helical rim with a central crust. Lesions can less commonly involve the antihelix.

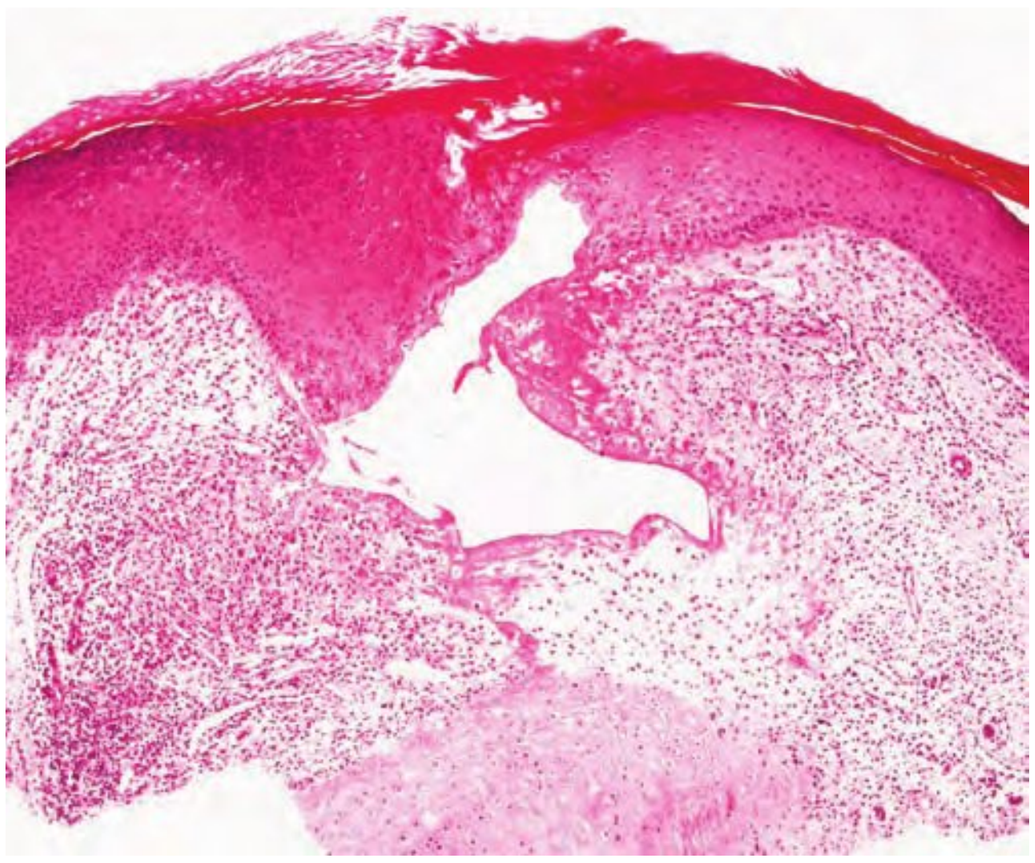


FIGURE 18-53. Chondrodermatitis nodularis helicis. There is a channel through the epidermis with adjacent epidermal hyperplasia. The dermis beneath shows fibrinoid degeneration of collagen that stains brightly eosinophilic and extends to the underlying perichondrium. The surrounding dermis shows a proliferation of small vessels, some mononuclear inflammation, and prominent solar elastosis.

common (442). The underlying perichondrial tissue may be thickened and appear to migrate to the base of the fibrinoid dermal necrosis. Degeneration of underlying cartilage with loss of cell nuclei can occur, although it is usually minimal. If cartilaginous degeneration is severe, there may be focal calcification and ossification. Nerve hyperplasia was found in 35 of 37 cases examined, potentially explaining the tenderness of lesions (444).

Pathogenesis. As the name implies, it was originally believed that this condition begins with cartilaginous degeneration. It is now generally considered to be an attempt at transepidermal elimination of damaged dermal collagen, a type of perforating disorder (442,445), although one report classified it as a necrobiotic process of collagen akin to granuloma annulare (446). The dermal collagen degeneration most likely results from vascular compromise, whether induced by trauma, pressure [during sleep or cell phone use (447)], cold, or complications of dermatoheliosis. The limited vasculature at this anatomic site and lack of subcutaneous fat insulation may contribute to the situation. In one case of CNH, serum autoantibodies to denatured type II collagen were detected (445).

Relapsing Polychondritis

Relapsing polychondritis (RP) is a rare systemic chondromalacia that affects cartilage in multiple sites, including the ear, nose, larynx, trachea, bronchi, and joints (448,449). It also affects proteoglycan-rich tissues, such as the eyes, aorta, heart, kidneys, and skin (449). It usually starts with auricular chondritis and runs an episodic, progressively destructive course. A mortality of about 25% has been reported, most commonly from damage to the respiratory tract or heart valves (450), although one study estimated the survival rate to be 94% at 8 years, a result of improvements in management (449). Disorders commonly associated with RP include rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and myelodysplastic syndromes (452). It may also be a paraneoplastic condition, reportedly occurring with non-Hodgkin's lymphoma (453) and chronic lymphocytic leukemia (454).

Primary involvement of the ears and nose, consisting of intermittent attacks of painful erythema and swelling, may lead to a dermatology consult. Rarely, only one ear is involved. Ultimately, the ears become soft and flabby as a result of cartilage destruction, and the nose assumes a saddle nose deformity.

Nonspecific dermatologic findings associated with RP are common, varied, and found most frequently in RP patients with myelodysplasia (455). They sometimes resemble the skin findings seen in Behçet's disease or inflammatory bowel disease: aphthosis, sterile pustules, limb ulcerations, or distal necrosis (455). It has been associated with Behçet's disease (456), described by the acronym MAGIC syndrome for "mouth and genital ulcers with inflamed cartilage" (457). Leukocytoclastic vasculitis is not uncommon (458,459), and, indeed, it has been suggested that the cartilaginous damage may be secondary to a primary vasculitis (460). Other associated

cutaneous lesions include purpuric or erythema nodosum–like lesions (458,459), chronic dermatitis, superficial phlebitis, livedo reticularis (455), septal and lobular panniculitis with vasculitis (461), erythema elevatum diutinum (462), epidermolysis bullosa acquisita (463), and pseudocyst of the auricle (464).

Histopathology. In early cartilaginous lesions, only the marginal chondrocytes appear degenerate, showing vacuolization, nuclear pyknosis, and loss of basophilia, which has been shown to result from the release of chondroitin sulfate from the cartilage matrix (465). A dense inflammatory infiltrate develops in the perichondrium, which comprises neutrophils, lymphocytes, eosinophils, plasma cells, and macrophages. Frequently there is edema or gelatinous cystic degeneration, and with progression, degenerated cartilage blends imperceptibly with the surrounding inflammatory cells, leading to the formation of granulation-type tissue (451). There may be fragmentation of the cartilage with necrosis and lysis of the cartilaginous plates (451). Elastic tissue stain shows clumping and destruction of cartilaginous elastic fibers (466). With successive episodes, fibrosis ensues.

Pathogenesis. Circulating antibodies to type II collagen, found exclusively in cartilage, are detected in patients with RP (467) and are generally found only in patients with active disease (468). The antibodies are directed against native and undenatured type II collagen, suggesting a primary role for these antibodies in the pathogenesis (rather than a secondary response to injured cartilage) (469). Immunoglobulin and complement components have also been identified in the inflamed cartilage (464,465). RP is strongly associated with HLA-DR4 (470).

Pseudocyst of the Auricle

In pseudocyst of the auricle, an asymptomatic, fluctuant swelling measuring about 1 cm in diameter is observed on the upper portion of the anterior aspect of the ear, usually in young men (mean age 38.9 years) (471). It is a form of chondromalacia that arises spontaneously or sometimes after minor trauma or infection, relapses frequently, and only rarely involves both ears. Pseudocyst is due to cavitation within the auricular cartilage, which, when punctured, releases only a few microliters of a clear, deep yellow, viscous fluid. In the differential of cystic swellings of the external ear, this feature aids in the diagnosis, so that if a relatively large amount of liquid is obtained, the cavity must be located outside of the cartilage (472).

Histopathology. A small intracartilaginous cavity without an epithelial lining is found on histologic examination. The wall of the pseudocyst consists of auricular cartilage, which is partially degenerated, appearing as faintly eosinophilic amorphous material (Fig. 18-54). The overlying epidermis, reticular dermis, and perichondrium are all normal (472). Until recently, inflammation was not considered a feature of this condition, but a study of 16 specimens consistently showed a perivascular lymphocytic infiltrate in the connective tissue just superficial to the cartilage (473); the authors believed that this was critical to the development of the condition.

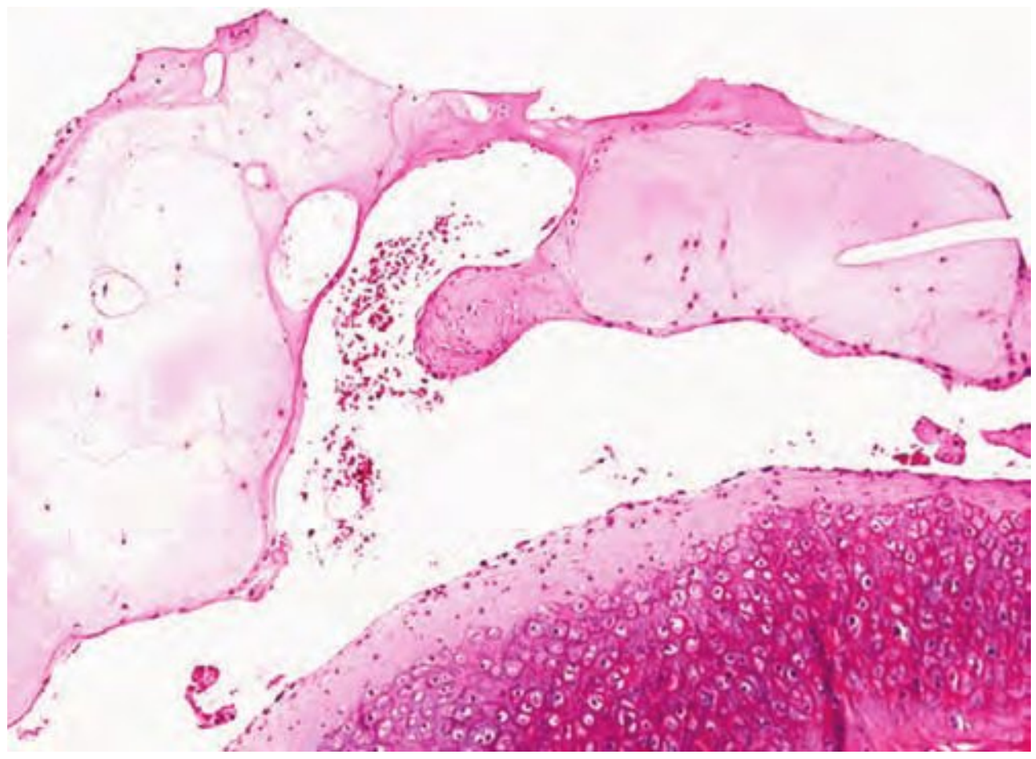


FIGURE 18-54. Pseudocyst of the auricle. There is an intracartilaginous cavity without an epithelial lining. The auricular cartilage is partially degenerated, appearing faintly eosinophilic and smudgy, with loss of nuclei.

Pathogenesis. It has been suggested that the intracartilaginous cavity forms after the release of lysosomal enzymes (474) or overproduction of glycosaminoglycans after repeated trauma or mechanical stimulation. Compared to normal serum, aspirated fluid has been found to contain elevated levels of lactate dehydrogenase (LDH), especially the LDH-4 and LDH-5 isozymes (475,476), as well as the cytokines IL-6 and IL-1((477); investigators hypothesized that these substances were released from the damaged cartilage. Pseudocyst of the auricle has been described in association with relapsing polychondritis (464).

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CHAPTER 19

Thomas D. Griffin

Inflammatory Diseases of the Nail

An understanding of the normal anatomy and histology of the nail unit precedes understanding the pathology that may occur there (see Chapter 3). Inflammatory pathologic processes in the nail unit affect mainly the matrix, nail bed, hyponychium, and nail folds. Changes in the nail plate occur secondarily. A basic understanding of where pathologic processes affect the nail unit will guide the practitioner in choosing a site of biopsy. As in other clinical situations, understanding the location and type of pathology leads to more effective diagnosis and treatment of the disease process.

Because of the unique anatomy of the nail unit, there is a limited number of possible reaction patterns to inflammatory processes. These reaction patterns may have different features from those seen in the skin. Because the nail unit produces a product, the nail plate, some inflammatory processes of the nail matrix may lead to irreversible damage resulting in an abnormal or absent plate, much akin to processes affecting the hair unit that lead to scarring alopecia. On the other hand, processes affecting the nail bed and hyponychium that do not affect the formation of the plate may affect its shape or adhesiveness. The nail bed responds to injury by becoming metaplastic, that is, by switching from onycholemmal keratinization (without keratohyalin granules) to epidermoid keratinization. It becomes hyperplastic, showing hyperkeratosis, parakeratosis, hypergranulosis, marked spongiosis, and exudative scale crust formation. The products of this reaction build up between the nail bed and plate. This process leads to the altered shape and shedding patterns of the nail plate that are common to several diseases affecting the nail bed, such as psoriasis and onychomycosis.

Inflammatory diseases may also affect the nail folds. When the ventral surface of the proximal nail fold is affected, inflammation of the cuticle and alterations of the dorsal surface of the nail plate may be seen. Eczema and contact dermatitis of the fingers may affect both the proximal and lateral nail folds.

Inflammatory processes affecting the nail may have many overlapping features. Although a specific diagnosis may be made in many cases, such as in lichen planus affecting the matrix, often it may be difficult to distinguish between, for example, psoriasis and eczema affecting the nail bed.

BIOPSY OF THE NAIL UNIT

Biopsy of the nail unit is recommended in many cases when the diagnosis is in doubt or when definitive histopathologic diagnosis is needed before beginning therapy.

Nail matrix biopsy is best performed after reflecting back the proximal nail fold (1). The nail plate may remain intact or may be avulsed before the biopsy. It is of utmost importance to avoid bisecting the matrix. A 2- to 3-mm punch biopsy from the center of the matrix should be obtained so that the excision is entirely within and surrounded by matrix. It is also important to avoid both the curvilinear portion of the lunula, which represents the distal nail matrix, and the most proximal portion of the matrix, since interruption of these areas may lead to defects in the nail plate.

The nail bed may be sampled by using a punch biopsy through the nail plate down to the periosteum (2). Longitudinal incisional biopsies may also be done. In this procedure, en bloc removal of the lateral nail fold, matrix, bed, and hyponychium is done. This procedure is excellent for defining disease processes of the nail unit. It is probably too extensive for routine nail biopsies and is not necessary for making a histopathologic diagnosis in most cases.

The proximal nail fold region may be sampled by a punch biopsy or a transverse excisional biopsy (2). The distal free margin of the proximal nail fold must be avoided to prevent notching.

Care must be taken to avoid biopsying so deep in the proximal nail area as to transect the tendon of the extensor digitorum communis, which inserts into the proximal dorsal portion of the terminal phalanx. Transection of this tendon will result in a drop deformity of the distal phalanx.

ECZEMATOUS DERMATITIS

Most forms of eczematous dermatitis affect the nail unit, with atopic dermatitis being most common. Contact dermatitis due to nail cosmetics or occupational exposure may affect all areas of the nail unit. Nail plate changes usually result from matrix or proximal nail fold involvement. Onycholysis may be due to nail bed involvement that begins distally at the hyponychium and spreads inward to involve the nail bed. Secondary chronic

paronychial infection may occur. The biopsy should be focused on the site of involvement, usually the nail bed or nail matrix. The histologic changes include spongiosis and exocytosis of mononuclear cells and an acanthotic epidermis. Stains for fungal organisms should be performed to rule out onychomycosis.

PSORIASIS

Nail involvement in psoriasis may occur in up to 50% of patients. Nail changes may occur in up to 80% of patients with psoriatic arthritis. In 10% of patients with psoriasis, nail involvement may be the only manifestation.

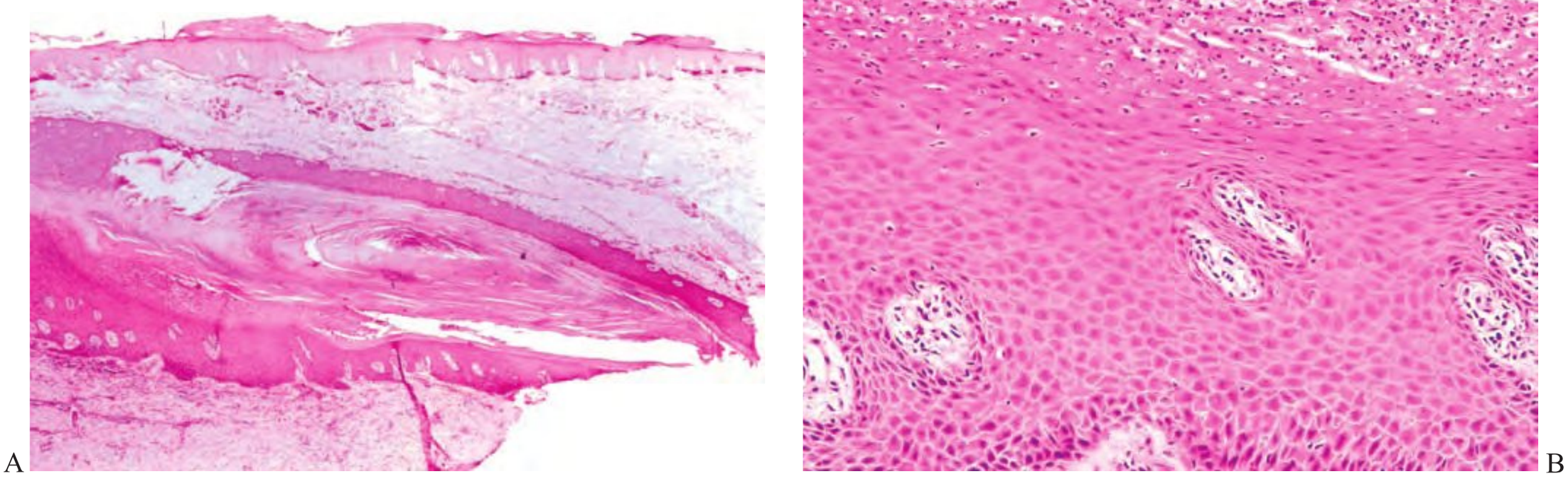
Psoriasis may involve any part of the nail unit, including the matrix, nail bed, hyponychium, and nail folds. Biopsy through the nail plate and nail bed is preferred for diagnosis of psoriasis involving the nail. Sections should be stained with hematoxylin and eosin and also with periodic acid-Schiff (PAS) stain or silver methenamine stain to rule out fungal infection. Because psoriasis and onychomycosis share many clinical and histologic features, a positive fungal stain is the only reliable way of distinguishing histologically between psoriasis and onychomycosis (3).

Psoriatic involvement of the proximal nail matrix causes clinical pitting and roughening of the surface of the nail plate. Histologically, foci of parakeratosis on the surface of the plate are seen, which when shed leave pits in the plate. Involvement of the mid- and distal matrix leads to clinical leukonychia. Once again, the histology is that of foci of parakeratosis in the nail plate; however, in leukonychia, the parakeratotic cells are located in the deeper portions of the plate.



FIGURE 19-1. Psoriasis of the nail. Onycholysis (oil drop sign) is seen in the distal nail plate.

The "oil drop sign" of psoriatic nails (Fig. 19-1) is a reddish-brown discoloration of the nail bed and hyponychium (4). It represents an early, acute focus of psoriasis involving the nail bed or nail matrix. Hyperkeratosis and parakeratosis with collections of neutrophils in the stratum corneum representing a Munro microabscess and spongiform pustules in the granular layer are seen (Fig. 19-2). The nail epithelium may show hypergranulosis with focal hypogranulosis. There is elongation of the dermal papillae with dilatation and proliferation of capillaries surrounded by lymphocytes, histiocytes, and occasional neutrophils. Distal nail onycholysis shows a similar histology and therefore has a similar histogenesis. The split in psoriatic onycholysis occurs between where neutrophils and parakeratotic



A B

FIGURE 19-2. Psoriasis of the nail matrix. A: There is absence of the granular layer, acanthosis of the epidermis, and vascular proliferation in the underlying papillary dermis. B: A spongiotic pustule is seen in the epidermis.

foci are located within the plate and the underlying hyponychium (5). The yellow leading edge of onycholytic nail correlates with the presence of neutrophils in the nail plate keratin.

Ultimately, well-developed psoriasis of the nail bed leads to subungual hyperkeratosis and exudate, which lift the nail plate off the bed. The nail bed epithelium shows psoriasiform acanthosis with elongated rete ridges and capillary proliferation. Neutrophils may be present in the superficial epidermis and within the keratin. Late or chronically traumatized psoriatic nails may develop features of lichen simplex chronicus (6), including marked compact orthokeratosis, hypergranulosis, and fibrosis of the papillary dermis, characterized by vertical streaks of coarse collagen fibers.

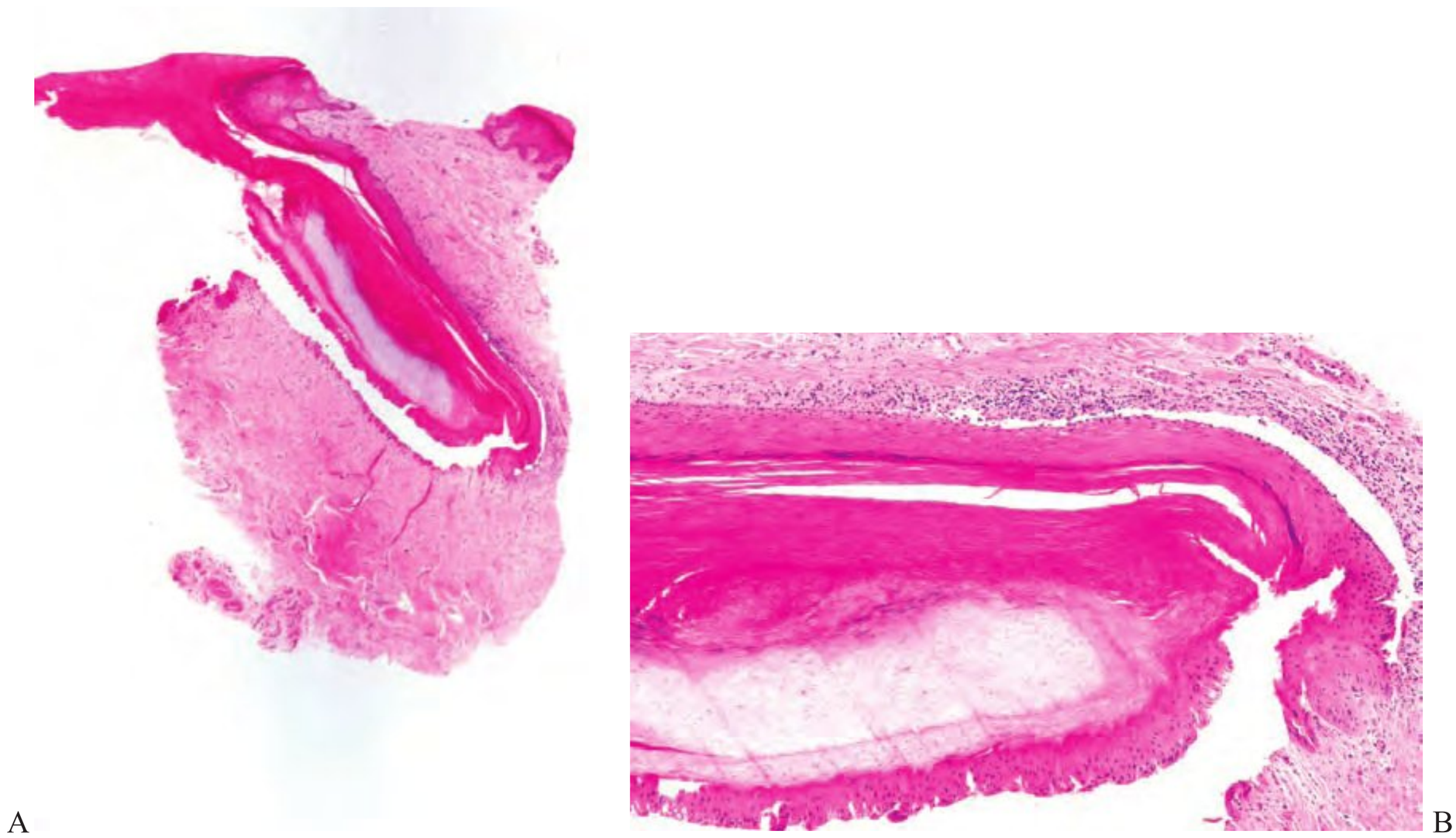


FIGURE 19-3. Lichen planus of the nail. Longitudinal grooves, atrophy, and splitting are seen in the nail plate.

LICHEN PLANUS

The incidence of nail involvement occurring in association with disseminated lichen planus ranges from 1% to 10% (7). Lichen planus may develop in the absence of cutaneous involvement and is most common in the fifth and sixth decades of life. Fingernails are more commonly affected than toenails (8). Lichen planus may involve the nail matrix, nail bed, and hyponychium. Examination and understanding of the pathogenesis of clinical changes will aid the clinician in determining where to sample the nail unit.

Involvement of the proximal nail matrix leads to longitudinal grooves and ridges (onychorrhexis) of the nail plate (Fig. 19-3). As in lichen planus of the skin, hyperkeratosis, hypergranulosis, vacuolar degeneration, necrotic keratinocytes, Civatte bodies, and a bandlike infiltrate of lymphocytes and histiocytes at the dermal–epidermal junction accompanied by melanophages can be seen (Fig. 19-4). Hyperpigmentation of the nail (melanonychia) may result. If lichen planus of the proximal nail matrix is treated early in its course, onychorrhexis may be reversible. As with other skin appendages, such as hair, if the process progresses, fibrosis and scarring may result, leading to permanent deformity.



A B

FIGURE 19-4. Lichen planus of the dorsal nail matrix epidermis. A: Hyperkeratosis and a superficial lymphocytic infiltrate are apparent at scanning magnification. B: At higher magnification, there is a bandlike superficial lymphocytic infiltrate along with vacuolar degeneration at the dermal–epidermal junction.

If the nail matrix is involved diffusely, onychoschizia (lamellar changes with fragility and brittleness) results. Once again, if treated before scarring occurs, the changes are reversible. When the lichenoid inflammation is severe and unchecked, the matrix is replaced by scar connecting the proximal nail fold to the nail bed. As a result, the two epithelia adhere and grow distally together, constituting a pterygium.

Occasionally, lichen planus of the nail bed alone may occur. Proximal onycholysis, to be differentiated from distal onycholysis in psoriasis, occurs because of involvement of the proximal nail bed. The nail plate is otherwise normal. Papular lesions of lichen planus may occur in various locations of the nail bed and lead to focal atrophy. As a result, the overlying nail plate will be focally dimpled or spooned (koilonychia). In some cases, complete shedding of the nail plate due to diffuse nail bed involvement may occur.

BULLOUS DISEASES

Several vesiculobullous diseases may affect the nail unit. In Darier-White disease, nail changes usually occur in association with other clinical findings. Rarely, involvement may be limited to the nail alone. Nail changes may occur in the proximal nail fold, matrix, nail bed, and hyponychium.

The proximal nail fold may show keratotic papules that are histologically similar to those of acrokeratosis verruciformis of Hopf. However, in addition to papillary epidermal hyperplasia, focal areas of suprabasilar acantholysis may be seen (9).

Involvement of the nail matrix in Darier-White disease is usually located in the distal lunula and manifests clinically as a white longitudinal streak. Histologically, this leukonychia is due to foci of persistent parakeratosis in the lower nail plate related to the histology of Darier-White disease of the distal matrix. The features seen are suprabasilar acantholysis, with formation of corps ronds and grains.

The nail bed and hyponychium are commonly involved in Darier-White disease. Involvement may be mild, leading to red and white longitudinal streaks. More severe involvement leads to wedge-shaped, distal, subungual keratosis, accompanied by nail fragility. In time, the nail plate may become markedly thickened. The nail bed epithelium becomes hyperplastic with parakeratosis between the nail bed and nail plate. Suprabasilar clefts are absent in the nail bed (9). An interesting finding is the presence of atypical keratinocytes in the nail bed epidermis, many of which may be multinucleated (9).

Nail involvement in pemphigus vulgaris is uncommon but may affect the proximal and lateral nail folds, leading to chronic paronychia and superficial nail plate changes (10). Biopsy of the involved nail fold reveals suprabasilar acantholysis and positive direct immunofluorescence with immunoglobulin G (IgG) and C3 in the intercellular spaces of the epidermis. Involvement of the matrix causes onychomadesis (proximal separation of the nail plate) (11). Pemphigus foliaceus may also affect the nail unit.

Bullous and cicatricial pemphigoid have been reported to involve the nail unit, with clinical effects implicating involvement of both matrix and nail bed, including longitudinal splits and pterygium formation (12).

Erythema multiforme and toxic epidermolysis may affect the nail matrix, resulting in either sloughing of the nail or, in some cases, scarring, leading to anonychia or pterygium formation (13). Epidermolysis bullosa in many of its manifestations affects the nail unit. Epidermolysis bullosa simplex may cause onycholysis or onychogryphosis. In epidermolysis bullosa simplex–herpetiformis, nail dystrophy or anonychia may result from subungual blister formation. Junctional epidermolysis bullosa may lead to dystrophy and anonychia in all of its forms. Nail changes have been described for the Cockayne-Touraine, albopapuloid, and Hallopeau-Siemens varieties of dystrophic epidermolysis bullosa (14).

CONNECTIVE TISSUE DISEASE

The nail unit is affected by most types of connective tissue disease, primarily in the microvasculature of the proximal nail fold (15). *In vivo* capillary microscopy reveals dilated capillary loops with adjacent hemorrhage and avascularity. This pattern is present in 80% to 95% of patients with progressive systemic sclerosis. However, an identical clinical pattern may be seen in patients with dermatomyositis, other connective tissue disease, and idiopathic Raynaud phenomenon. A crescent-shaped biopsy of the proximal nail fold reveals deposits of eosinophilic PAS-positive material in the keratin of the cuticle (15). These deposits tend to be more extensive in patients with connective tissue disease and in patients with more severe *in vivo* capillary microscopy abnormalities. Direct immunofluorescence can also be performed on a proximal nail fold biopsy revealing vascular deposits in connective tissue disease. More data are needed to determine if a proximal nail fold biopsy to evaluate for the presence and degree of PAS-positive deposits is of value in predicting the development of connective tissue disease in patients with idiopathic Raynaud phenomenon.

INFECTION

Fungal infection of the nails may be the most common nail disorder, accounting for up to 50% of nail disorders (16–19). Onychomycosis is present in 2% to 8% of the general population, rising to 14% to 28% in adults >60 years of age. There are four main types: distal subungual onychomycosis, proximal subungual onychomycosis, white superficial onychomycosis, and candidal onychomycosis. Dermatophytes, mainly *Trichophyton rubrum* and *Trichophyton mentagrophytes* are the most common fungi to cause onychomycosis, accounting for 60% of fungal infections. Nondermatophytes, mainly *Acremonium* sp., *Fusarium*, and *Scopulariopsis*,

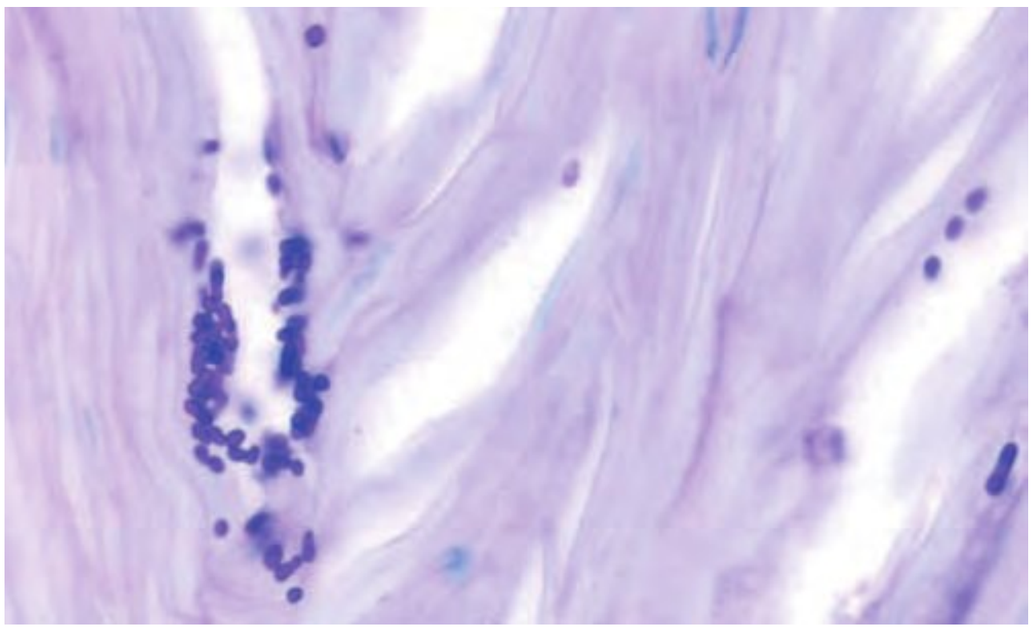


FIGURE 19-5. Candidiasis of the nail plate. Nail clippings showing budding yeasts culture proven to be C. parapsilopsis.

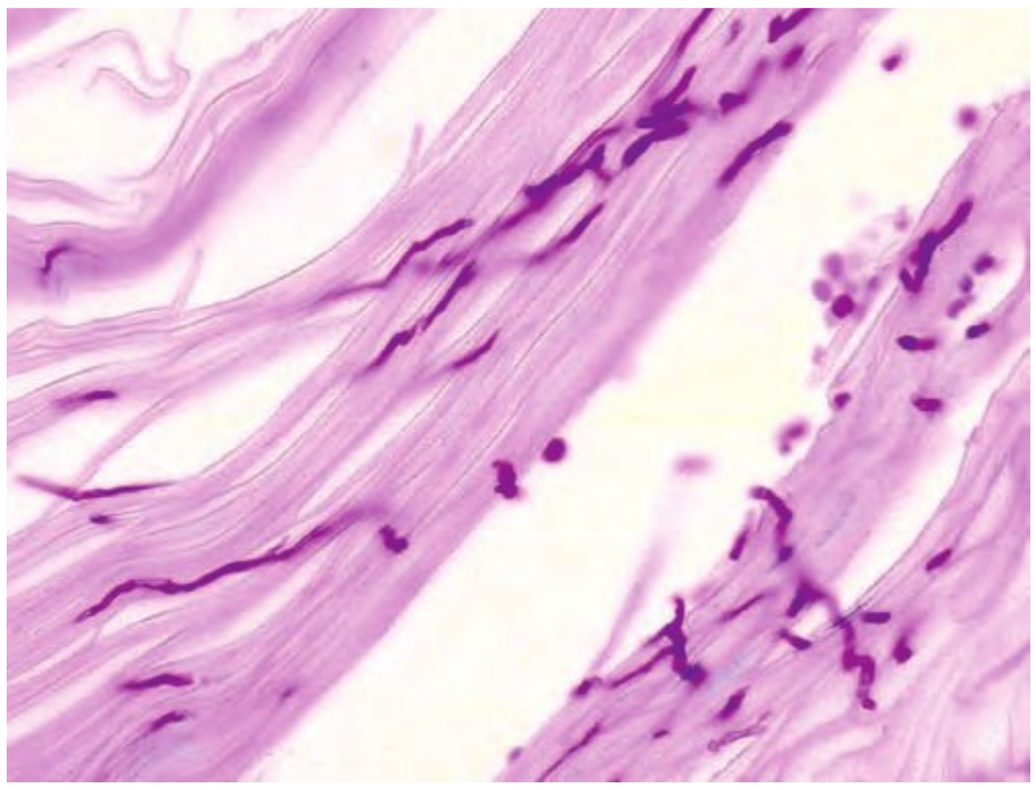


FIGURE 19-6. Onychomycosis of the nail plate. Nail clippings stained by using PAS with diastase showing septate hyphal elements culture proven to be Trichophyton sp. within the nail plate keratin.

and yeasts, mainly *Candida* sp., mostly *Candida parapsilosis* (Fig. 19-5), each account for 20% of infections (20). Ninety percent of toenail infections are caused by dermatophytes of *Trichophyton*, *Microsporum*, and *Epidermophyton* sp.. On the other hand, up to one third of fingernail infections may be caused by yeast forms. Biopsy accompanied by PAS staining has been shown to be the most sensitive test (99%) for diagnosing onychomycosis. PAS stain also has the highest negative predictive value (19). Potassium hydroxide (KOH) with chlorazole black E done on scrapings has been shown to be the most cost-effective test, with a sensitivity of 94%, while culture is the least sensitive test. A PAS with diastase stain should be performed to rule out fungal infection on all nail biopsies because of the overlapping features seen in inflammatory dermatoses involving the nail. This stain reveals fungal organisms that are usually located in the lower stratum corneum near the nail bed epidermis. A PAS with diastase stain performed on a nail biopsy, clippings of infected nail plate, or scrapings of subungual debris will yield a diagnosis of onychomycosis more quickly than fungal culture but will not identify the organism (Fig. 19-6). Distal subungual onychomycosis (Fig. 19-7) is the most common form of onychomycosis and is usually caused by *T. rubrum*. The fungus initially invades the hyponychium and lateral nail folds, causing yellowing, onycholysis, and eventual subungual hyperkeratosis. The nail bed epidermis shows acanthosis, spongiosis, and exocytosis of lymphocytes and histiocytes. In proximal subungual onychomycosis, infection initially involves the area of the proximal nail fold. Proximal white subungual onychomycosis is rare in the general population but common in patients affected with HIV (17). In these patients, proximal white subungual onychomycosis is caused by *T. rubrum*. On the other hand, superficial white onychomycosis is caused by *T. mentagrophytes*, located on the superficial nail plate only (16). In HIV-infected persons, superficial white onychomycosis is usually caused by *T. rubrum* (17). *Candida* sp. are a common cause of chronic paronychia. *Candida* may involve the nail plate and nail bed in patients with chronic mucocutaneous candidiasis and in HIV-infected patients. *Candida albicans* is the major fungus affecting the nail in pediatric patients with AIDS and may cause hypertrophic nail bed infection (17).

Bacterial infections caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa* occur mainly in the nail folds and lead to acute paronychia. Bacteria may also be involved along with *Candida* in chronic paronychia. *Pseudomonas* may colonize onycholytic nail plates, leading to green discoloration (16).



FIGURE 19-7. Onychomycosis of the nail. Distal subungual onychomycosis is seen in the thumb nail.

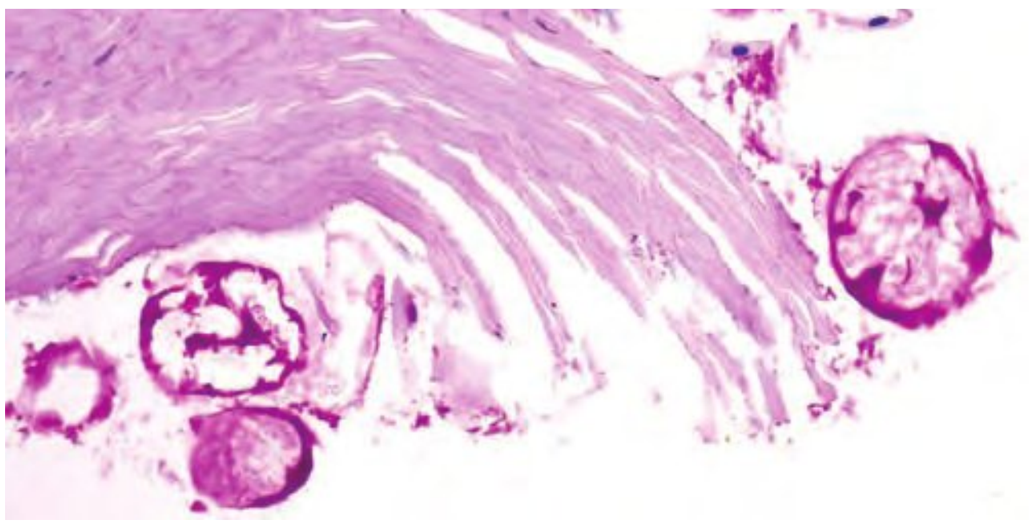


FIGURE 19-8. Scabies of the distal nail. Scrapings of the distal hyponychium stained by using PAS with diastase, which highlights the organism S. scabei.

Sarcoptes scabiei may involve the nail unit. Organisms are often present in distal subungual hyperkeratotic debris found in the hyponychium (Fig. 19-8) and may be a cause of persistent epidemics of scabies because they are seldom identified and treated. Norwegian scabies may cause severe involvement of the nail folds (18).

Herpes simplex type I or II may cause herpetic whitlow or herpetic paronychia involving the nail folds.

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CHAPTER 20

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Abelardo Moreno
Felix Contreras

Inflammatory Diseases of the Subcutaneous Fat

CLASSIFICATION OF PANNICULITIS

A histopathologic classification of panniculitis is based on the microscopic and macroscopic changes in the subcutaneous fat. The diseases presented in this chapter are divided into groups based on their patterns of involvement of the anatomic structures in the subcutis (1–3) (Table 20-1). However, for definite diagnoses, it is important to consider whether or not there are associated changes, such as in the overlying dermis and epidermis, as well as what types of inflammatory cells are involved (4). Clinical history and distribution of lesions often are important. The subcutaneous fat can be divided into the following anatomic regions: the septa between fat lobules, the fat lobules themselves, the blood vessels, and the nerves. When the septa are involved by inflammation, the histologic changes include septal widening due to edema, hemorrhage, and fibrosis or inflammatory infiltration by neutrophils, eosinophils, and macrophages, with or without granuloma formation. Involvement of the fat lobules includes necrosis, cellular infiltration, and fibrosis. Necrosis of fat is common, and the different types of necrosis have been classified by etiology as ischemic, traumatic, enzymatic, metabolic, inflammatory, and infectious. The cellular infiltrate associated with necrosis can be composed predominantly of polymorphonuclear leukocytes (neutrophils and eosinophils), lymphocytes (occasionally with germinal centers), and macrophages (with or without granulomas). Fibrosis of the fat lobules is a late event, which is the end result of multiple causes of lobular panniculitis ranging from that due to simple trauma to that due to complex connective tissue diseases. By analysis of the patterns of involvement of these regions, it is possible to make a specific diagnosis in a patient with panniculitis even when the interactions between inflammatory cells and target cells in panniculitis show considerable overlap in their basic mechanisms at the cellular and molecular levels.

Although the classification of panniculitis stresses the differences between the lobules of fat and the interlobular septa, there is an intimate relationship between the two. The septa contain the major blood vessels and nerves that supply the delicate plexus of vessels within the fat lobules and also contain the major vessels that pass on to the overlying dermis. When blood vessels are the target of inflammation, the different sizes of the blood vessels and their wall structures can cause certain diseases to be localized in the fat. Inflammation of the walls of large vessels often involves only the fat lobules immediately adjacent to the vessels. The medium-sized vessels are in the septa, and inflammation of their walls leads to septal panniculitis and in some cases also leads to secondary ischemic destruction of the fat lobules. Inflammation of the small vessels can affect the septa, lobules, or both. The relatively sluggish blood flow through the small vessels in the fat facilitates the exudation of substances and the emigration of inflammatory cells into the panniculus. For example, immune complexes or medications can be deposited in the walls of these vessels. Moreover, the subcutaneous fat cells, or adipocytes, form a closely regulated metabolic reserve, on which certain chemical compounds interact preferentially; for example, pancreatic lipases that have been released into the circulating blood or fat-soluble chemicals and medications can localize in the fat and cause metabolic or inflammatory changes. Hereditary and gender differences exist in fat metabolism, and these can be expressed in metabolic differences in different anatomic sites in the same individual. For example, *in vivo* and *in vitro*, abdominal subcutaneous adipose tissue is more responsive metabolically to beta-adrenergic stimulation than is the subcutaneous fat of the thigh. The thickness and orientation of the septa differ in normal males versus females and hypoandrogenized males, which suggests that this is under hormonal control (5). The septa are thicker in areas of the skin that are subjected to greater weight bearing, suggesting that genetic programming and mechanical forces both influence the thickness of the normal septa.

In the upper portion of the panniculus are the secretory coils of eccrine and apocrine glands and the lower portion of hair follicles. Consequently, diseases of the skin appendages can involve the panniculus secondarily. The subcutis also has a lower border on the fascia and inflammatory diseases that affect the fascia can penetrate upward into the septa and lobules.

Unfortunately, a significant problem is that the clinical appearance of the lesions of panniculitis is not very specific, since most patients have deep erythematous nodules. A consideration of the clinical distribution, number of lesions, and whether or not they are ulcerated help in the formulation of a clinical differential diagnosis. Some early clinical studies led to the description of clinical "entities," such as Weber-Christian

TABLE 20-1 Classification of Panniculitis

I. With prominent vasculitis (septal or lobular)
  A. Neutrophilic
    1. Leukocytoclastic immune complex vasculitis
    2. Subcutaneous polyarteritis nodosa
    3. Thrombophlebitis
    4. Type 2 leprosy reaction (erythema nodosum leprosum; Lucio's phenomenon)
    5. Behçet's syndrome
  B. Lymphocytic
    1. Nodular vasculitis
    2. Perniosis
    3. Angiocentric lymphomas
    4. Lupus erythematosus
  C. Granulomatous
    1. Nodular vasculitis/Erythema induratum of Bazin
    2. Type 2 leprosy reaction
    3. Wegener's granulomatosis
    4. Churg-Strauss allergic granulomatosis
II. Without prominent vasculitis
  A. Septal inflammation
    1. Lymphocytic and mixed
      a. Erythema nodosum
      b. Variants of erythema nodosum
    2. Granulomatous
      a. Palisaded granulomatous diseases
      b. Sarcoidosis
      c. Subcutaneous infection
        i. Tuberculosis
        ii. Syphilis
      d. Necrobiosis lipoidica
      e. Necrobiotic xanthogranuloma
    3. Sclerotic
      a. Scleroderma/Morphea
      b. Eosinophilic fasciitis
      c. Ischemic liposclerosis
      d. Toxins, particularly injected ones
      e. Postirradiation panniculitis
  B. Lobular inflammation
    1. Neutrophilic
      a. Infection
      b. Ruptured folliculitis and cysts
      c. Pancreatic fat necrosis
      d. Alpha-1 antitrypsin deficiency
    2. Lymphocytic
      a. Lupus panniculitis (lupus profundus)
      b. Poststeroid panniculitis
      c. Ischemic lipomembranous panniculitis
      d. Localized lipedema (minimal infiltration)
      e. Lymphoma/Leukemia
    3. Macrophagic
      a. Rosai-Dorfman disease
      b. Histiocytic cytophagic panniculitis
      c. Ischemic lipomembranous panniculitis
      d. Insulin-resistant diabetes with CD68+ infiltrate
    4. Granulomatous
      a. Erythema induratum/Nodular vasculitis
      b. Palisaded granulomatous diseases
      c. Sarcoidosis
      d. Crohn's disease
      e. Ruptured follicular cyst
    5. Mixed inflammation, with many foam cells
      a. Alpha-1 antitrypsin deficiency
      b. Weber-Christian disease
      c. Traumatic fat necrosis
      d. Factitial panniculitis (foreign body panniculitis)
    6. Eosinophilic
      a. Eosinophilic panniculitis
      b. Arthropod bite reaction
      c. Hypersensitivity reaction to internal parasites or medications
    7. Enzymatic fat necrosis
      a. Pancreatic enzyme panniculitis
      b. Alpha-1 antitrypsin deficiency panniculitis
    8. Crystal deposits
      a. Sclerema neonatorum
      b. Subcutaneous fat necrosis of the newborn
      c. Gout
      d. Oxalosis
      e. Calcific panniculitis/Calciphylaxis
      f. Cold panniculitis
      g. Poststeroid panniculitis
    9. Altered fat pattern
      a. Lipoatrophy
      b. Lipodystrophy
      c. Lipedema
    10. Sclerotic
      a. Ischemic lipodermatosclerosis
      b. Membranous panniculitis (lipomembranous panniculitis)
      c. Postirradiation panniculitis
      d. Eosinophilic fasciitis, late stage
      e. Morphea and scleroderma
III. Mixed patterns: In the natural progression of lesions of vasculopathic panniculitis, as well as in septal or lobular panniculitis, a complex mixture of patterns can result depending on the stage of evolution of the disease. For example, factitial panniculitis can exhibit a mixed pattern with microscopic features (hematoma, foreign bodies, dermal lesions, and fibrosis) that fit into more than one category. Subcutaneous panniculitic T-cell lymphoma may present with patterns of leukemic infiltration, lupus erythematosus–like lesions, granulomatous lesions, and angiodestructive vasculitic lesions.

disease or panniculitis of Rothmann and Makai, which unfortunately exhibit nonspecific histopathologic changes that occur in a variety of actual diseases that cause panniculitis.

Another major problem in the classification of panniculitis is that often the size of the biopsy is inadequate. The individual lobules of fat may be more than 1 mm in diameter, and several lobules and septa are needed to discern accurately a pattern of involvement. Consequently an adequate biopsy should be an elliptical, excisional, or incisional one that gives at least a specimen of fat 6 mm in greatest dimension and should include deep subcutis as well as the overlying skin. Only a few diagnoses can be made on a specimen of aspirated fat or a needle or punch biopsy of a nodule in the subcutis; the use of these biopsy modalities is to be discouraged for purposes of histologic classification of panniculitis.

A third problem is that most of the lesions have a time course in which there occurs an early form of inflammation with varying degrees of vascular changes, followed by a stage of phagocytosis of fat and a more or less pronounced granulomatous reaction, and by a final stage of fibrosis. Such a time course is evident in the overall lesion and may be different in various areas of the lesion. With small biopsies or with a nonspecific pattern of inflammation, a simple categorical diagnosis of "panniculitis" may be necessary until further studies and clinical follow-up information allows the placement of the disease into a more exact category (6–8).

Table 20-1 presents a summary of the classification of panniculitis. Not all of the disease entities are presented in detail in this chapter, and some can be found elsewhere in this text: leukocytoclastic vasculitis (Chapter 8), systemic polyarteritis nodosa (Chapter 8), sarcoidosis (Chapter 14), granuloma annulare (Chapter 14), rheumatoid nodule (Chapter 14), necrobiosis lipoidica (Chapter 14), scleroderma (Chapter 10), necrobiotic xanthogranuloma (Chapter 26), and gummatous tertiary syphilis (Chapter 22).

ERYTHEMA NODOSUM

Clinical Presentation. An acute form and a chronic form of erythema nodosum exist, which differ in their clinical manifestations but do not have uniformly recognized differences in their histologic characteristics (1,2,7,9).

In the *acute form* of erythema nodosum, there is a sudden appearance of tender, bright red or dusky red-purple nodules to plaques that only slightly elevate the level of the skin surface (Fig. 20-1). The lesions vary from 1 to 5 cm in diameter and have a strong predilection for the anterior surfaces of the lower legs, although they may occur elsewhere, especially on the calves, thighs, and, in severe cases, on the forearms, hands, and even the face. They occur mostly on the dependent regions of the body and tend to be distributed symmetrically. The lesions do not ulcerate and generally involute within a few weeks without leaving a depressed scar. As a result of the intermittent appearance of new lesions, the disease may persist for several months. The acute disease often is accompanied by fever, malaise, leukocytosis, and arthropathy (10). The lesions are tender and warm. Lesions near a joint can mimic an arthritis. Focal hemorrhages are common and can cause the lesions to resemble bruises (erythema contusiforme), even to changing in color from red to purple and on to green and blue, as they age and resolve. Bilateral hilar adenopathy can be present in patients with acute erythema nodosum without sarcoidosis since a number of pulmonary infections can produce both hilar adenopathy and erythema nodosum. Erythema nodosum occurs in 10% to 20% of patients with sarcoidosis and is thought to portend a good prognosis (10).

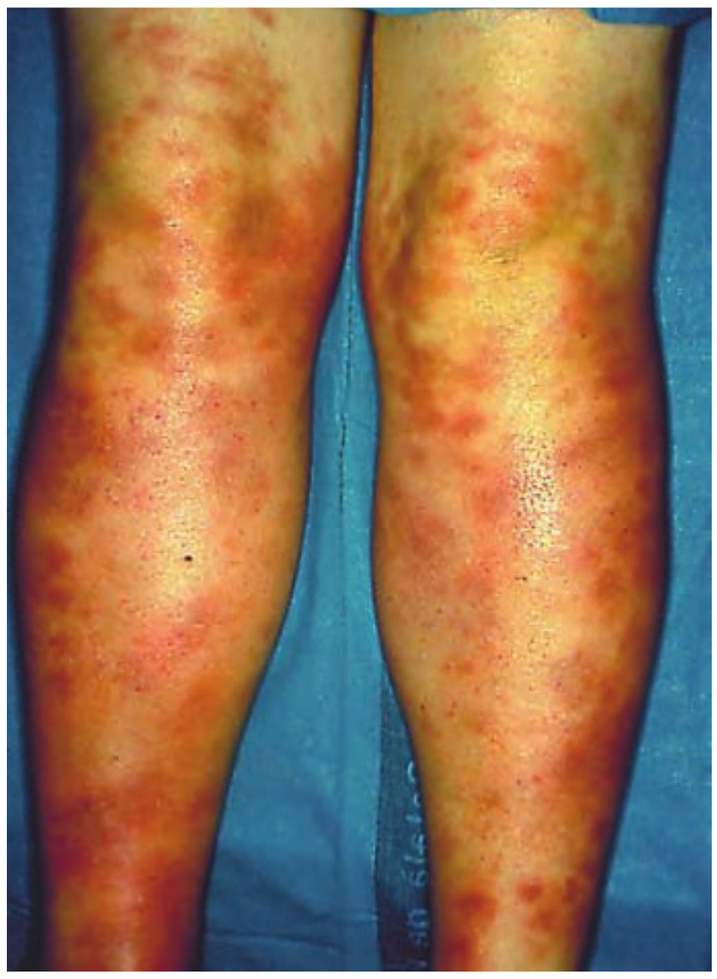


FIGURE 20-1. Erythema nodosum. Erythematous nodules are abundant on the anterior shins bilaterally.

The *chronic form* of erythema nodosum is also known as *erythema nodosum migrans* (11) or *subacute nodular migratory panniculitis of Vilanova and Pinol* (12). There are one or several red, subcutaneous nodules that are found, usually unilaterally, on the lower leg. Vilanova observed that almost all of the patients were women (16 to 65 years of age) with a solitary lesion and a recent history of sore throat and arthralgia. Tenderness is slight or absent. The nodules enlarge by peripheral extension into plaques, often with central clearing. The duration may be from a few months to a few years.

Histopathology. The histologic changes are present mainly in and near the septa of the subcutaneous tissue (Fig. 20-2). The overlying dermis often has only a minimal to moderate, superficial and deep perivascular lymphocytic infiltrate.

In the *early lesions of acute erythema nodosum*, there is edema of the septa with a lymphohistiocytic infiltrate, having a slight admixture of neutrophils and eosinophils (13) (Fig. 20-3A1, B, C). Focal fibrin deposition and extravasation of erythrocytes occur frequently (6) and can be revealed by spectral microscopy (Fig. 20-3A2). Often, the inflammation is most intense at the periphery of the edematous septa and extends

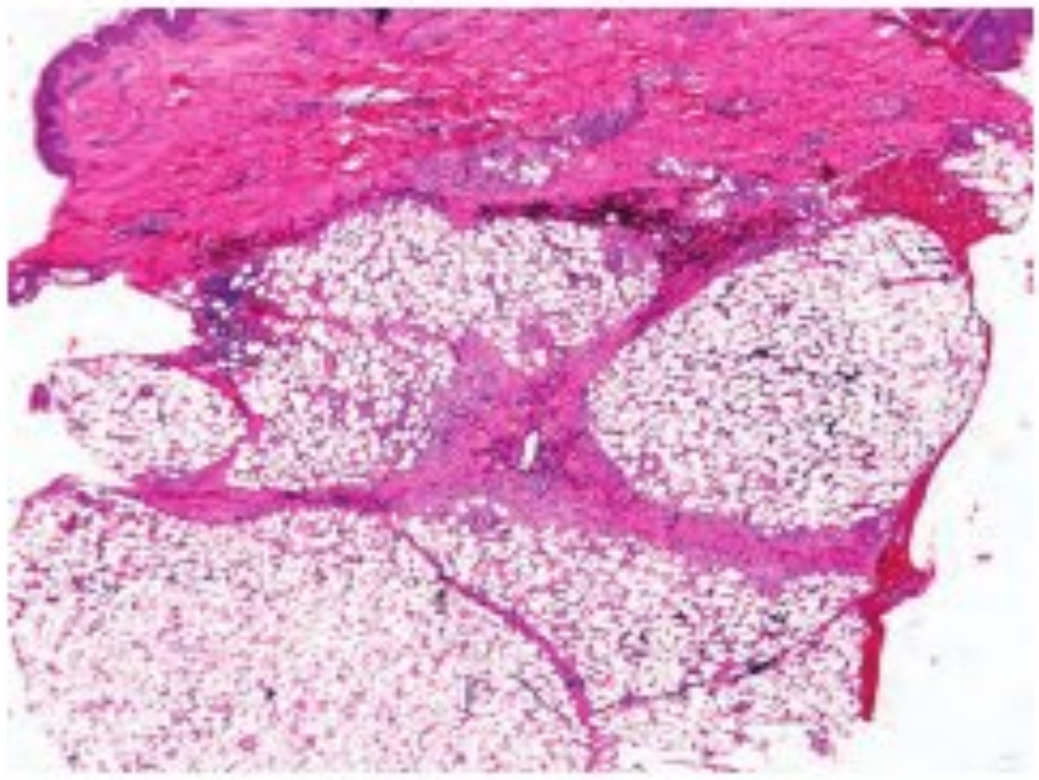


FIGURE 20-2 Acute erythema nodosum. Most of the inflammation is in the subcutis, in and near the septa. The septa at the bottom of the figure are almost normal in thickness, whereas the upper portion of the subcutis has thickened septa.

into the periphery of the fat lobules between the individual fat cells in a lacelike fashion. Necrosis of the fat is not prominent. Rarely, clusters of neutrophils are present or the infiltrate is predominantly neutrophilic (14) (Fig. 20-4). Clusters of macrophages around small blood vessels, or a slitlike space, occur in early lesions and are known as *Miescher's radial nodules* (15,16) (Fig. 20-5). Some authors have failed to find central vessels (2) and have considered Miescher's nodules to be characteristic of erythema nodosum, stating that they can be found in all stages of erythema nodosum (16). The degree of vascular involvement is variable (6,17) (Fig. 20-6). Usually, there is edema of the walls of veins with separation of the muscular layers (Fig. 20-6B). Infiltration by lymphocytes is common, but neutrophils and eosinophils can be present as well. Necrosis of the vessel walls is very rare but has been observed in a few patients with lesions clinically indistinguishable from erythema nodosum (9,18). For example, focal vasculitis has been found in a few patients with acute erythema nodosum secondary to infections (19) and in a few cases of recurrent

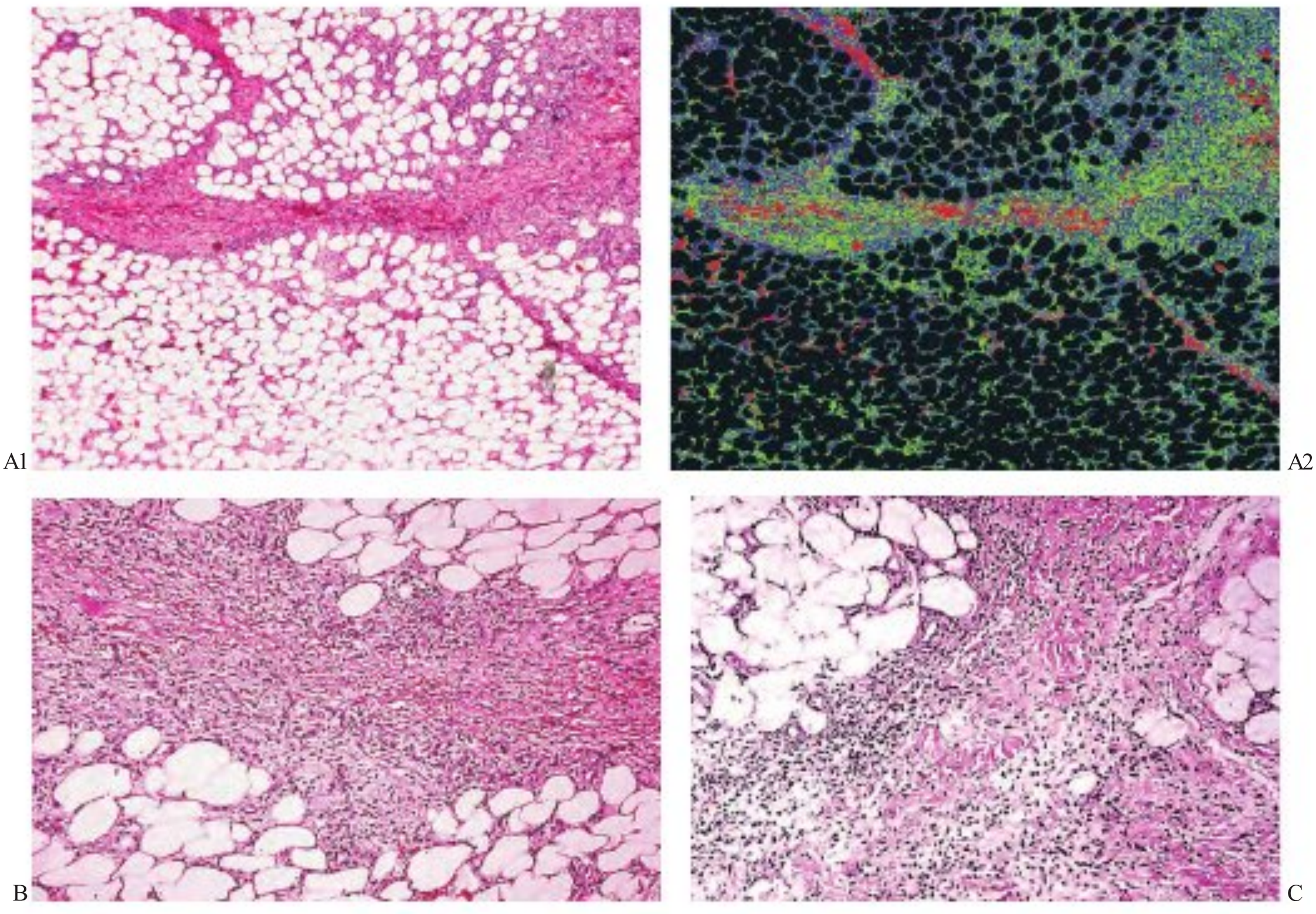


FIGURE 20-3 Acute erythema nodosum. A1: Acute erythema nodosum with inflammation at the junction of the septa and lobules with some hemorrhages. A2: A matching spectral image showing the spectral domains of red blood cells in the hemorrhages in red, as distinguished from the spectral domain of the eosin-stained collagen here shown in green. Hematoxylin in nuclei is shown in blue. B, C: Higher magnification of a septal region showing the paraseptal inflammation (B) and early fibrosis of the edematous septa in acute erythema nodosum (C).

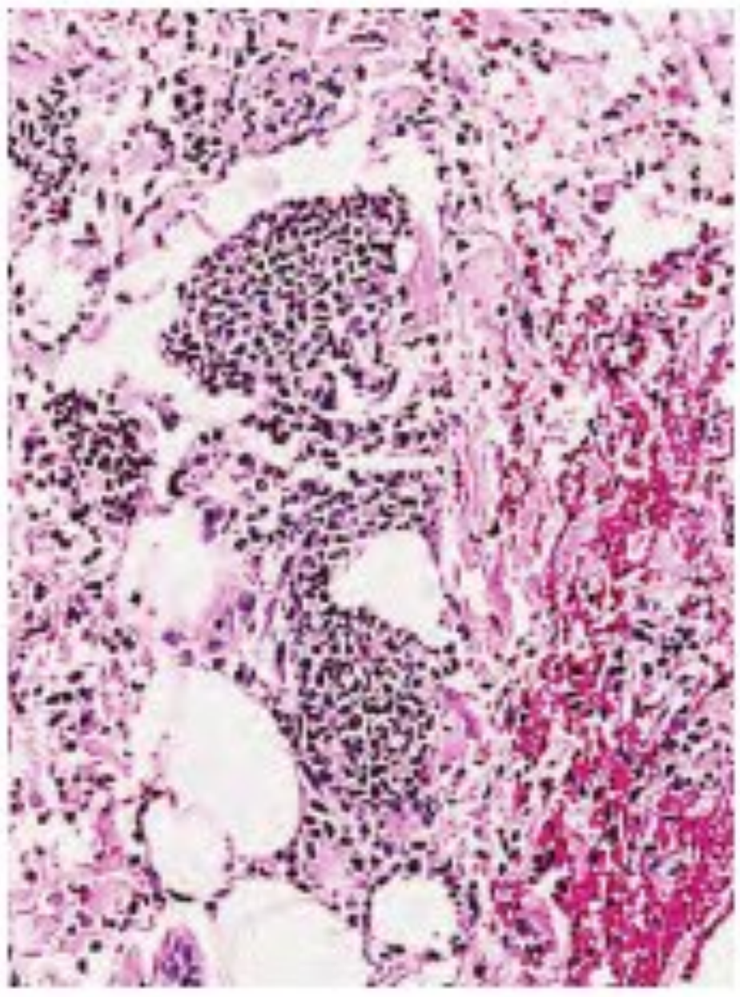


FIGURE 20-4 Acute erythema nodosum. Clusters of neutrophils can be found in the paraseptal region, without evidence of intact bacteria.

erythema nodosum that is secondary to medications or estrogenic oral contraceptives (Fig. 20-6C).

Later lesions of acute erythema nodosum show widening of the septa, often with fibrosis and with inflammation at the edges of the septa and involving the periphery of the fat lobules (Fig. 20-7). Neutrophils usually are absent, and the vascular changes are less prominent than in early lesions. There are more macrophages in the infiltrate. Macrophages at the edges of the fat lobules show phagocytosis of lipid from damaged adipocytes, and the small droplets of lipid in their cytoplasm give them a "foam cell" appearance. Granulomas formed by macrophages, without lipid deposition, are more frequent

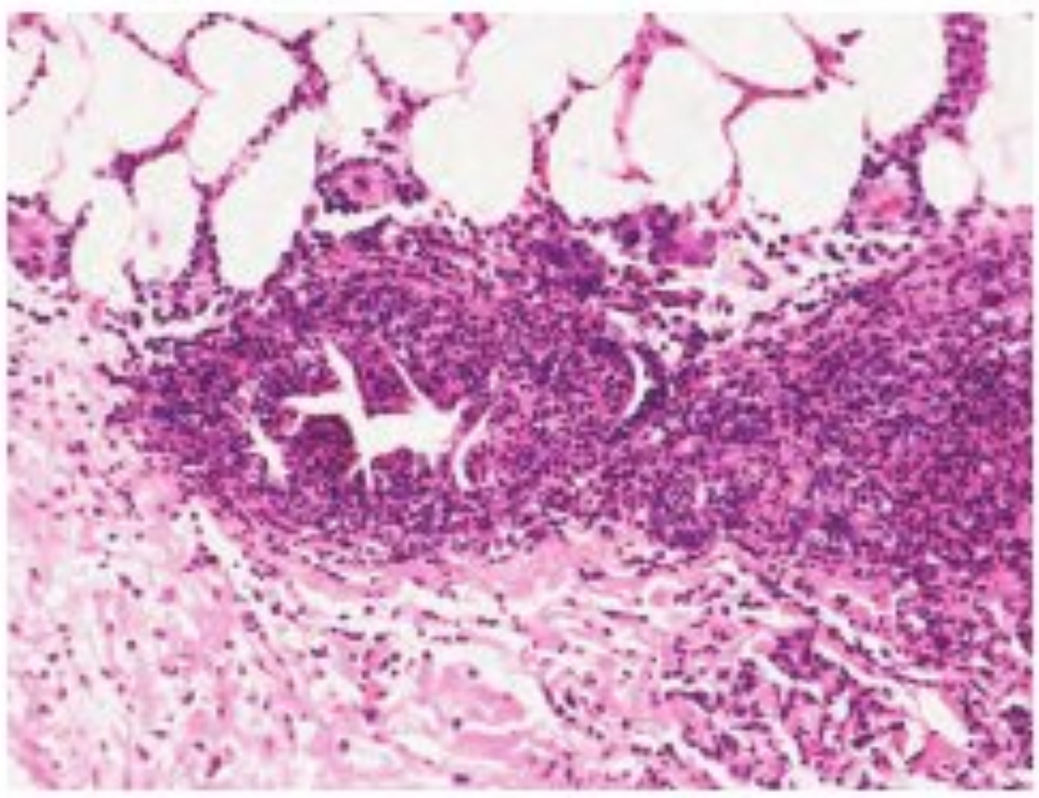
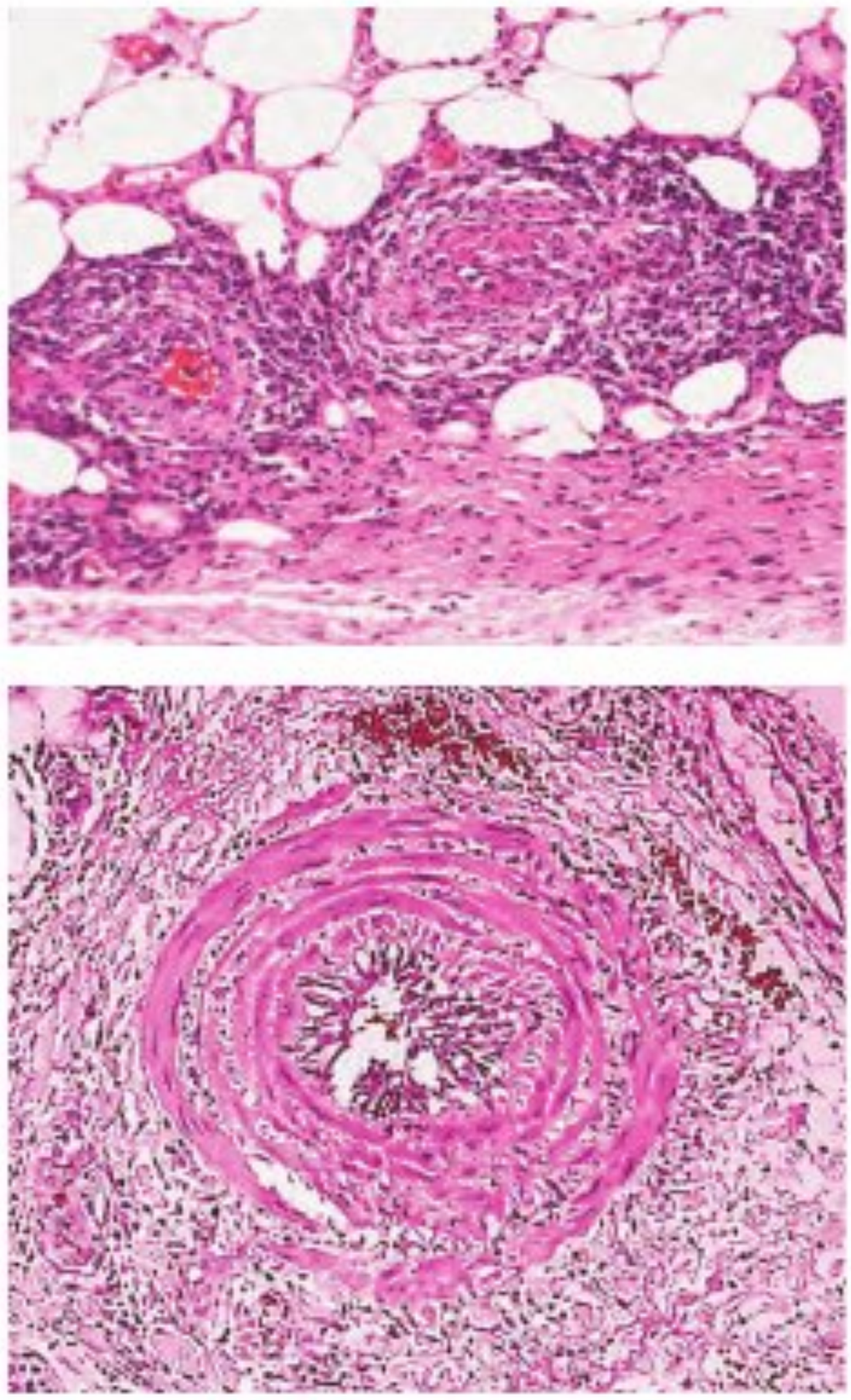
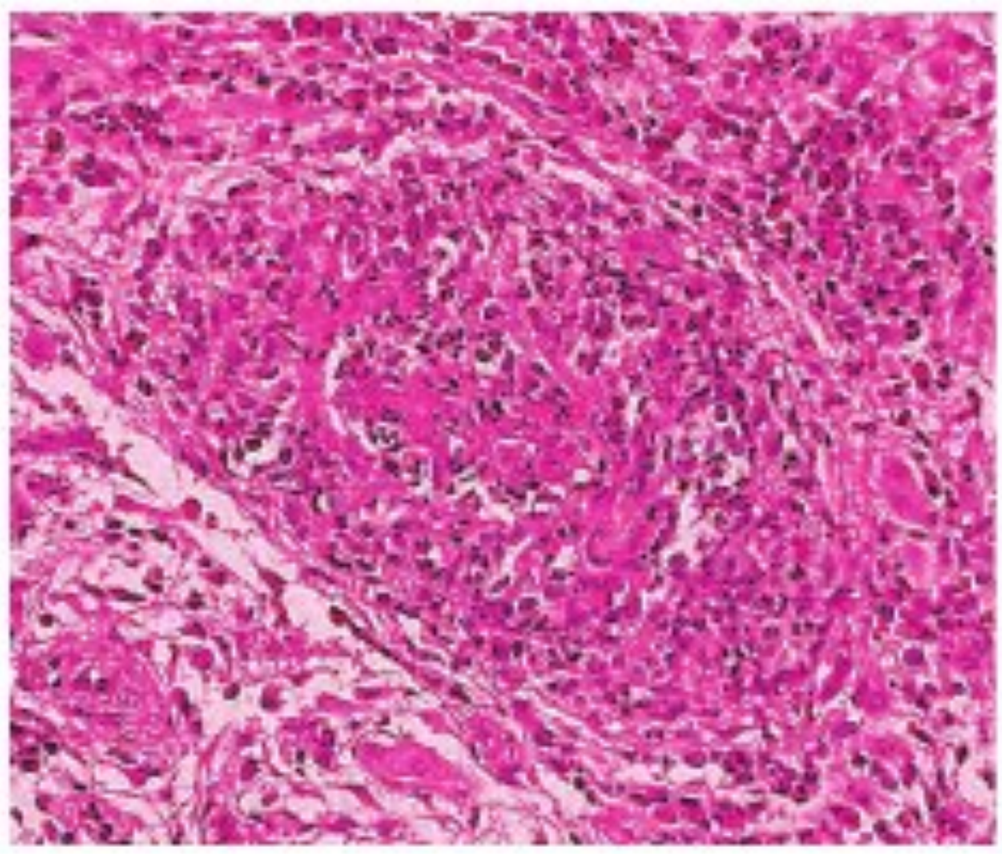


FIGURE 20-5 Acute erythema nodosum. Miescher's radial granulomas are characteristic findings and are formed by macrophages and neutrophils.



A

B



C

FIGURE 20-6 Acute erythema nodosum. Vasculitis is uncommon but can be found in the paraseptal and septal blood vessels. A: Vascular damage with a mixed neutrophil and macrophage infiltrate and thrombosis. B: Edema and inflammation in the wall of a small vein in the septa. C: More advanced inflammation of the wall of a vein in erythema nodosum.

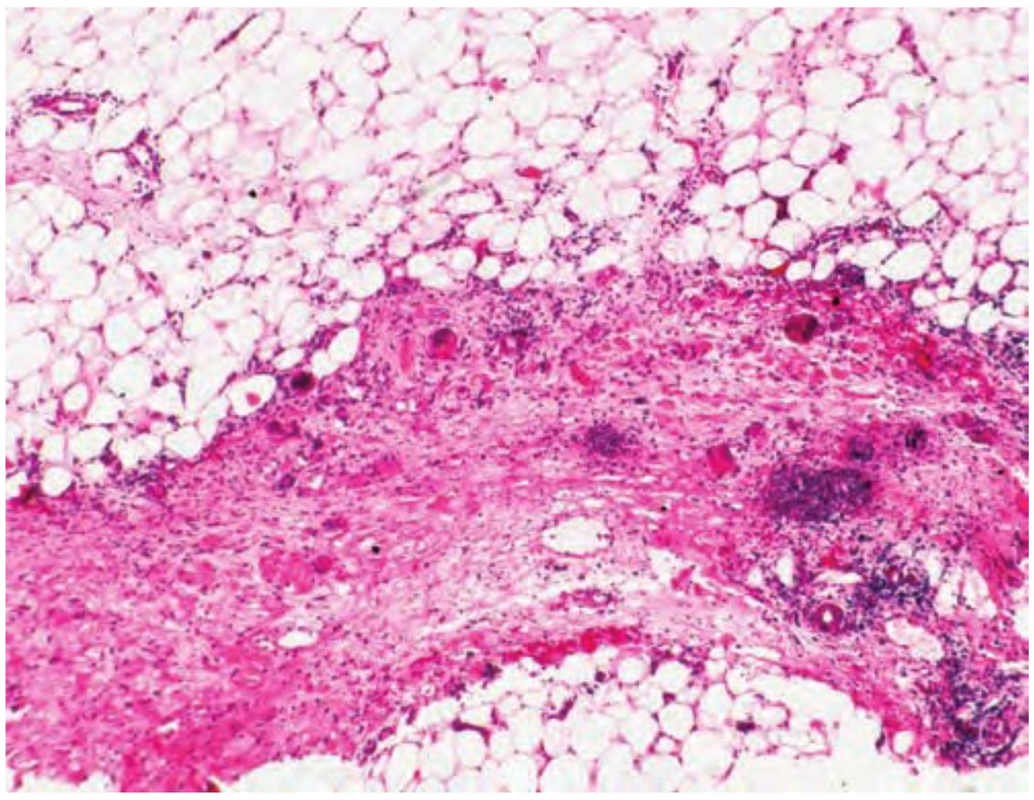


FIGURE 20-7 Late erythema nodosum. Fibrosis of the thickened septa is advanced and accompanied mainly by a lymphocytic infiltrate, often with a few eosinophils.

when late lesions are compared with early ones (Fig. 20-8). The granulomas often are loosely formed with macrophages predominating in a focus with multinucleated giant cells. Occasionally, well-formed, discrete sarcoidal granulomas occur in small numbers in the septa. The multinucleated cells usually have an irregular distribution of the nuclei in the cytoplasm. The oldest lesions have septal widening and fibrosis with a decrease in all of the inflammatory cells.

In *chronic erythema nodosum*, the histologic findings are generally similar to those of the late stages of acute erythema nodosum. However, granulomas and lipogranulomas often are more pronounced in chronic erythema nodosum. There is vascular proliferation and thickening of the endothelium with extravasation of erythrocytes (20). In some instances,

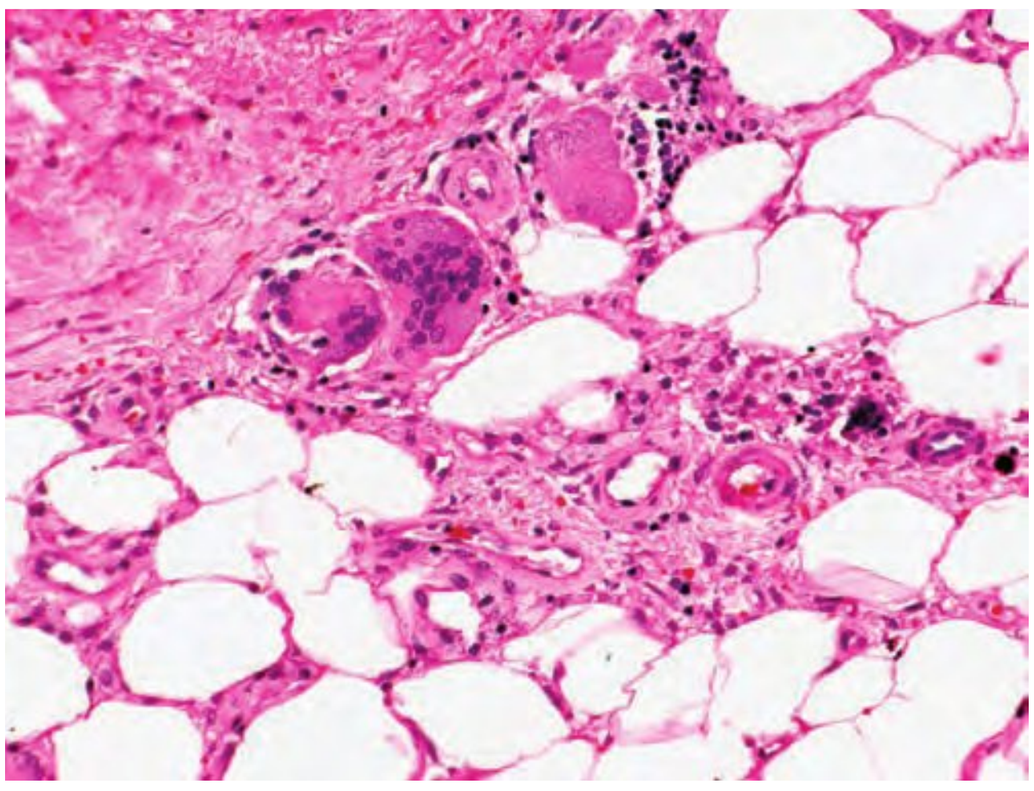


FIGURE 20-8 Late erythema nodosum. Multinucleated giant cells are common in the septa of late lesions. Tuberculoid granulomas can also be found.

numerous well-formed granulomas can be found and consist of epithelioid macrophages and giant cells without caseous necrosis (6). Although significant degrees of vasculitis have been observed by some authors (12,21), others have found vascular changes to be slight or absent (22,23). The presence of thickened fibrotic septa with marked capillary proliferation and massive granulomatous reaction have led several authors to consider *erythema nodosum migrans* as an entity separate from the late lesions of acute erythema nodosum (24). Other authors consider all of these histologic patterns to be included within the spectrum of chronic erythema nodosum (2,9).

Pathogenesis. Although the cause of erythema nodosum cannot always be determined in an individual patient, streptococcal infection is the most common among the known causes, especially in children, as evidenced by elevation of antistreptolysin O titers. The diseases that can be associated with erythema nodosum are numerous and have been reviewed recently (2,25). In short, they may be divided into the following: infections with bacteria, fungi, or protozoa; viral diseases; malignancies; medications; and miscellaneous conditions. The most frequent bacterial infections are streptococcal infection, tuberculosis, *Yersinia enterocolitica* infection (26), brucellosis, leptospirosis, tularemia, *Chlamydia* infection, and *Mycoplasma pneumoniae* infection. The most frequently associated fungal infections are coccidioidomycosis, histoplasmosis (27), dermatophytosis, aspergillosis, and blastomycosis, depending on the geographic location and immune status of the patient. Protozoal infections such as toxoplasmosis, amoebiasis, and *Giardia* infection can cause erythema nodosum. Among the associated viral and rickettsial infections are herpes simplex, infectious mononucleosis (due to Epstein-Barr virus infection), lymphogranuloma venereum, ornithosis, and psittacosis. Erythema nodosum occurs with some cases of leukemia, Hodgkin's disease, and non-Hodgkin's lymphomas, as well as with some other cancers, particularly after irradiation or other treatment releases antigens into the circulation by tumor necrosis. Among the miscellaneous associations are several diseases that can cause considerable difficulty in diagnosis, particularly acute sarcoidosis, which can have erythema nodosum as part of a symptom complex along with slight hilar adenopathy, fever, arthralgias, and occasionally acute iritis, uveitis, and parotid swelling (*uveoparotid fever*). The sarcoidal granulomas that can occur in erythema nodosum are less frequent, are septal in location, and are associated with edema, in contrast to the abundant granulomas that occur in subcutaneous sarcoidosis, without much edema and mostly in the lobules of the subcutaneous fat. Likewise, Crohn's disease can be associated with erythema nodosum (10), and the two diseases can be difficult to distinguish from each other histologically in the skin involvement unless there is ulceration, which does not occur in erythema nodosum (28). Other associated conditions are ulcerative colitis, and Behçet's disease (29). The panniculitis in Behçet's disease may resemble erythema nodosum clinically but often is different histologically in having neutrophilic and

lymphocytic vasculitis, which is predominantly lobular in distribution (30). Erythema nodosum and Sweet's syndrome have been reported in the same patient (31). Among the many medications that can cause erythema nodosum, the most common ones are sulfonamides, estrogens, and oral contraceptives (32). There are rare associations with aminopyrine, antimony compounds, arsphenamine, bromides, iodides, phenacetin, salicylates, immunizations, and vaccinations (2). Such a great diversity in inciting agents and circumstances suggests that several mechanisms may be capable of triggering the clinical and histopathologic changes that are classified as erythema nodosum.

Direct immunofluorescence studies have shown deposits of immunoglobulins only very rarely in the blood vessel walls in erythema nodosum (7). Small amounts of complement in the vessel walls and abundant fibrin around the vessels are frequent but nonspecific findings. On electron microscopic examination, nonspecific vascular changes consisting of damage to endothelial cells and lymphocytic infiltration have been described (33).

The occurrence of erythema nodosum as a response to medications and to tuberculin skin testing in patients with a positive reaction suggest that a type IV delayed hypersensitivity reaction may play an important role, especially given the paucity of reports of immunoglobulin deposition and the usual failure to detect circulating immune complexes (34). However, in some patients, a type III immune complex reaction could be responsible. Circulating immune complexes and rheumatoid factors have been detected in some patients with sarcoidosis and erythema nodosum (35). In approximately 50% of cases, there is no cause identified (36). The predilection for the anterior shins and for dependent parts of the body suggests that trauma or sluggish blood flow play a role in the localization of the lesions, but other factors such as the distribution of immunoreactive macrophages and dendritic cells need investigation as well.

Differential Diagnosis. Erythema nodosum needs to be distinguished from *erythema induratum* and *nodular vasculitis*. Vasculitis and zones of fat necrosis are absent in erythema nodosum and frequent in erythema induratum. In patients suspected to have erythema nodosum but with necrotizing vasculitis, the possibility of *cutaneous polyarteritis nodosa* must be considered. In the latter disease, medium-sized arteries rather than veins or small-caliber blood vessels are affected, with necrosis of the walls of affected arteries. In contrast, *nodular vasculitis* has mainly lymphocytic infiltration with fibrous thickening and obliteration of vascular lumens. *Superficial migratory thrombophlebitis*, unlike erythema nodosum, has a large vein containing thrombus in the center of the lumen. *Syphilitic gummas* are ulcerative irregular granulomatous lesions that produce depressed scars. *Subcutaneous tuberculosis* can mimic erythema nodosum in lesions that are extending from underlying organs, soft tissues, or bone. Stains for acid-fast organisms and cultures are needed. Subcutaneous tuberculosis can spare the upper portion of the panniculus, whereas erythema nodosum does not. Erythema nodosum does not have granulomas or sclerosis in the overlying dermis, and in this way can be distinguished from most cases of sarcoidosis, scleroderma, necrobiosis lipoidica diabeticorum, ruptured follicular cysts, and factitial traumatic panniculitis.

EOSINOPHILIC PANNICULITIS AND FASCIITIS

Clinical Features. The diagnosis of eosinophilic panniculitis is based on the histologic appearance of numerous eosinophils in the fat, which can be found as a reaction pattern in the following clinical diseases or conditions: erythema nodosum, vasculitis, arthropod bites, parasitic infection, drug injections, Well's syndrome, eosinophilic fasciitis, hypereosinophilic syndrome, and eosinophilic leukemia (37–41).

Histopathology. Usually, there is a mixed inflammatory infiltrate of lymphocytes, macrophages, and numerous eosinophils, involving both septa and lobules of the subcutis (Fig. 20-9). A pure infiltrate of normal eosinophils indicates the hypereosinophilic syndrome, in contrast to eosinophilic leukemia, in which the eosinophils are cytologically atypical. The overlying dermis should be studied carefully for important findings as well. The eosinophils aggregate often on dermal collagen fibers and degranulate to form masses of eosinophilic granules, which are called *flame figures* in Well's syndrome. The histologic sections should be searched for parasites, but they may be at a site distant from the skin, such as in the gastrointestinal tract or other sites, in which case the panniculitis is a reaction to circulating antigens.

Differential Diagnosis. The differential diagnosis includes reactions to foreign bodies (need to test for polarizable material in the sections), reactions to parasites, deep arthropod bite reactions, or drug injections. Peripheral blood studies will rule

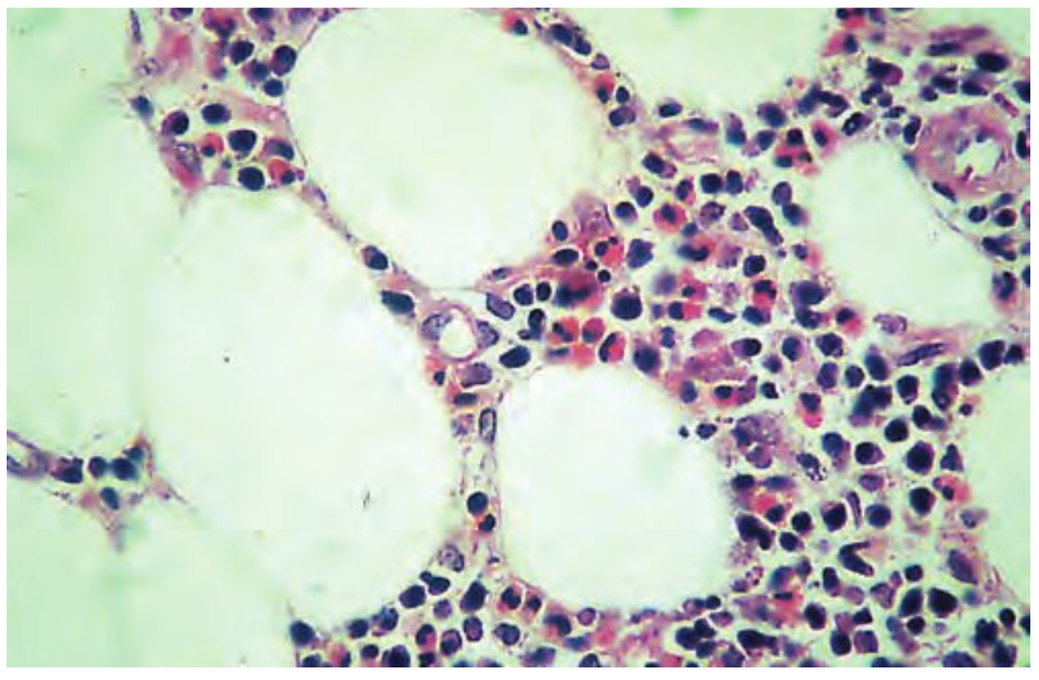


FIGURE 20-9 Eosinophilic panniculitis. Eosinophils in abundance in the fat lobules is not a specific finding, which can be seen in a variety of disorders, most commonly in arthropod bite reactions.

in or out eosinophilic leukemia, which also has eosinophilic precursor cells in the infiltrate in the subcutis. Macrophages can ingest eosinophil granules from degranulated eosinophils in a variety of hypersensitivity reactions and should be distinguished from true eosinophilic myelocytes and metamyelocytes. Several patients have been reported to have a hypereosinophilic syndrome with lymphoid abnormalities that are clonal T-cell proliferations (42,43). In eosinophilic fasciitis, the involvement of the overlying subcutis can produce dense hyalinized sclerosis resembling scleroderma, even with plasma cells. However, if the biopsy includes the fascia itself, the fascia contains eosinophils, which is the finding that separates eosinophilic fasciitis from morphea and scleroderma. Eosinophilic fasciitis may present as Shulman's syndrome, characterized by the sudden onset of thickened, bound-down skin, which follows in some cases a clear episode of intense exercise. Eosinophilic fasciitis also can be a presentation of a reaction to a drug, such as L-tryptophan, toxic oil, or infection (2,44,45).

PANNICULITIS ASSOCIATED WITH SEVERE ALPHA-1 ANTITRYPSIN DEFICIENCY

Clinical Features. Patients born with a severe deficiency of alpha-1 antitrypsin (AAT) have exaggerated damage due to inflammation in the skin—for example, after trauma to the subcutis. AAT deficiency is estimated to be present in 1 in 3,500 live births in the white population (46). This enzyme is the major component of the alpha-1 peak on serum electrophoresis and is an inhibitor of the serine proteases trypsin, chymotrypsin, plasmin, thrombin, and neutrophil-produced elastase. The antitrypsin proenzyme is produced in the liver but is not secreted in most of the affected individuals. Liver disease is often the presenting problem, including hepatomegaly, neonatal cholestatic jaundice, and cirrhosis in children (47,48). Large period acid-Schiff (PAS)-positive, diastase-resistant globules of proenzyme can be seen in hepatocytes, especially near the fibrous septa. Inflammation in the lung leads to unopposed release of neutrophil elastase that produces panacinar emphysema, involving destruction of respiratory bronchioles, alveolar ducts, and alveoli. The pulmonary disease usually becomes evident in young to middle-aged adults. Skin lesions present after trauma as recurrent nodules that can drain a yellow fluid derived from the enzymatic breakdown of the fibrous tissue and fat (49–51) (Fig. 20-10).



FIGURE 20-10 Alpha-1 antitrypsin deficiency panniculitis. The inflammatory lesions in the subcutis are often accompanied by dermal inflammation and can perforate through the epidermis.

Histopathology. Biopsies of well-developed lesions show a mixed pattern of septal and lobular inflammation characterized by many neutrophils and destruction of the fat and the fibrous septa (Fig. 20-11). Sterile abscesses surround and isolate fat lobules (52) (Fig. 20-12). Late lesions have an infiltrate of macrophages and lymphocytes with many foam cells and fibrosis (53). The macrophages can exhibit cytophagic activity and particularly can ingest neutrophil fragments and extravasated erythrocytes. Biopsies of early lesions have not been studied in a series of cases, but in some patients, the early manifestations are neutrophilic infiltrates between collagen bundles in the dermis, with scattered solitary neutrophils and small collections of neutrophils in the septa and lobules of the subcutaneous fat (54). Depending on the size of the lesion, the subcutaneous involvement can be patchy with necrotic foci contrasting with the normal fat lobules in the vicinity (51,53).

Differential Diagnosis. The histopathologic changes are not specific for AAT deficiency but rather are shared by a number of diseases than can be responsible for *necrotizing panniculitis.* A biopsy of a subcutaneous nodule occasionally shows a nonspecific pattern of necrotizing acute inflammation characterized by fat necrosis and a massive neutrophilic infiltrate, often accompanied by karyorrhexis, fibrin deposition, focal vasculitis, and histiocytic reparative reaction. These changes also can be produced

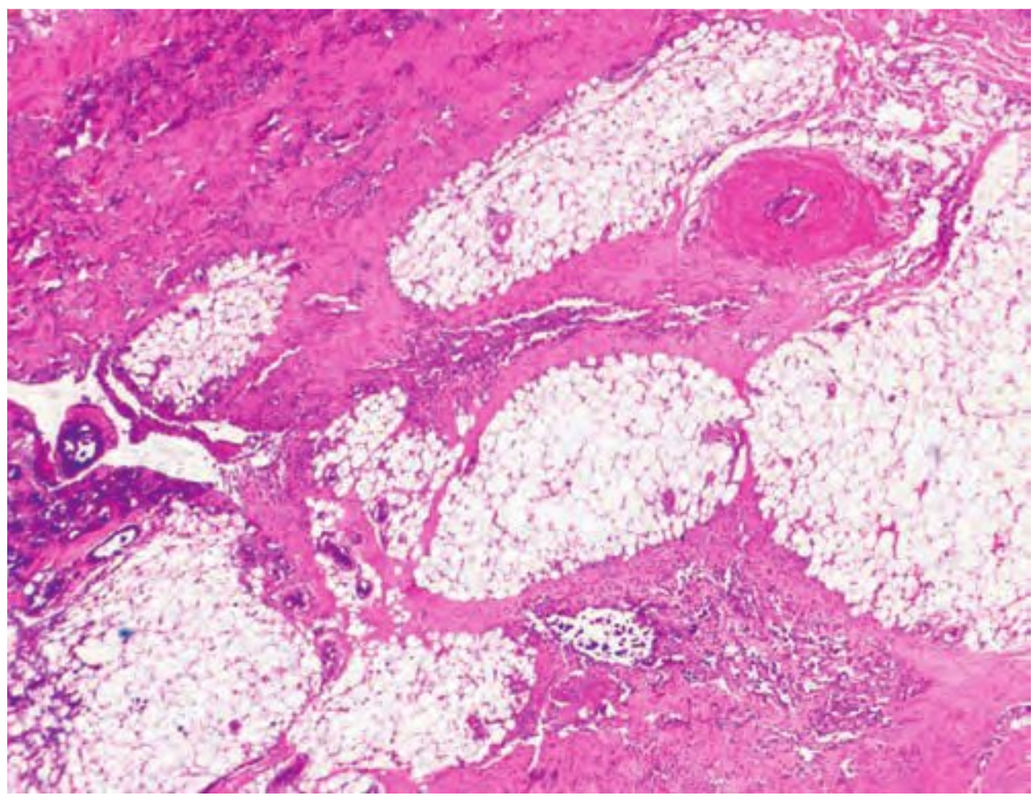


FIGURE 20-11 Alpha-1 antitrypsin deficiency panniculitis. Abscesses dissect between the fat lobules and involve the lower dermis.

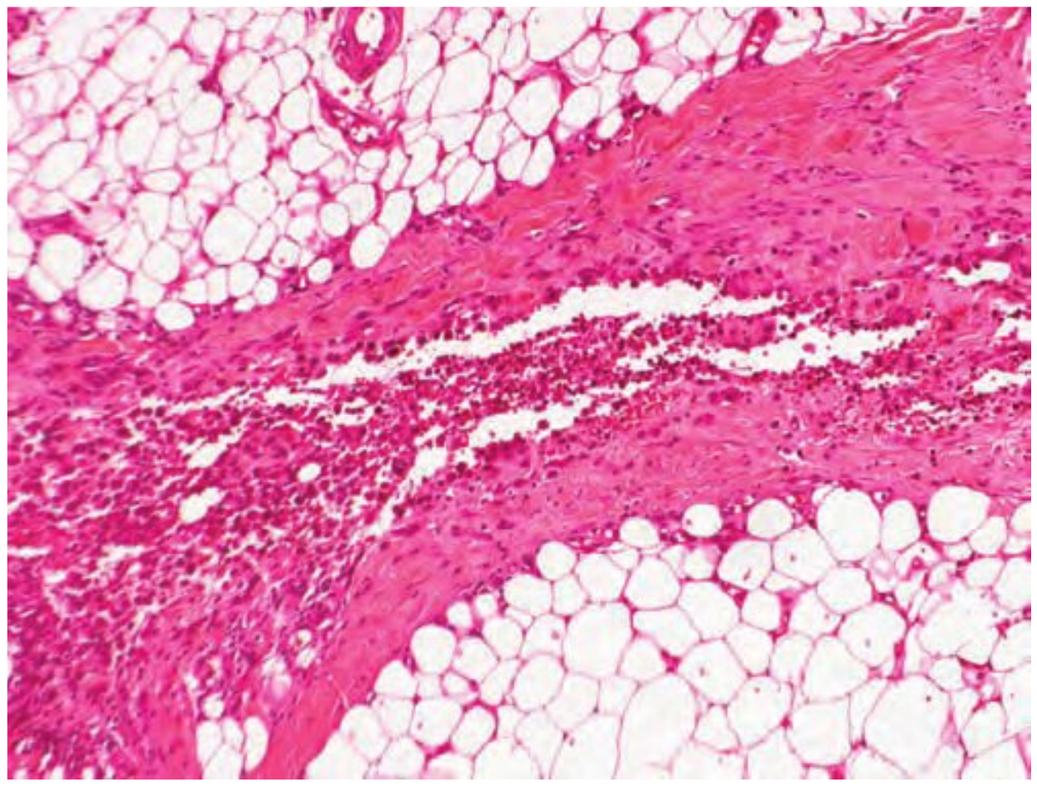


FIGURE 20-12 Alpha-1 antitrypsin deficiency panniculitis. High magnification of an abscess showing the neutrophils in the septa.

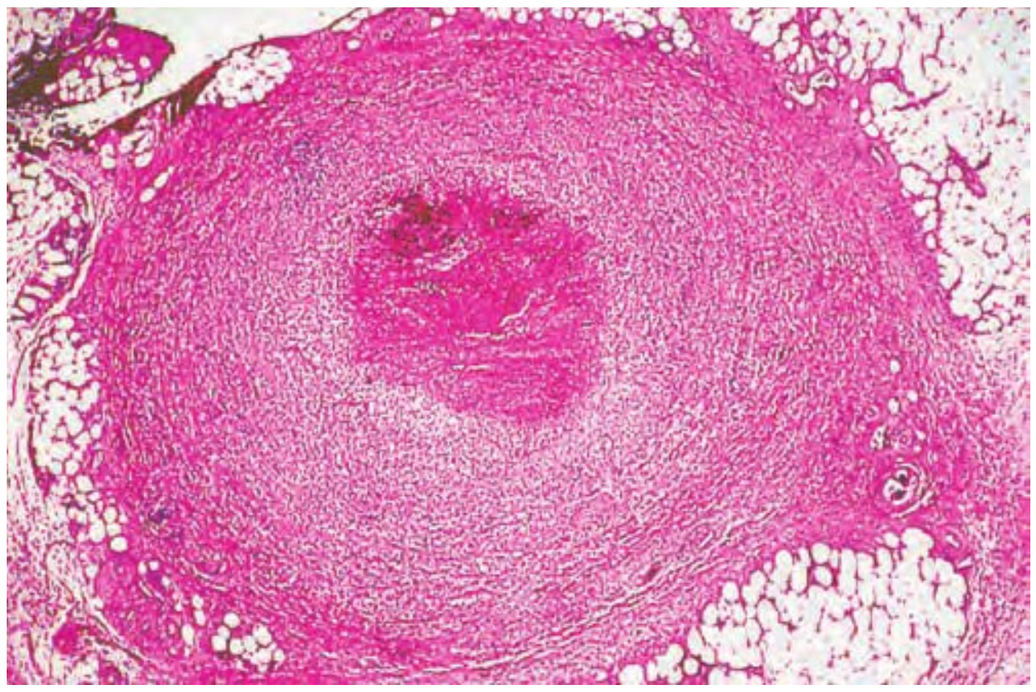


FIGURE 20-13 Superficial migratory thrombophlebitis. A vein is filled with thrombus, and the inflammation involves the adjacent septa and lobules.

by very acute necrosis (liquefaction necrosis) in cases of *nodular vasculitis*, pyoderma gangrenosum, and inflammatory reaction near ulcers from a variety of causes and can represent changes due to infection by pyogenic bacteria, including mycobacteria (55). If a meticulous study, including cultures and enzymatic studies, fails to reveal a satisfactory final diagnosis, then the term *necrotizing panniculitis* can be a suitable histologic diagnosis until other methods or information become available.

The clinical features of AAT deficiency overlap with those of Weber-Christian disease to the extent that a determination of serum levels of the enzyme should be performed on all cases clinically suspected of having Weber-Christian disease or any patient with ulcerating and necrotizing panniculitis. Weber-Christian disease is more restricted to the fat lobules than AAT deficiency panniculitis, which involves septa, lobules, and overlying dermis (54). Histiocytic cytophagic panniculitis (often a form of subcutaneous T-cell lymphoma with reactive histiocytosis) is in the differential diagnosis due to the fact that macrophage cytophagic activity also can occur in AAT deficiency. The prominence of neutrophils in AAT deficiency is in contrast to the lymphocytes in histiocytic cytophagic panniculitis. In the early lesions, infection needs to be ruled out since erysipelas and even some mycobacterial infections can have a similar histology (55). Serum electrophoresis is important in detecting carriers and affected individuals with AAT deficiency.

SUPERFICIAL MIGRATORY THROMBOPHLEBITIS

Clinical Presentation. Multiple tender, erythematous nodules are found usually on the lower legs but occasionally on the arms and trunk (56,57). After several days, a cordlike induration a few centimeters long can be felt along the course of the inflamed vein (58). As the old lesions resolve, usually within a few weeks, new nodules may erupt. Recurrent migratory thrombophlebitis can occur as a manifestation of Behçet's syndrome. It is also part of Trousseau's syndrome, in which there is an associated visceral carcinoma. Hypercoagulability and stasis are precipitating factors (56,57).

Histopathology. The lesion is centered around a large vein in the subcutis, usually in a septal location and occasionally in the deep vascular plexus, at the junction of deep dermis and subcutis (Fig. 20-13). The affected vein has a thick wall with the smooth muscle distributed in fascicles in the wall. The lumen often is completely occluded by thrombus. An inflammatory infiltrate extends between the muscle bundles and only a short distance into the tissue surrounding the vein (2,59). In early lesions, the infiltrate is composed of many neutrophils, but later it consists mainly of lymphocytes, macrophages, and a few giant cells (56,57). If recanalization of the lumen of the vein takes place, granulomas with giant cells can be found even in the lumen of the affected vessel. These granulomas participate in the reabsorption of the thrombus (58).

Differential Diagnosis. Owing to the elevated hydrostatic pressure in the veins of the lower legs in ambulatory patients, the walls of the veins have an increased amount of elastic fibers and smooth muscle in their walls. They can be distinguished from arteries when there is minimal inflammation and when elastic tissue stains show an absence of an internal elastic lamina. Thrombus usually occludes the lumen of veins in superficial migratory thrombophlebitis. Polyarteritis nodosa affects arteries and is recognized if the affected vessels can be identified as arteries based on lumen diameter, wall thickness, internal elastic lamina, and location.

SUBCUTANEOUS POLYARTERITIS NODOSA

Clinical Presentation. Systemic polyarteritis nodosa can affect the skin by several types of presentations. The affected arteries are deeply located, in the deep dermal vascular plexus at the

junction of dermis and subcutis or in the deep subcutis itself. A common clinical manifestation is a region of netlike erythema (*livedo reticularis*), with some tenderness to palpation. This livedo is fixed and not transient or altered by the temperature of the environment. To obtain a biopsy of the affected deep artery, it has been shown that the exact site and depth are important. The affected artery may lie deep beneath the center of the pale area, which is surrounded by a rim of redness due to vasodilation at the periphery of the ischemic region. Biopsies into those red netlike lines visible at the skin surface often miss or show very little of the affected artery. Systemic manifestations can be reflected in hypertension, proteinuria, elevated circulating immune complexes, decreased complement levels, deep muscle tenderness and pain, and cerebral infarcts. In *Sneddon's syndrome*, the combination of livedo reticularis and cerebral infarcts can be due to polyarteritis nodosa, hypercoagulable states, or lupus erythematosus. Cutaneous manifestations of polyarteritis nodosa are common in hepatitis C infection. Superficial biopsies may show only telangiectasia and extravasation of erythrocytes, or occasionally a mild leukocytoclastic vasculitis, probably depending on the sizes of the circulating immune complexes, and the degree of permeability of the endothelium. Some patients with histologically demonstrated polyarteritis nodosa on skin biopsy have a form of polyarteritis that tends to remain limited to the skin for prolonged time periods. Some cases have not shown involvement other than in the skin and subcutaneous tissue for as many as 15 years, which has given dermatologists the impression that there is a distinct entity of skin-limited polyarteritis nodosa, often named *cutaneous polyarteritis nodosa*. Follow-up studies of such patients have shown that despite being initially limited to the skin histologically and clinically, cutaneous polyarteritis nodosa may show signs of systemic disease at variable time periods after initial diagnosis in a considerable proportion of the patients. Hypertension, hematuria, testicular and muscle biopsies showing polyarteritis, and serum tests indicative of hepatitis B or C infection all point to systemic rather than localized cutaneous polyarteritis (60). Perhaps the exact nature and sizes of the circulating immune complexes could explain the overlapping features and why the disease manifestations are limited to the skin for a long time in some patients. Polyarteritis nodosa can lead to deep ulceration of the skin into the subcutis. Some authors have analyzed the same information and have presented the entity of cutaneous polyarteritis as a special distinct condition by discounting the overlap with systemic disease and the importance of following the patients over time (2).

Histopathology. The inflammatory infiltration into the walls of arteries and arterioles tends to be focal. Segments along the length of the artery are involved differently and may have only a portion of its cross-sectioned profile involved by the destructive inflammation (Fig. 20-14). The focal areas have fibrin deposition in the vessel wall with necrosis of the intimal and medial portions of the vessel. Early lesions have mostly neutrophilic infiltration, with

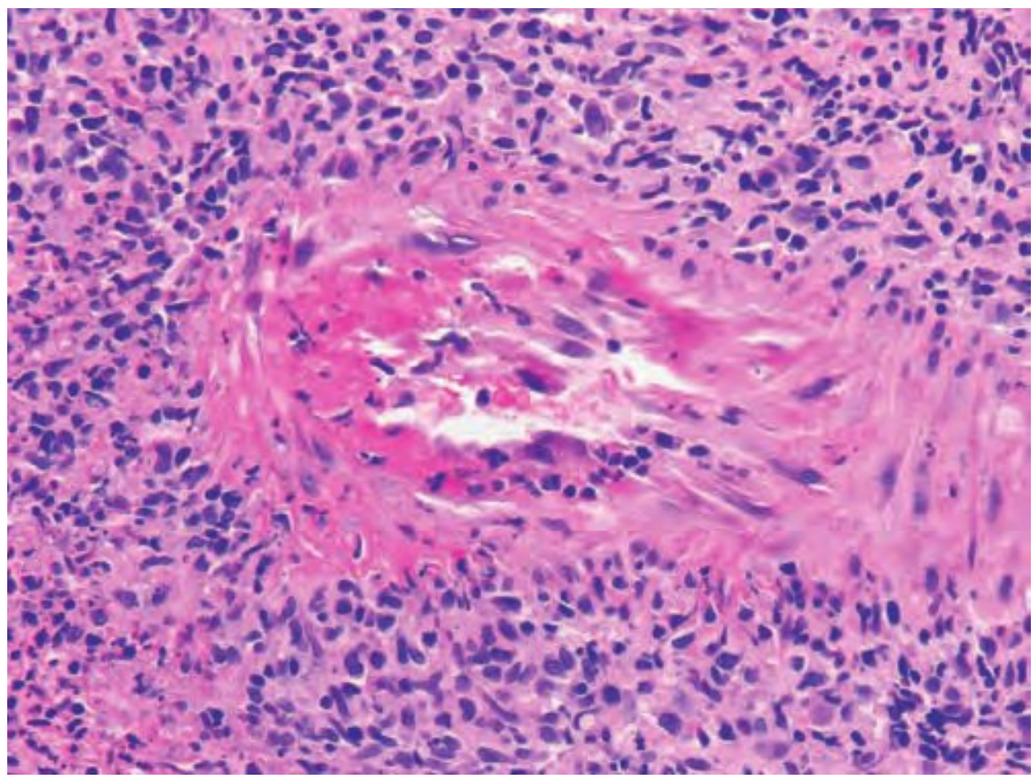


FIGURE 20-14 Subcutaneous polyarteritis nodosa. The small arteries in the septa have focal inflammation of their walls, with neutrophils and fibrin deposition.

destruction of them to produce fragmented segments of the nuclei, *nuclear dust*. Later lesions have more lymphocytic infiltrate into the vessel as well as around it. Macrophage infiltration is also part of the process of resolution of the lesion. Immunofluorescence has shown immune complexes in the vessel walls (immunoglobulins G and M [IgG; IgM] and C3). The vascular destruction often does not completely occlude the lumen, which is in part a consequence of the tendency of dermatologists to biopsy early lesions rather than ulcerated ones. Some authors have stressed a difference in the localization of the lesions to the bifurcations of arteries in systemic polyarteritis and not in cutaneous polyarteritis (2). Such differences, if they are present, may be related to hydrostatic shear stress forces being greater at bifurcations and greater in patients with hypertension. Since the arteries tend to be in the deep dermal plexus and in the septa, the inflammatory process in the subcutis is classified as a septal panniculitis with vasculitis.

Differential Diagnosis. The distinction between polyarteritis and thrombophlebitis has been discussed previously in the section on thrombophlebitis (previous page). The distinction between systemic versus localized cutaneous polyarteritis depends heavily on the degree of investigation of the systemic factors, including the presence of proteinuria or hematuria (the glomeruli filter out circulating immune complexes). Elevations in muscle enzymes and muscle tenderness could lead to muscle biopsy as part of the investigation. Hypertension may also be a related systemic phenomenon. Investigation into the possible circulating viral antigens, such as hepatitis B or C, could also be revealing of systemic disease. It is most unlikely that arteritis will remain localized only to the skin when it is due to circulating immune complexes. Hypercoagulable states and lupus erythematosus need to be excluded.

ERYTHEMA INDURATUM (NODULAR VASCULITIS)

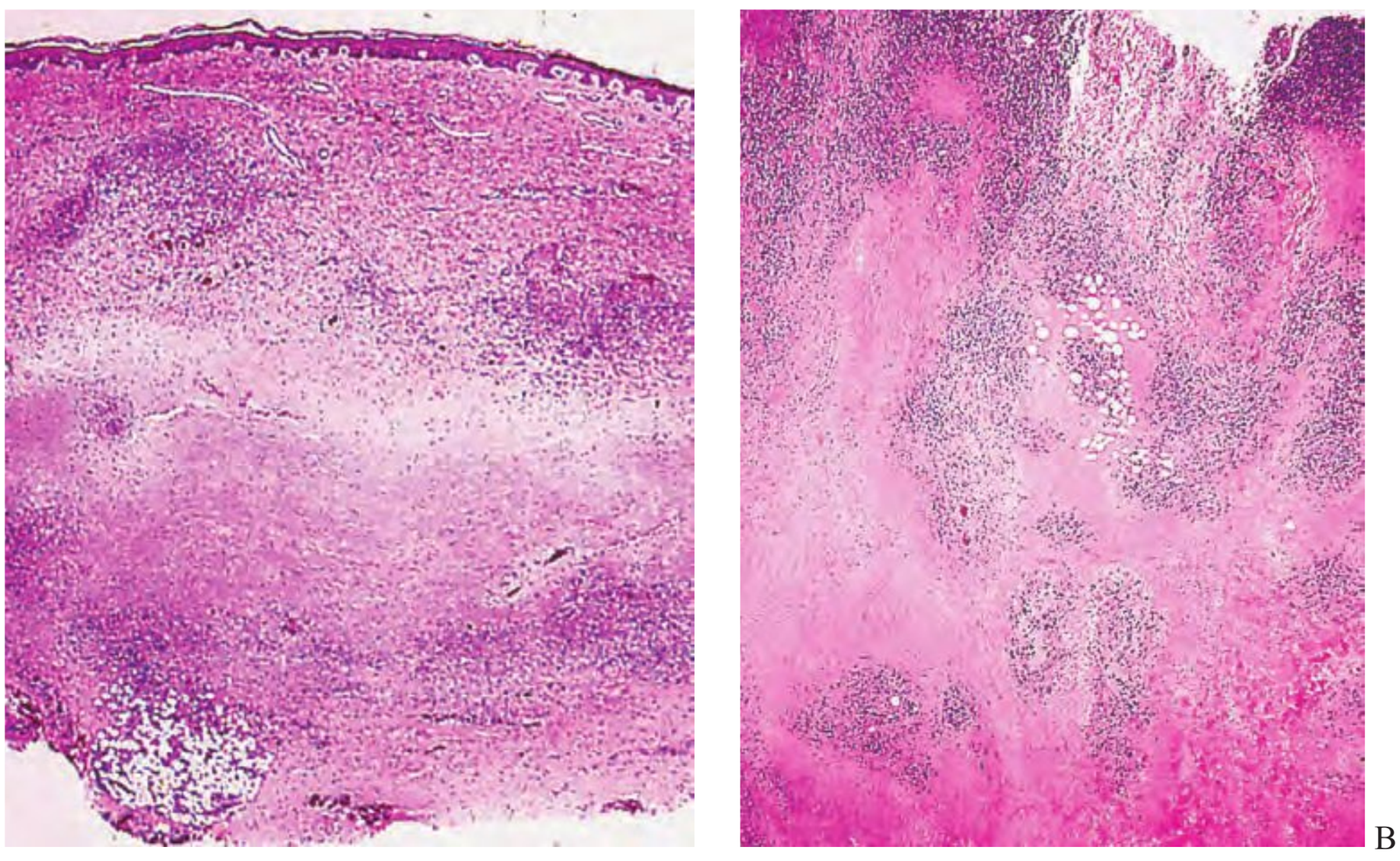
Clinical Presentation. The lesions of *erythema induratum*, also sometimes referred to as *nodular vasculitis*, consist of painless to tender, deep-seated, circumscribed nodules to plaques, usually on the lower legs with a predilection for the posterior calves. Gradually, the lesions extend toward the surface, forming blue-red plaques that can ulcerate before healing with atrophy and scarring (Fig. 20-15). Recurrences are common and often are precipitated by the onset of cold weather. Women are more commonly affected than men. *Erythema induratum of Bazin* refers to erythema induratum associated with tuberculosis. *Nodular vasculitis* was the name proposed by Montgomery for those cases with erythema induratum-like lesions that were not associated with tuberculosis (20,59).

Histopathology. In contrast to erythema nodosum that is mainly a septal panniculitis, erythema induratum (nodular vasculitis) initially is mainly a lobular panniculitis due to vasculitis that produces ischemic necrosis of the fat lobules with relatively less involvement of the structures of the septa. The fat necrosis can be extensive, caseous as well as coagulative, and elicits granulomatous inflammation (Fig. 20-16). Epithelioid cells and giant cells form broad zones of inflammation surrounding the necrosis but also can form well-delimited granulomas of the tuberculoid type (Fig. 20-17). Ziehl-Neelsen stains do not reveal intact mycobacteria (61). In approximately one third of cases, granulomas are sparse or absent and lymphocytes and plasma cells predominate (61). Both the tuberculoid granulomas and lymphoid infiltrate extend between the fat cells, largely replacing them.



FIGURE 20-15 Nodular vasculitis/erythema induratum. Advanced disease presents as hemorrhagic ulcers and depressed lesions with a predilection for the posterior calf region.

Vascular changes are extensive and severe. Arteries and veins of small and medium size show infiltration of their walls by a dense lymphoid or granulomatous inflammatory infiltrate (Fig. 20-18A) associated with endothelial swelling and edema of the vessel walls and fibrous thickening of the intima (59).



A B

FIGURE 20-16 Erythema induratum. A: Large areas of caseous necrosis replacing the subcutaneous fat, septa, and portions of the overlying dermis. B: A region of perforation of the inflammation through the skin surface.

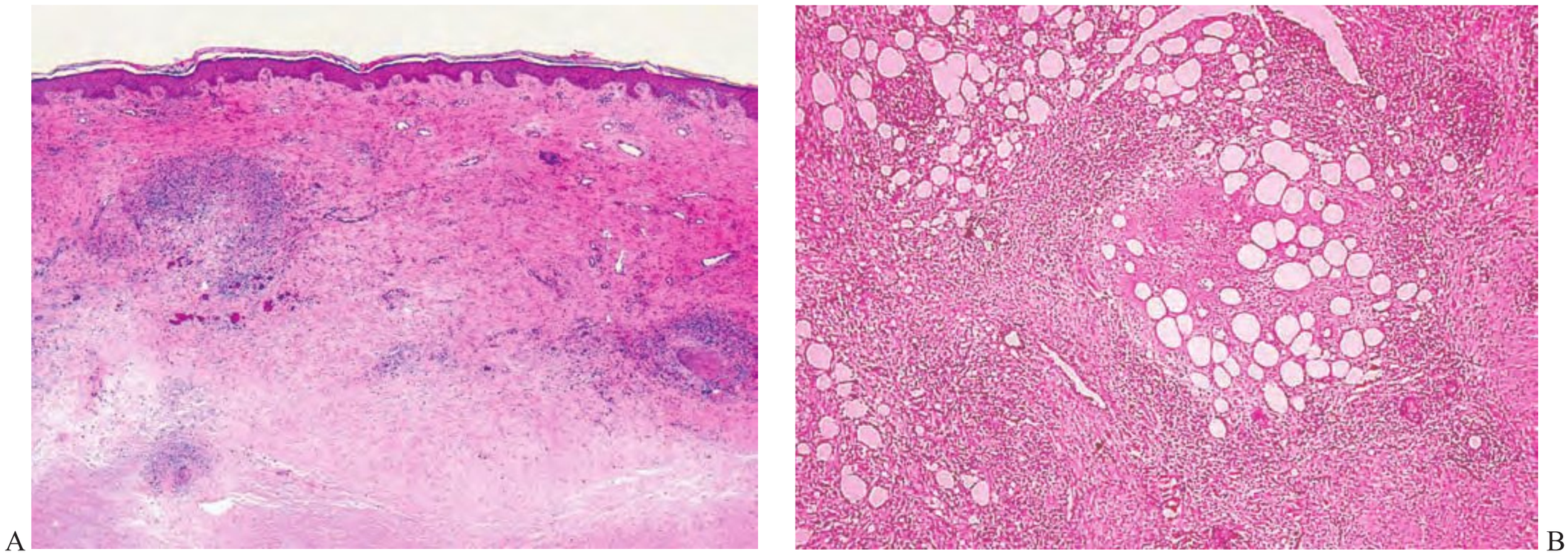


FIGURE 20-17 Erythema induratum. A: A region of caseous necrosis at lower magnification, with mainly lymphocytic infiltrates around remaining subcutaneous and dermal blood vessels. B: A smaller region of lobular fat necrosis with surrounding lymphocytes, macrophages, and multinucleated cells.

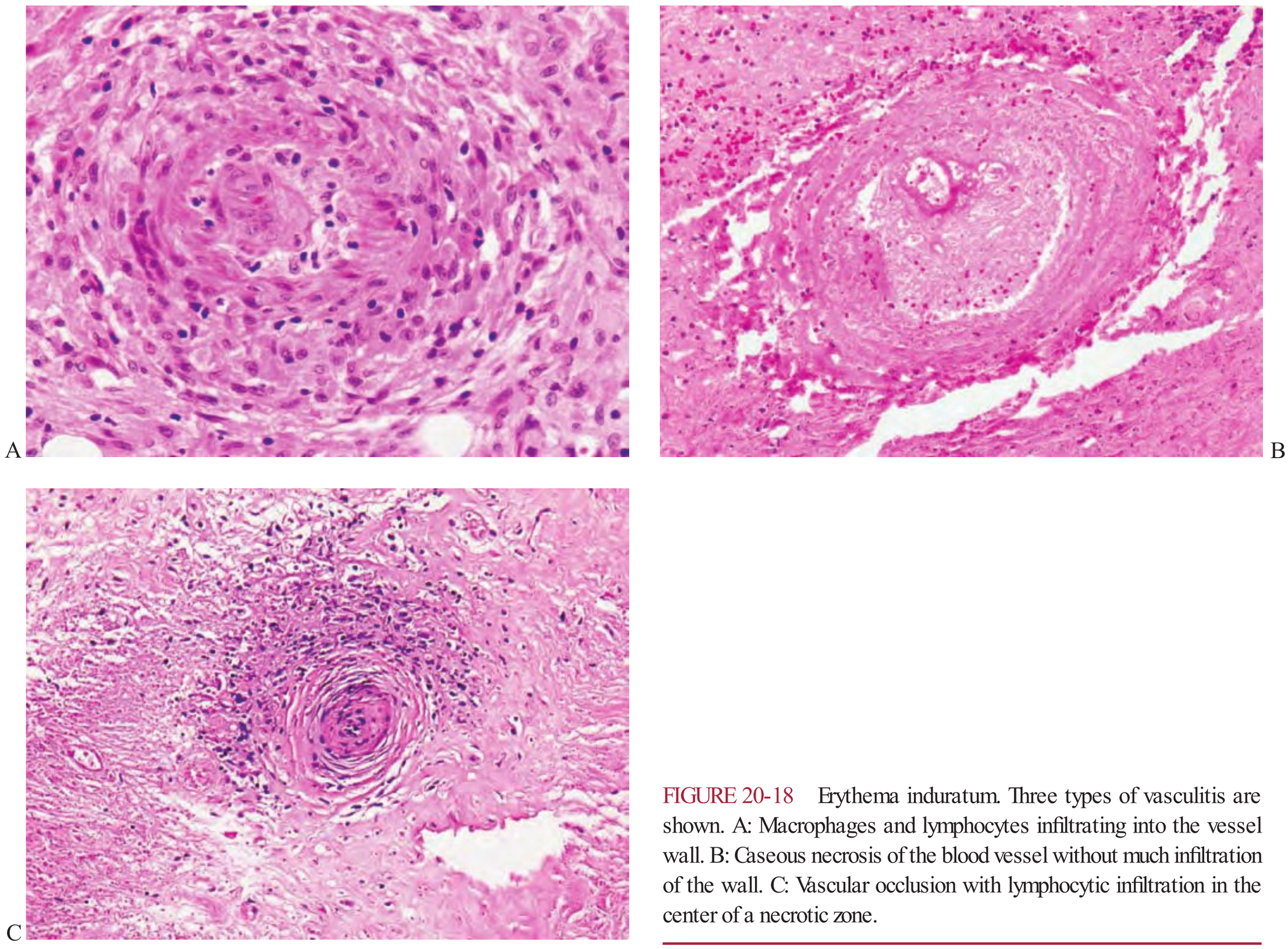


FIGURE 20-18 Erythema induratum. Three types of vasculitis are shown. A: Macrophages and lymphocytes infiltrating into the vessel wall. B: Caseous necrosis of the blood vessel without much infiltration of the wall. C: Vascular occlusion with lymphocytic infiltration in the center of a necrotic zone.

Thrombosis and occlusion, or just compromise, of the lumen can produce extensive ischemic and caseous necrosis of the fat in about half of the cases (Fig. 20-18B, C). Extensive necrosis leads to involvement of the overlying dermis and subsequent ulceration. The necrotic fat contains large fat globules, with surrounding amorphous, finely granular, eosinophilic material with some pyknotic nuclei. Later lesions contain many foamy histiocytes surrounding areas of fat necrosis.

Pathogenesis. The primary event in erythema induratum is a vasculitis of the subcutaneous arteries and veins. If fat necrosis develops, it is the result of ischemia following vascular damage. Erythema induratum in the past usually has been caused by a hypersensitivity reaction to tuberculosis, which is a "tuberculid" reaction (62–64). However, neither inoculation of lesional tissue into guinea pigs nor cultures of such tissue have yielded isolates of tubercle bacilli. Also, erythema induratum responds to treatment with corticosteroids (65). In contrast, evidence against erythema induratum being a tuberculid consists of the finding that active tuberculosis is no more frequent in patients with erythema induratum than in the general population. Also, patients with tuberculosis can develop erythema nodosum (66). A delayed hypersensitivity reaction seems likely to be the basis of nodular vasculitis in nontuberculous patients since S100-positive, dendritic cells are increased in number within granulomas near the vessels in nodular vasculitis and not in polyarteritis nodosa (67). These dendritic cells could present antigens to T cells and trigger an intense inflammatory reaction.

Differential Diagnosis. Erythema induratum can be distinguished from erythema nodosum by the prominent lymphohistiocytic vasculitis in erythema induratum, which can be found only very rarely in erythema nodosum. When caseation necrosis is present, it clearly separates erythema induratum from erythema nodosum. Direct cutaneous mycobacterial infection lacks the vasculitis of erythema induratum. Mycobacteria can be difficult to find in subcutaneous lesions of tuberculosis and are absent from erythema induratum with the Ziehl-Neelsen method for acid-fast staining. Detection of DNA from *Mycobacterium tuberculosis* in lesions of erythema induratum by polymerase chain reaction (68) but with negative cultures suggests a hypersensitivity reaction to fragments of tubercule bacilli (63).

The difficult distinctions are between *erythema induratum*, *thrombophlebitis*, and *subcutaneous polyarteritis nodosa*, all of which can produce the clinical picture of nodules on the legs with vasculitis. Polyarteritis nodosa has neutrophilic infiltrates and fibrinoid necrosis of arterial vessel walls, whereas erythema induratum and nodular vasculitis have lymphohistiocytic infiltrates of the vessel walls with intimal proliferation and thrombosis. Elastic tissue stains are helpful in some lesions for distinguishing small arteries affected by polyarteritis from small veins affected by thrombophlebitis. However, the anatomic distinction between arteries and veins can be difficult when the inflammation destroys the elastic fibers or when the elastic tissue is increased in the walls of veins due to venous hypertension that is commonly present in patients with stasis in the lower legs. Deep biopsies and step sections in the tissue blocks may be necessary to demonstrate the focal necrotizing vasculitis in polyarteritis nodosa, since thrombosis and reactive changes near these foci can closely resemble nodular vasculitis in routine sections. At times, only a general diagnosis of "panniculitis with vasculitis" can be given until other biopsies or additional clinical information clarify the nature of the disorder.

LUPUS ERYTHEMATOSUS PANNICULITIS

Clinical Features. In patients with chronic cutaneous lupus erythematosus, the lesions can be deep and can involve the dermis and subcutis or just the panniculus alone (69–71). The patients can have either chronic discoid lupus erythematosus or systemic lupus erythematosus. In about two thirds to one half of patients with these uncommon lesions, there are firm, indurated subcutaneous nodules with no specific clinical changes in the overlying skin. Histology is more sensitive and detects changes of discoid lupus erythematosus in 67% of these patients (72).

The lesions are deep nodules and plaques that tend to involve the skin of the trunk and proximal extremities, particularly the lateral aspects of the upper arms, thighs, and buttocks. Symmetrical lesions on the anterior chest or upper arms can suggest a traumatic or factitial etiology, and indeed trauma may play a role in the localization of the lupus inflammation to these sites. Approximately 70% of these patients also have other lesions that are typical of discoid lupus erythematosus, and 50% have evidence of mild systemic lupus erythematosus (71). The lesions are painful and have a tendency to ulcerate and to heal leaving depressed scars. When the overlying skin is involved, there is loss of hair, erythema, poikiloderma, and epidermal atrophy. Some patients present with localized depressions without erythema, clinically resembling lipoatrophy (73). The term *lupus profundus* has been used both for lupus panniculitis and also for discoid lupus erythematosus lesions that involve the dermis and extend deeply into the subcutis. Over time, lesions that begin as pure panniculitis can develop dermal sclerosis and leave deep depressions in the skin surface.

Histopathology. The histologic sections reveal a deep lymphocytic infiltration in the fat lobules and in the septa (69). Lymphoid aggregates, nodules, and germinal centers, also known as *follicular centers*, are common (69,74). The dermis can have just a superficial and deep perivascular lymphocytic infiltrate with plasma cells or can have all of the changes of lesions of discoid lupus erythematosus. A distinctive feature is the so-called "hyaline necrosis" of the fat, in which portions of the fat lobule have lost nuclear staining of the fat cells and have an accumulation of fibrin and other proteins in a homogeneous eosinophilic matrix between the residual fat cells and extracellular fat globules (69) (Fig. 20-19). Blood vessels are infiltrated by lymphoid cells and can have restriction of their lumen

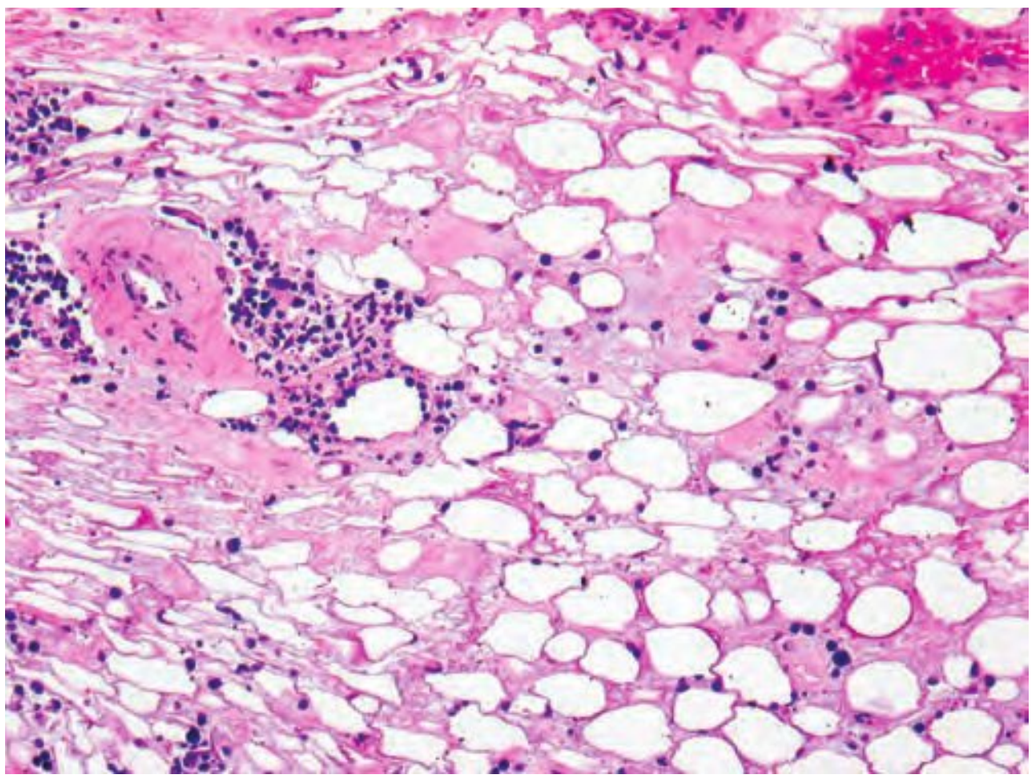


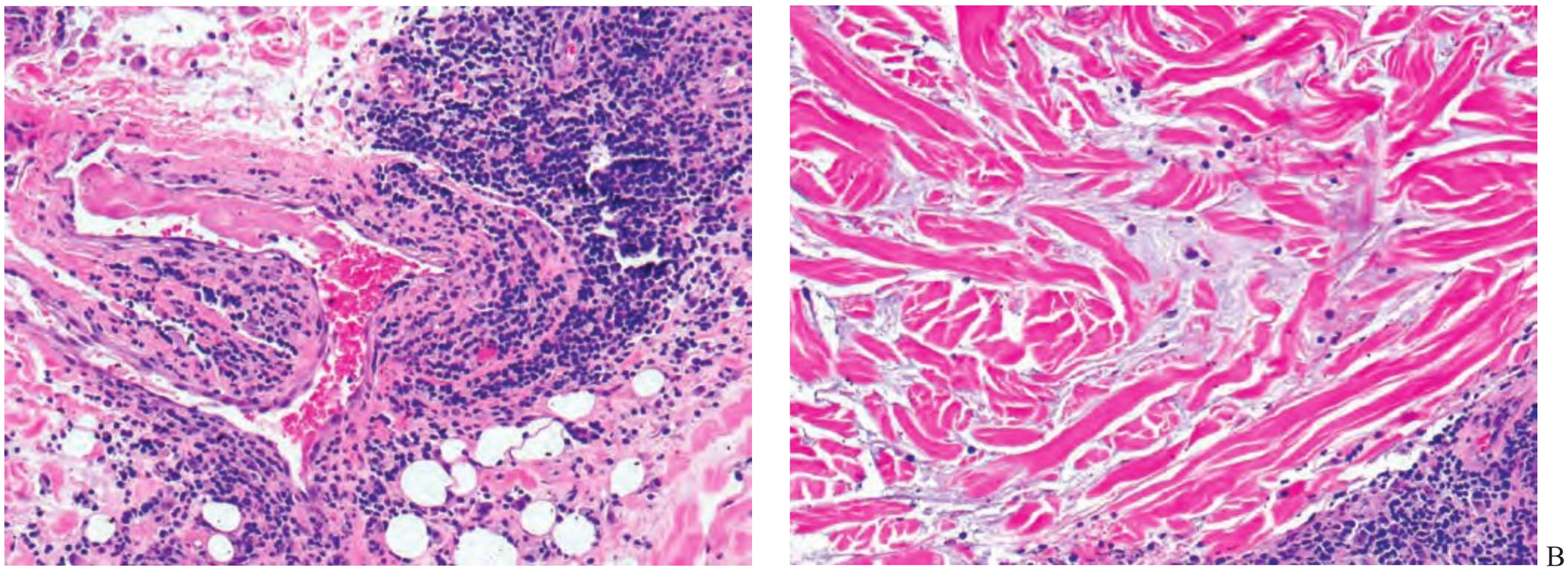
FIGURE 20-19 Lupus erythematosus panniculitis. Fat necrosis is accompanied in the lobules by the deposition of hyaline material and a lymphocytic infiltrate.

diameter (Fig. 20-20A). Usually, there is mucinous edema of the septa and the overlying dermis (Fig. 20-20B). Calcification may be present in older lesions.

Pathogenesis. Approximately 50% of patients with lupus profundus have positive immunofluorescence findings at the dermal–epidermal junction and at hair follicle basement membranes. Usually there is granular deposition of IgM and C3 with linear deposition of fibrin. Granular deposits of IgG and immunoglobulin A (IgA) may be present also in active lupus cases. Many patients have similar deposits in deep dermal and subcutaneous blood vessel walls. Fibrin is distributed diffusely in the panniculus, both in the lobules and in the septa in areas with hyaline necrosis. It seems likely that trauma is involved in the localization of lesions, perhaps through increased vascular permeability and leakage of circulating antinuclear antibodies or immune complexes into the fat lobules. A few patients with lupus panniculitis have a partial genetic deficiency of C2 and C4 (75). A lupus-like syndrome has been reported in approximately one third of patients with C2 deficiency (76,77). In patients with complement at the dermal–epidermal junction, deposition of the so-called membrane-attack complex, composed of C5b-9, can be demonstrated as well.

Differential Diagnosis. Patients with lupus panniculitis have been given a clinical diagnosis of *Weber-Christian disease* in the past. The overlap in appearances may prevent any distinction between these two diseases by routine histology. However, Weber-Christian disease can be sharply localized just to the fat lobules; in contrast, lupus panniculitis causes mucinous edema (detectable with Alcian blue stains) and inflammation around the blood vessels of the dermis and subcutis. Immunofluorescence and serologic studies allow a positive diagnosis of lupus erythematosus in many instances.

A particularly troublesome differential diagnosis is between lupus panniculitis and *subcutaneous T-cell lymphoma* (78). Although each of these two entities may have dense lymphoid infiltrates in the fat, usually the lymphoma has cytologically atypical lymphocytes. However, some cases of subcutaneous T-cell lymphoma are composed of small cells that lack obvious cytologic atypia in routine sections. A mixed population of $CD4^+$ and CD8-positive T cells may be found, making T-cell receptor gene rearrangement studies necessary for showing a significantly high level of clonality in the lymphoid infiltrate. After these studies, there remain a few indeterminate cases on a spectrum from lupus panniculitis to subcutaneous T-cell lymphoma because they have been classified as lupus panniculitis, responsive to chloroquine and/or prednisone therapy, but have some slightly atypical cells, with CD5 and CD7 diminution, and DNA analysis that is suggestive of the presence of some clonal



A B

FIGURE 20-20 Lupus erythematosus panniculitis. A: Distinctive lymphocytic infiltration through blood vessel walls that can be concentric and induce fibrosis. B: Frequently abundant blue-gray mucinous change between collagen bundles in the dermis and septa of the panniculus.

lymphocytes in the population (78). Subcutaneous panniculitic T-cell lymphoma of the alpha/beta subtype, without evidence of a hemophagocytic syndrome, has an excellent prognosis (i.e., an 82% 5-year survival), even with some patients having conservative treatment. In contrast, subcutaneous T-cell lymphoma of the gamma/delta subtype has a much worse prognosis (i.e., an 11% 5-year survival), even with intensive chemotherapy. Also, the gamma/delta subtype often involves overlying skin, with ulceration, and multiple other organ systems. The gamma/delta subtype should instead be classified as "gamma/delta T-cell lymphoma," with specification of the degree of involvement of the skin, subcutis, and internal sites. A natural killer (NK)/T-cell lymphoma ($CD2^+$ $CD3^-$ $CD56^+$ EBV^+) can also be in the differential diagnosis (79).

Erythema induratum, like lupus panniculitis, also shows hyaline necrosis and vasculitis but has more granulomatous inflammation than in most cases of lupus panniculitis. Erythema induratum lacks the mucinous edema of the dermis.

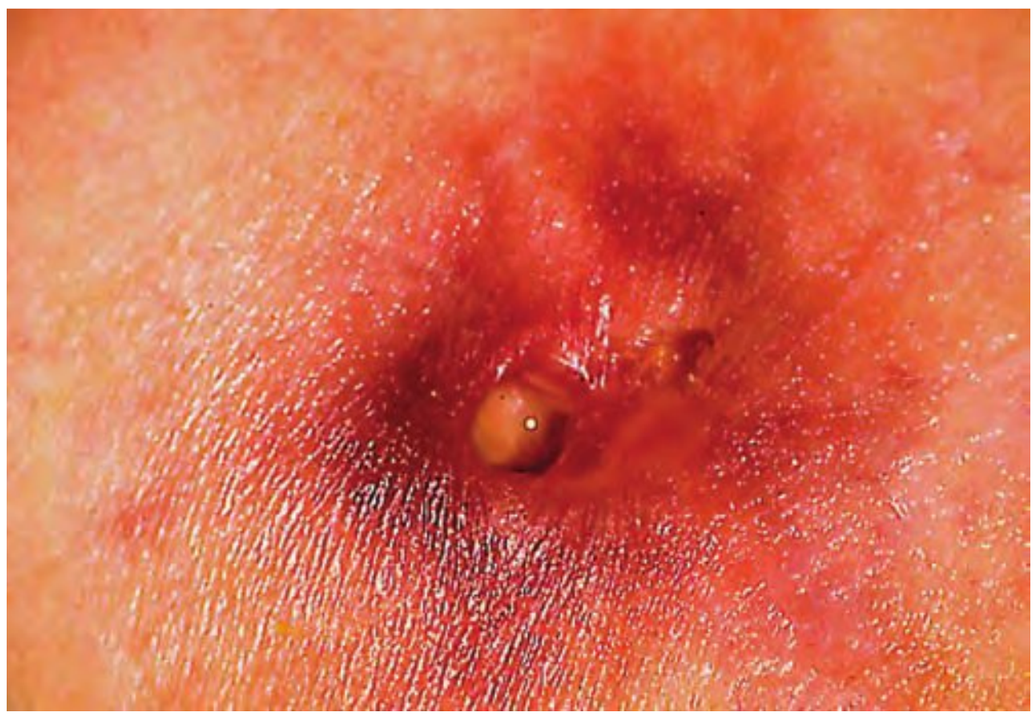
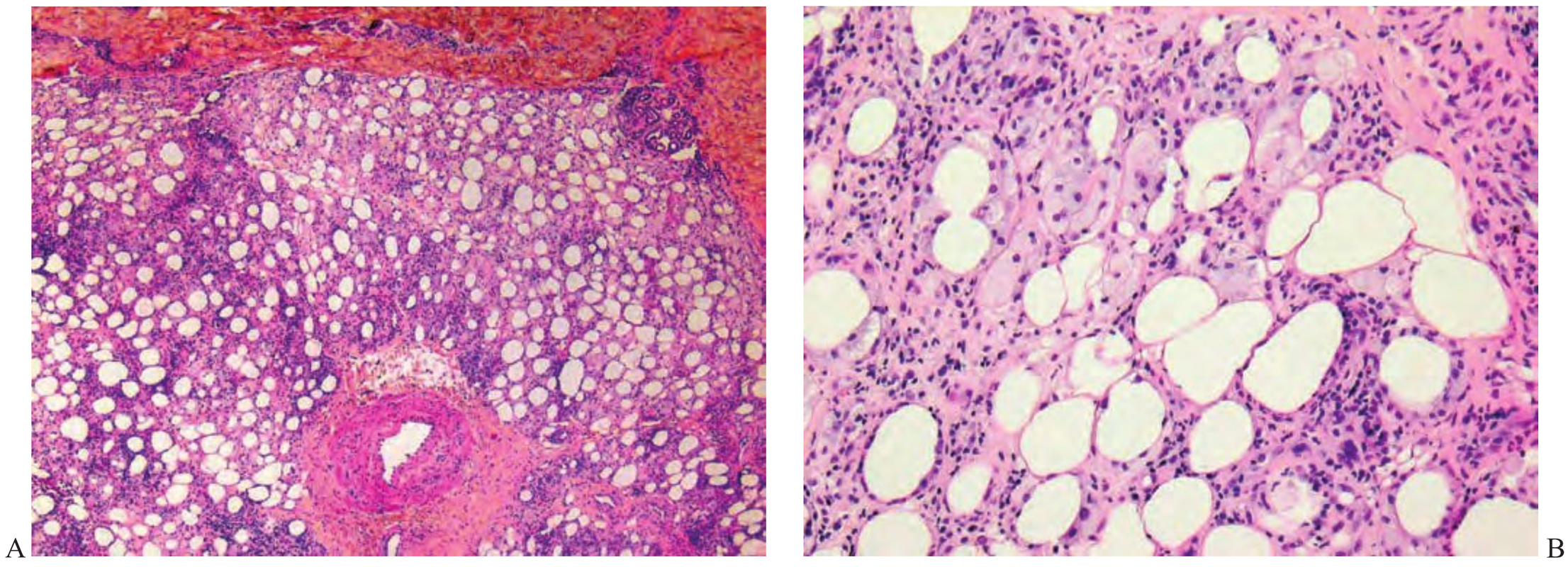


FIGURE 20-21 Weber-Christian disease. An indurated nodule on the leg has developed a perforation and drains a turbid, sterile, oily fluid with some necrotic tissue.

RELAPSING FEBRILE NODULAR NONSUPPURATIVE PANNICULITIS (WEBER-CHRISTIAN DISEASE)

Clinical Presentation. Weber-Christian disease now is a nonspecific clinical impression but is a pathologic diagnosis of exclusion. The diagnosis is made much less frequently now than it was in the period from 1950 to 1970, probably due to the greater power of current laboratory testing to reveal lupus erythematosus panniculitis, AAT panniculitis, or histiocytic cytophagic panniculitis in cases that might have been classified as Weber-Christian disease in the past. The classical clinical description is a disease characterized by the appearance of crops of tender nodules and plaques in the subcutaneous fat, usually associated with mild fever. The lower extremities are favored sites, but lesions may occur elsewhere and may ulcerate (Fig. 20-21). The disease occurs mostly in middle-aged women but has been described in all ages and in both sexes. In general, the disease has a good prognosis. However, if internal organ fat necrosis also is present, it may be fatal (80–82).

Histopathology. The histopathologic appearance itself is not sufficiently specific to exclude other diseases (Fig. 20-22). The classical description of the disease is that it evolves through three stages. In the first phase, there is only erythema and induration clinically. Histologically, acute inflammation is found in the fat lobules with degeneration of fat cells and an infiltrate of neutrophils, lymphocytes, and macrophages. The second phase has an infiltrate discretely localized to the fat lobules, consisting mainly of macrophages, foam cells, and extracellular lipid droplets. In some cases, the lesions perforate the skin surface and discharge a sterile, oily liquid. The third phase



A B

FIGURE 20-22 Weber-Christian disease. A: Sharp localization of the inflammation in the fat lobules that is a distinctive but nonspecific finding. B: Higher magnification showing fat-laden macrophages and lymphocytes in the lobules.

has depressed and indurated clinical lesions. Fibroblasts, collagen, and scattered lymphocytes and a few plasma cells replace the fat. Vascular changes are mild (14,80–86).

Systemic lesions occur in some cases of Weber-Christian disease and serve to distinguish this disease from most other types of panniculitis, except for histiocytic cytophagic panniculitis, gamma/delta T-cell lymphoma, and AAT deficiency panniculitis. In autopsy studies, inflammatory changes have been found in perivisceral fat as well as intravisceral fat in the liver, spleen, bone marrow, or near the pleural or peritoneal cavity. A large amount of oily fluid may accumulate in the pleural or peritoneal cavity (82,86–88).

Pathogenesis. If Weber-Christian disease exists as a distinct disease, the cause is unknown, but circulating immune complexes have been found in some cases (14,82,89).

Differential Diagnosis. The histologic appearance of Weber-Christian disease is most distinctive in the second phase, when there is an infiltration by lymphocytes and macrophages between fat cells that is discretely localized to the fat lobules. *Erythema nodosum* with unusual predominance of neutrophils can resemble the early phase of Weber-Christian disease, except for the localization of erythema nodosum primarily in the septa and Weber-Christian mainly in the lobules. Likewise, *AAT deficiency* can resemble early Weber-Christian disease except that the neutrophilic infiltrate in AAT deficiency usually affects the dermis and septa as well as the lobules. *Subcutaneous fat necrosis of pancreatic disease* can produce some of these findings but usually can be recognized by the extensive necrosis and deposition of bluish calcium precipitates with fatty acids. *Histiocytic cytophagic panniculitis* has some of the clinical features but histologically has a lymphoid infiltrate with macrophages that have ingested sufficient lymphocytes, neutrophils, and eosinophils to be called *bean bag cells* (90).

Subcutaneous panniculitic T-cell lymphoma can underly a histiocytic cytophagic panniculitic reaction, so lymphoma needs to be considered. After adequate investigation for all these other diseases, very few unexplained cases remain to be classified as Weber-Christian disease.

PANNICULITIS ROTHMANN-MAKAI

The term *panniculitis Rothmann-Makai* was proposed in 1945 as a designation for a "heterogeneous group of cases of idiopathic panniculitis that do not fit into any of the distinctly defined syndromes, such as Weber-Christian disease, erythema nodosum, or erythema induratum" (91). This diagnosis is based entirely on negative criteria (92) and consequently should be avoided. It seems preferable to refer to such cases as *unclassified panniculitis* until more definitive studies are available.

PALISADED GRANULOMATOUS PANNICULITIS

Clinical Features. Several granulomatous disorders that usually affect the dermis can also produce deep subcutaneous nodules. Some of these disorders can present in the subcutis without granulomas in the overlying dermis. In the subcutis, these diseases may form lesions that differ clinically and histologically in some aspects from their counterpart dermal lesions. *Subcutaneous granuloma annulare*, for example, is more frequent in young children and young adults, whereas the dermal form is more frequent in adults. The subcutaneous nodules may not produce erythema of the overlying skin. The lesions are most frequent on the head, hands, buttocks, and shins but can occur at other sites. Approximately 25% of patients with subcutaneous granuloma annulare also have dermal lesions. *Rheumatoid nodule* most typically is a deep subcutaneous nodule but can also involve the overlying dermis. Rheumatoid nodules tend to be on the elbows, fingers, and knees and are present in approximately 20% of patients with rheumatoid arthritis, almost all with a positive serum rheumatoid factor. Although they usually occur in patients with severe deforming joint disease, rheumatoid nodules can be the initial clinical presentation of rheumatoid arthritis. The subcutaneous lesions of granuloma annulare and rheumatoid nodule rarely perforate through the skin without associated trauma. The occurrence of granuloma annulare–like lesions in association with systemic disease has been reported (93–95). The list of systemic diseases is long, but rheumatoid arthritis is one of the main associated diseases. Other causes include thyroid disease, collagen-vascular diseases, viral infections (such as with parvovirus B19), and medications. One of the clinical clues that these are granuloma annulare–like reactions to systemic disease is that the lesions often occur in anatomic sites that are unusual for true granuloma annulare (94).

Histopathology. Both subcutaneous granuloma annulare and rheumatoid nodules produce necrosis of the fat lobules, and any involved septa, with a palisade of histiocytic cells around the focal areas of necrosis, which can be relatively large when compared with the size of typical dermal lesions (Fig. 20-23).

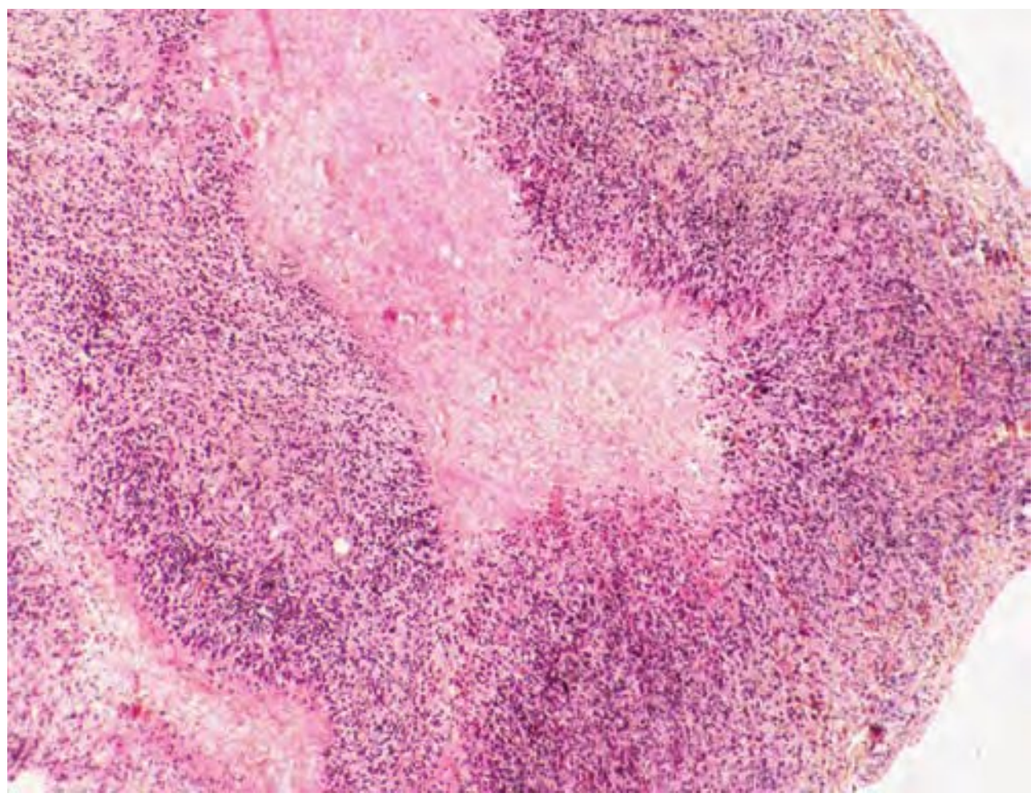


FIGURE 20-23 Subcutaneous granuloma annulare. This is different from the dermal lesions of granuloma annulare in that larger palisaded granulomas with central mucinous deposition and fibrosis are common in the subcutis.

Usually, subcutaneous granuloma annulare has abundant mucin in the necrotic centers of the lesions. The mucin is so abundant as to be visible in routine hematoxylin and eosin–stained sections. The presence of mucin can be confirmed on Alcian blue or colloidal iron stains. However, the detection of small amounts by these sensitive special stains can be less specific for granuloma annulare. In contrast, rheumatoid nodules have more fibrin in the necrotic centers of the lesions in routine sections. Immunofluorescence is so sensitive that it can detect fibrin in the centers of both granuloma annulare and rheumatoid nodules. When both mucin and fibrin are visible in the routine sections of the necrotic centers, a granuloma annulare–like lesion associated with a systemic disease should be suspected. In all of these instances, the macrophages appear similar in that they are enlarged, have abundant eosinophilic cytoplasm, and are aggregated closely together to give them an "epithelioid" appearance. Multinucleated giant cells may be present. Neutrophils may be found in the small vessels in the necrotic centers of the granuloma annulare–like lesions. Neutrophilic infiltrates in the vessels and in the interstitium around collagen bundles are more typical of rheumatoid nodules and papules.

Pathogenesis. The etiology of granuloma annulare is unknown, even in the ordinary dermal form and certainly in the subcutaneous form. With the recognition of the granuloma annulare–like lesions in systemic diseases, multiple etiologies could produce a granuloma annulare–like lesion. If this is true, then granuloma annulare becomes a reaction pattern of the dermis and/or subcutis. Studies of patients with granuloma annulare by routine immunofluorescence showed deposition of immune complexes (IgG, IgM, C3, with fibrin) in the small blood vessel walls in the centers of some lesions. These findings were only present in biopsies of early lesions (96). It is recognized now that the binding of certain types of IgG to the surface of fibroblasts in culture can cause overproduction of mucin by these fibrobasts (97). Therefore, it seems a reasonable hypothesis that the mucin production in granuloma annulare relates to the deposition of IgG on the surface of collagen bundles and fibroblasts. In rheumatoid nodules, the deposition of rheumatoid factor (IgM/IgG complexes) locally in the tissue might stimulate the fibroblasts in some patients to produce sufficient mucin to give the morphology called *granuloma annulare–like lesion in systemic disease*. Further studies are needed on the pathogenesis of these reactions. The presence of anti-Ro and anticardiolipin antibodies in some patients may produce vasculitis and pauciinflammatory vascular thrombosis in association with rheumatoid arthritis lesions (98).

Differential Diagnosis. The distinction between subcutaneous granuloma annulare (mucin depostion) and rheumatoid nodule (fibrin deposition) can be made in many cases in the routine histology. When the lesions exhibit an unusual clinical distribution of lesions for granuloma annulare, and when the lesions have both mucin and fibrin in the necrotic centers, then the diagnosis of granuloma annulare–like lesion in systemic disease can be offered, but it needs further investigation and correlation with the clinical findings in the patient. *Necrobiotic xanthogranuloma* is usually a dermal lesion, but the lesions can be large and involve the subcutis as well. It can have some histologic features in common with the palisaded granulomas, but the necrotic centers contain cholesterol clefts and are surrounded by macrophages with abundant lipid-filled, pale cytoplasm. *Crohn's disease* can produce subcutaneous granulomas with necrosis, but the granulomas usually do not have a palisaded appearance. Most subcutaneous lesions of Crohn's disease are around the perineum or oral sites. They tend to occur near areas of rectal involvement or ileosotomy sites. *Sarcoidosis* may produce granulomas in the septa or in the lobules or both. The lesions tend to remain as discrete granulomas and usually lack necrosis. In large granulomas, the centers may have fibrin deposition but without the granular debris of necrosis. Treatment of sarcoidosis with systemic steroids can produce central necrosis in the granulomas. The lesions lack palisading but may have slight mucin deposition in the stroma around the periphery but not in the centers of the granulomas. Small polarizable crystals have been found in some lesions of sarcoidosis but not in the other disorders in this section (99,100). The presence of other polarizable material raises the question of possible factitial panniculitis.

PANNICULITIS DUE TO PHYSICAL OR CHEMICAL AGENTS

Clinical Features. Trauma may be due to physical injury or to chemical injury, such as that produced by the injection of noxious substances. Physical injury can be produced by blunt pressure or impact, cold or excessive heat, or electrical injury. All of these factors can produce firm nodules in the subcutaneous fat. In many instances, these various inciting agents can be distinguished best by the clinical history and distribution of the lesions. Surreptitious injections of noxious substances can produce bizarre clinical and histologic patterns of lesions but can be suspected clinically by the distribution of lesions only in areas easily reached by the patient (*factitial panniculitis*). Drug injections by nurses usually are located in the deltoid region or on the buttocks. Self-injection of insulin often involves the thigh or lower abdomen and can produce subcutaneous lesions. Meperidine hydrochloride (Demerol) (101) and pentazocine (Talwin) (102) injections are known to produce traumatic panniculitis. The injection of oily substances such as hydrocarbons or silicone was common in the past for certain cosmetic effects, but reactions to these substances or to contaminants in them produce a panniculitis with varying degrees of inflammatory infiltration (103,104). The long-term effects of injection of buttock fat autotransplants to sites, such as the backs of hands, for cosmesis have yet to be studied. Mentally ill persons and drug addicts may purposely or inadvertantly inject themselves with foreign substances, such as feces or milk, sometimes used to dilute or cut narcotics. These various physical and chemical traumas lead to indurated subcutaneous nodules that may undergo liquefaction, ulcerate, and discharge pus

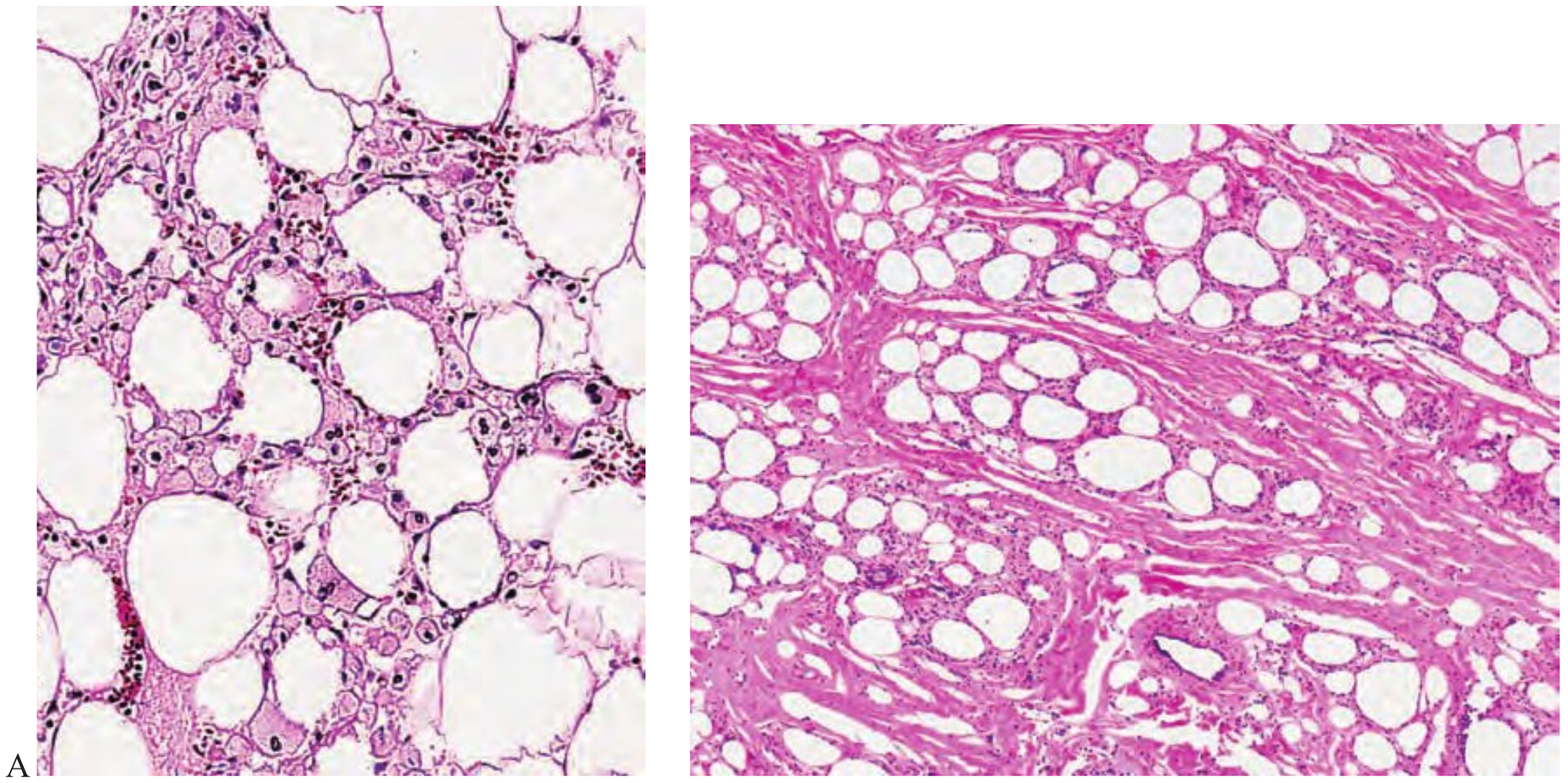


FIGURE 20-24 Traumatic fat necrosis. A: Acute area of fat necrosis with lymphocytes and macrophages in the fat lobules. B: Late lesion in which the fat lobules and septa have been replaced by dense fibrosis.

or a thick oily fluid. Healing leaves depressed scars (105). Lesions produced by extreme cold usually do not ulcerate unless associated with pernio or vasculitis with cryoglobulinemia. Cold injury may occur in children after eating an iced food such as an ice pop (106–108). The cold injury produces nodules or plaques that appear from 1 to 3 days after exposure and that subside spontaneously within 2 weeks. Excessive heat and electrical injury usually are accompanied by ulceration and eschar formation.

Histopathology. The injection of the various toxic agents will produce a variable histologic picture of acute inflammation, with aggregation of neutrophils and focal fat necrosis with hemorrhage (105). Older lesions have infiltrates of lymphocytes and macrophages (Fig. 20-24A) with fibrosis (102) (Fig. 20-24B). Vasculitis usually is absent with injections but can be present with heat-induced injury and with perniosis associated with cold, damp conditions. Polarized light reveals certain types of foreign material in injection sites (101), but polarizable crystals have been found in some lesions of sarcoidosis (99,100). The injection of oily liquids leads to the formation of many pockets of fatty material ("fat cysts"), often with a surrounding fibrous reaction containing foamy macrophages that overall impart a "Swiss-cheese appearance" to the tissue after the fat has been extracted by routine histologic processing (103,104). Fixation of the tissue in osmium tetroxide may be useful since endogenous lipids (but not most exogenous lipids) contain many unsaturated double bonds that react readily with osmium tetroxide to produce a black deposit of reduced osmium oxides (109,110). Injections of granulocyte-monocyte colony-stimulating factor or interleukin (IL)-2 can produce nodules at the sites of injections in the skin and subcutis that mimic leukemic or lymphoma infiltration due to their content of very highly stimulated monocytes or lymphocytes (111). Trauma due to cold injury initially has an infiltrate of lymphocytes and macrophages near the blood vessels of the deep plexus at the junction of dermis and subcutis. Such changes have also been described in perniosis. Biopsies at the third day, at the height of reaction, show rupture of the fat cells with fat pockets in the tissue surrounded by an infiltrate of lymphocytes, macrophages, neutrophils, and occasional eosinophils (107,112).

Pathogenesis. The subcutaneous fat of children is more sensitive to cold injury than that of older children and adults. In all newborn infants and in 40% of infants 6 months of age, the application of an ice cube to the skin produces nodules of cold panniculitis. By 9 months of age, such cold reactivity is rare (108). The greater degree of saturation of the lipids in newborns raises the crystallization temperature of the fat and produces greater susceptibility to cold injury (113,114). This mechanism of injury is involved also in *sclerema neonatorum*.

LOCALIZED LIPOATROPHY AND LIPODYSTROPHY

Clinical Features. Both localized lipoatrophy and lipodystrophy can have lesions with a similar clinical appearance; however, lipoatrophy usually involves one or several circumscribed, round, depressed areas, from 1 cm to several centimeters in diameter. In contrast, lipodystrophy produces the loss of large areas of subcutaneous fat, particularly in *acquired generalized lipodystrophy* (115). Most cases of lipodystrophy are of the cephalothoracic type and involve the face, neck, upper extremities, and upper trunk. Some cases have been noted that extend downward from the iliac crest. Lipodystrophy has been

reported with diabetes (116) and with glomerulonephritis (117). Lipoatrophic panniculitis also occurs in *connective tissue panniculitis* (118). In HIV-positive patients on highly active antiretroviral therapy including protease inhibitors, their prolonged life span has revealed that this therapy can produce a striking lipodystrophy syndrome. Loss of subcutaneous fat on the face and extremities can be severe and is accompanied by redistribution of fat to produce a "buffalo hump" and an increase in visceral fat deposits. This syndrome includes insulin resistance, diabetes mellitus/carbohydrate intolerance, hypertriglyceridemia, reduced high-density lipoprotein cholesterol, elevated low-density lipoprotein cholesterol, and reduced levels of the adipocyte cytokine *adiponectin* and the adipocyte hormone *leptin* (119,120).

Histopathology. Lesions of lipodystrophy are described most dramatically as a total loss of the subcutaneous fat resulting in dermis adjacent to the fascia (116). However, localized lipoatrophy has been described as having two types: inflammatory and noninflammatory or "involutional" types. In *the inflammatory type,* multiple lesions are common and have a lymphocytic infiltrate around the blood vessels and are scattered diffusely in the fat lobules (73,121). Areas of fat necrosis can be present with infiltration by macrophages.

In *the involutional type,* usually there is only a solitary lesion that exhibits a decrease in size of the individual adipocytes. They are separated from each other by abundant eosinophilic, hyaline material or in some instances by mucoid material (121).

Pathogenesis. Adipose tissue in adult mammals is under complex hormonal control. Insulin receptors on the surface of the fat cells inhibit lipolysis and stimulate lipogenesis. This contributes to increased fat deposition, whereas stimulation of beta-adrenergic receptor sites on the plasma membrane of fat cells increases lipolysis. Glucagon can also increase lipolysis. Although the fat cells themselves in the subcutis receive no direct innervation, innervation of the small blood vessels of the fat may produce noradrenergic stimuli for lipolysis. When normal adult adipose tissue is subjected to lipolysis by such stimuli or by fasting for 72 hours, significant changes in the morphology of the fat take place. Unilocular fat cells can become multilocular in senstive fat regions after only 48 hours of fasting. With prolonged fasting, the unilocular engorged fat cells lose their fat droplets and become more spindle-shaped cells that are indistinguishable from fibroblasts or undifferentiated perivascular mesenchymal cells (122,123).

Hormonal influences seem likely to be related to lipoatrophy (e.g., that which is commonly associated with aging). The SIR 2 gene product NAD^+ dependent histone deacetylase is a regulator of aging that has been conserved in evolution from yeast to mammals. In mammals, the SIR T1 gene regulates white adipose tissue, and its overexpression reduces the amount of fat, in the presence of low levels of insulin, and decreases blood glucose. The SIR T4 gene in the nucleus produces a protein in mitochondria that affects energy metabolism. The effects of caloric restriction seem mediated by SIR 2 gene activation. Both SIR 2 activation and direct caloric restriction can produce a slight prolongation of life span in experimental animals (124).

LIPEDEMA

Clinical Features. Lipedema is an entity that is relatively poorly recognized by pathologists but is more prominent in the literature of surgeons and radiologists. In its localized tumefactive form, it presents as localized swelling, sometimes affecting both buttocks, the thighs, or the legs in middle-aged women (125–130). The swelling persists despite elevation of the extremities and is a nonpitting edema. In the tumefactive form, the swelling is not uniform and may have deep depressions in it. More commonly, the swelling is not tumefactive but is more diffuse, painless, bilateral and symmetrical and involves the thighs and lower legs but not the feet (125).

Histopathology. In a localized area, there are increased interspaces between fat cells, without dilation of blood vessels or evident dilation of lymphatic spaces, without increased mucin on Alcian blue or colloidal iron stains, and without much inflammation. In some cases, trauma to these protuberant masses can result in deep depressions in the lesions, which correspond histologically to zones of loose fibrous tissue that lack fat cells and have slight amounts of hemosiderin in macrophages. Mast cells may be slightly increased in the lesions but are probably reactive. There is no collagenous capsule at the periphery of the tumefactive form. There is no atypia of the adipocyte nuclei.

Pathogenesis. The result of the lipedema is great thickening of the subcutaneous tissues without much evidence of classical lymphedema. However, careful studies have shown microaneurysms of the lymphatic vessels localized to the areas of lipedema (131). It is different from *cellulite*, which produces a diffuse peau d'orange pebbly appearance to the skin of the thighs and buttocks regions of women. The cellular basis of cellulite is extension of adipose tissue from the subcutis up into the reticular dermis and not edema of the fat lobules. The anatomic construction of the border between reticular dermis and subcutis is more densely collagenous in males than in females, predisposing women to the development of cellulite (5). Another possible relationship is to *Durcum's disease* or *adiposis dolorosa*, which differs in being painful clinically and in having inflammation of nerves. Further careful histologic and clinical studies of these cases are needed.

Differential Diagnosis. The tumefactive nature of the swelling in some cases of lipedema leads toward a differential diagnosis that includes lipoma with edema or mucinous change, lymphedema, scleredema, or scleromyxedema. The lack of a delicate capsule makes lipedema different from lipoma. The lack of increased mucin on Alcian blue stains separates lipedema from scleredema, scleromyxedema, or myxoid lipoma.

SUBCUTANEOUS NODULAR FAT NECROSIS IN PANCREATIC DISEASE

Clinical Features. In patients with pancreatitis or pancreatic neoplasms, the release of lipase enzymes into the blood can lead to nodules of fat necrosis in the subcutis. The pretibial region is the most common site of the nodules, but they may occur on the thighs, buttocks, and elsewhere (Fig. 20-25). The nodules usually are tender and red and may be fluctuant (132), but they only rarely discharge oily fluid through fistulas (133).

Histopathology. The histologic appearance of the subcutaneous nodules in pancreatic disease is characteristic in most instances (134). In the foci of fat necrosis, there are ghostlike fat cells having thick, faintly stained cell peripheries and no nuclear staining (Fig. 20-26). Calcification forms basophilic granules in the cytoplasm of the necrotic fat cells and sometimes forms lamellar deposits around individual fat cells or patchy basophilic deposits at the periphery of the fat necrosis (132) (Fig. 20-27). A polymorphous infiltrate surrounds the foci of fat necrosis and consists of neutrophils, lymphoid cells, macrophages, foam cells, and foreign body giant cells (135). There can be extensive hemorrhage into the lesions. Old lesions have macrophages, foam cells, lymphocytes, and fibroblasts, with fibrosis and hemosiderin deposition (132). In some cases of pancreatic enzyme panniculitis, possibly with early lesions, biopsies of subcutaneous nodules show only a nonspecific pattern of necrotizing panniculitis with a neutrophilic inflammatory response. Multiple biopsies and deep biopsies or biopsies of lesions of different ages may allow a definitive diagnosis.

Systemic Lesions. Fat necrosis also occurs in internal organs. The symptoms of arthralgia can be due to periarticular fat necrosis (135). Fat necrosis is common also in the pancreas and surrounding fat tissue and in the fat of the omentum, mesentery, pericardial, and perirenal regions as well as in the mediastinum and bone marrow (132). Calcium precipitation with the released fatty acids can be extensive enough to produce life-threatening hypocalcemia.

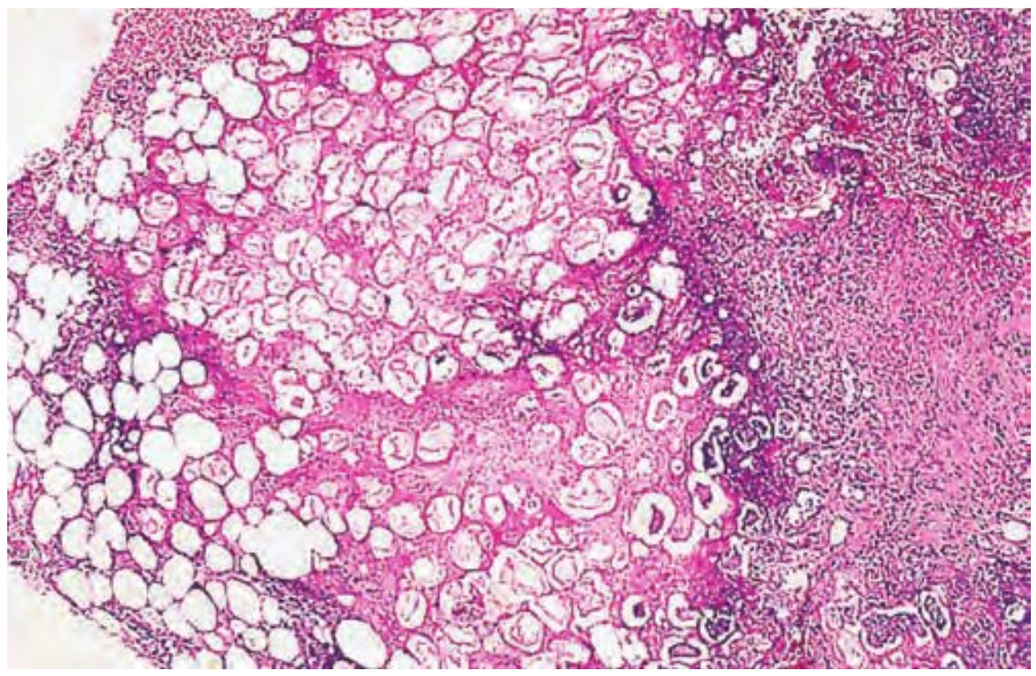


FIGURE 20-26 Pancreatic enzyme panniculitis. Necrotic fat cells contain eosinophilic deposits of partially hydrolyzed fat. Calcification forms granular basophilic material. Focal hemorrhage is frequent.

Pathogenesis. The damaged or tumorous pancreatic acinar cells release lipase, phospholipase, trypsin, and amylase into the surrounding tissues and blood. The serum values for amylase and lipase usually are elevated transiently and may not be detected in all cases. Amylase levels often peak 2 to 3 days after the appearance of the subcutaneous nodules (134). Lipase can be detected in the regions of fat necrosis and in ascitic fluid (136). It is not clear how the pancreatic proenzymes become activated in the tissues to produce fat necrosis. Local changes in vascular permeability due to trauma or other circulating enzymes, such as trypsin or phospholipase A2, may allow the pancreatic lipase to enter the interstitial compartment of the fat lobules and produce fat necrosis. Free fatty acids released by the lipolysis combine with calcium to form the soapy basophilic deposits in the tissue (137). Enzymatic damage to the integrity of the vascular wall can produce extensive hemorrhage.



FIGURE 20-25 Pancreatic enzyme panniculitis. Erythematous nodules appear most commonly on the lower legs.

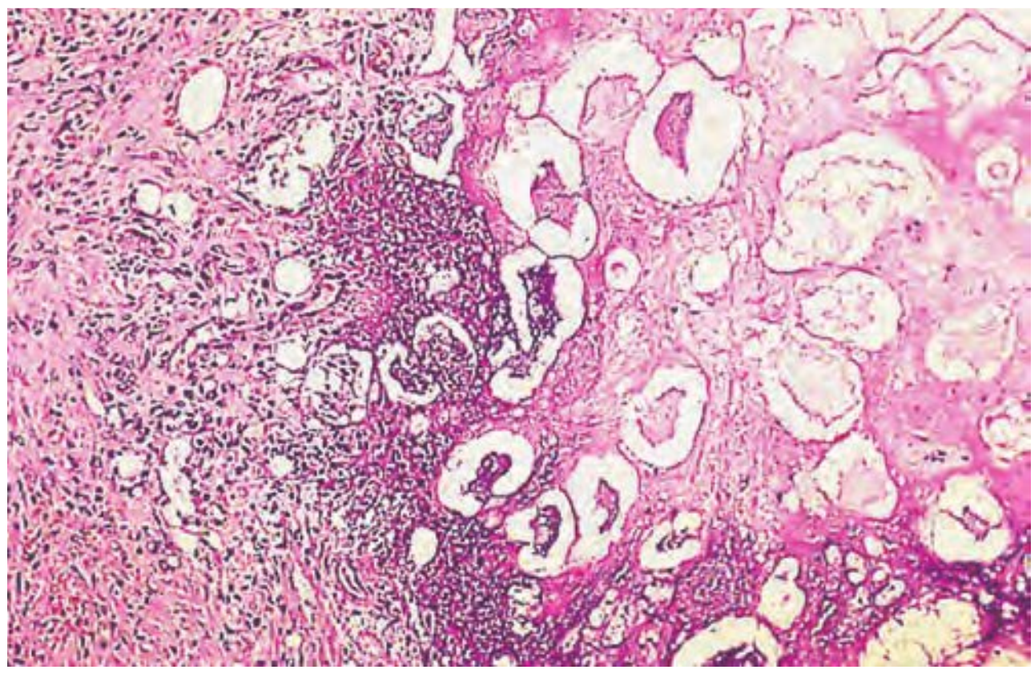


FIGURE 20-27 Pancreatic enzyme panniculitis. Many neutrophils are present in the margin of the zone of calcification and of fat necrosis.

Differential Diagnosis. The usual diagnostic distinction histologically is whether the fat necrosis is due to pancreatic disease or to physical trauma. Clinically, other considerations may include also erythema nodosum, erythema induratum, nodular vasculitis, AAT deficiency, disseminated infection, or Weber-Christian disease. Only pancreatic enzyme fat necrosis produces the basophilic deposits of calcium precipitated with abundant free fatty acids. All of the entities can have neutrophils in the fat. Basophilic DNA debris from neutrophil nuclei must be distinguished from calcium deposits. Von Kossa stains for calcium phosphate are positive on the calcium deposits in pancreatic enzyme fat necrosis and negative on necrotic nuclei. Septic foci of bacterial or fungal infection can require special stains to detect these organisms, especially in the presence of calcific and DNA debris. Despite vascular damage and hemorrhage, neutrophilic vasculitis usually is absent in fat necrosis due to pancreatic disease. Old lesions that have reabsorbed the calcium soaps cannot be distinguished easily from the other entities.

SCLEREMA NEONATORUM

Clinical Features. Sclerema neonatorum is a very rare disorder, usually in premature infants, that is characterized by a diffuse, rapidly spreading, nonpitting hardening of the subcutaneous fat of neonates in the first few days of life. The skin seems waxlike, tight, cold, and indurated. If untreated, death usually supervenes in a few weeks. On autopsy, the subcutis is greatly thickened, hardened, and lardlike. Most infants with sclerema neonatorum are cyanotic at birth, have difficulty maintaining their body temperature, and have a major debilitating illness (114).

Histopathology. The subcutaneous tissue owes its thickening to the increase in the size of the fat cells and to the presence of wide, intersecting fibrous bands (113,114). The lipid crystals inside the fat cells produce rosettes of fine needle-like clefts after lipid extraction in routine processing. In frozen sections, the crystals are not extracted and are visible in polarized light (138). In most instances, there is very little evidence of any inflammatory reaction to the fat necrosis, but very rarely, an inflammatory reaction containing giant cells can be found (138,139). Characteristically, the changes develop rapidly, are extensive, and elicit less inflammatory reaction than those of subcutaneous fat necrosis of the newborn or of localized cold panniculitis in young children.

Systemic Lesions. In most cases of sclerema neonatorum, the changes are limited to the subcutaneous fat (114). However, in two cases, autopsy revealed lesions in the visceral fat that were identical to those in the subcutis. In one case, the lesions were widespread (138), while in the other, the systemic lesions were limited to the perirenal and retroperitoneal fat (139).

Pathogenesis. Compared with the fat of the adult, the subcutaneous fat of the newborn has a greater ratio of saturated to unsaturated fatty acids, which raises the solidification point of the fat closer to room temperature. In sclerema neonatorum, these changes are exaggerated so that the neutral fat (triglyceride) crystallizes at room temperature. The increased ratio of saturated (palmitic or stearic acid) to unsaturated fatty acids (such as oleic acid) may be produced by defective enzyme pathways that lead to an excess of saturated fatty acids (114). X-ray diffraction studies have shown that the crystals in the fat cells are due to triglycerides (140). It is likely that the use of thermally controlled incubators for premature infants has caused this disease to be extremely rare. This same mechanism of injury is operative in localized cold panniculitis in infants.

Differential Diagnosis. Generalized edema due to an immature renal system can mimic some aspects of sclerema neonatorum clinically. However, in renal failure, the generalized edema is pitting while in sclerema it is not. Lymphedema (Milroy's disease) can produce nonpitting edema, particularly of the legs, in an otherwise healthy infant. Biopsies are not advised but show dilation of lymphatics. Erysipelas is more demarcated, warm, and tender than sclerema.

SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN

Clinical Features. Subcutaneous fat necrosis of the newborn usually occurs in premature or full-term infants, often after a complicated delivery by forceps or by cesarean section (141). Indurated, erythematous to violaceous nodules and plaques appear in the subcutis a few days to a week after birth. Rarely, in cases with numerous nodules, the lesions may discharge a caseous material (142). The patient's health generally is good, and the nodules resolve spontaneously after a few weeks or months. Rarely, some infants are severely ill and die (142). In 16 reported cases, the subcutaneous fat necrosis was associated with hypercalcemia, and 3 patients died (143). Thrombocytopenia, hypertriglyceridemia, and hypoglycemia have also been reported (144). The development of extensive fat necrosis has been reported in infants following induced hypothermia used in cardiac surgery (145) or after surface hypothermic treatment of birth asphyxia, producing hypercalcemia 7 weeks later. An underlying defect in composition and metabolism of fat has been assumed to exist in such cases. The cases need to be followed for the development of hypercalcemia, which may occur in approximately one third of cases (141). Subcutaneous fat necrosis has been reported also in a number of rare associations (3), including with maternal cocaine use and intrapartum administration of calcium channel blockers.

Histopathology. Focal areas of fat necrosis are present in the fat lobules and are infiltrated by macrophages and foreign body–type giant cells (Fig. 20-28). Fat deposits in the macrophages and giant cells contain crystalline fat, which after lipid extraction appears as needle-shaped clefts in a radial arrangement (146) (Fig. 20-29). In frozen sections, the radial clefts contain doubly refractile crystals. Calcium deposits usually are small and scattered in the necrotic fat. If the necrosis is

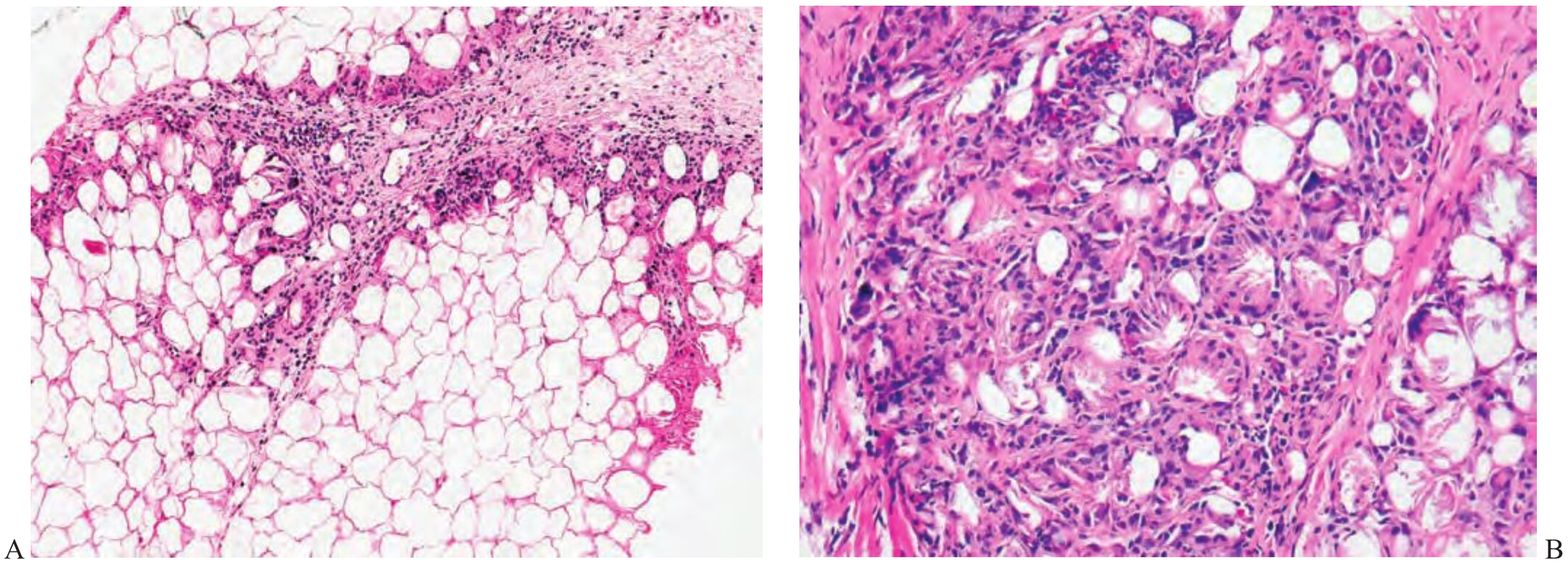


FIGURE 20-28 Subcutaneous fat necrosis of the newborn. A: Early lesion with many macrophages and multinucleated cells at the periphery of the damaged fat lobule. B: Later lesion with replacement of the fat lobules by macrophages and multinucleated cells.

extensive, calcium deposits may be large and require several years to be reabsorbed.

Pathogenesis. Electron microscopic examination shows that the phagocytosis of fat crystals starts with the invasion of fat cells by cytoplasmic projections of macrophages. Subsequently, fat crystals are seen within the cytoplasm of macrophages and of foreign body–type giant cells, which result from fusion of the macrophages (146).

The cause of subcutaneous fat necrosis of the newborn is not known. There is debate about the role of trauma, as many of the patients have been premature infants who were born by forceps delivery or who otherwise endured a difficult delivery. However, lesions have been reported in children delivered by cesarean section (3,141).

Differential Diagnosis. Both subcutaneous fat necrosis of the newborn and sclerema neonatorum have crystalline arrays of needle-like clefts in the fat. Sclerema is a catastrophic diffuse illness that gives little time for extensive inflammation; thus, in sclerema, there is an absence of focal areas of fat necrosis with macrophages and giant cells. In sclerema, there is also an absence of calcifications and the presence of wide bands of fibrous tissue in the subcutis (114). Treatment of children with high doses of steroids—for example, as was done for rheumatic fever—can produce poststeroid panniculitis with subcutaneous lesions very similar histologically to those of subcutaneous fat necrosis of the newborn (147). The deep nodules usually occur within 1 to 30 days after the cessation of high-dose steroid treatment. Traumatic fat necrosis has focal areas of necrosis and inflammation but lacks the crystals in the fat. Localized infection can be difficult to exclude clinically, but the infants with subcutaneous fat necrosis are generally rather healthy and are not septic.

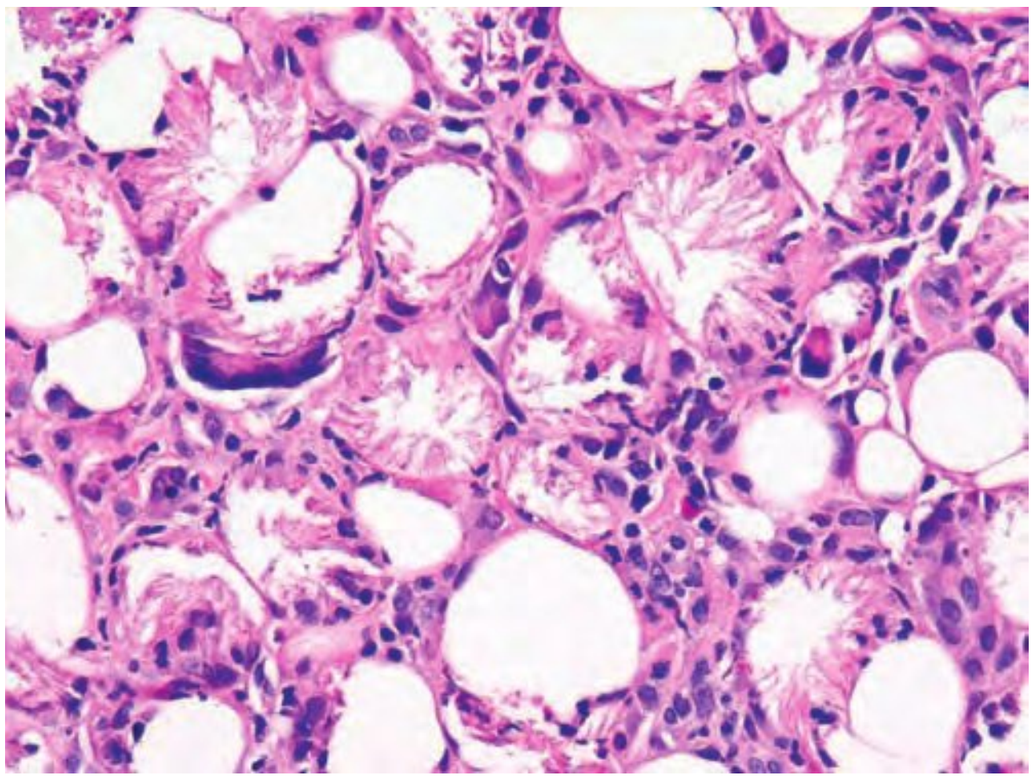


FIGURE 20-29 Subcutaneous fat necrosis of the newborn. A higher magnification shows that the radial arrays of crystalline fat leave clefts in the cytoplasm of the macrophages and damaged adipocytes.

CALCIFYING PANNICULITIS

Clinical Features. Patients with end-stage renal disease or hyperparathyroidism may develop indurated, erythematous, cold, subcutaneous and dermal nodules and plaques (Fig. 20-30). The lesions can progress to extensive dry gangrenous necrosis of the skin and subcutis. The lesions can be related to the prior administration of medications containing calcium or phosphates so that the balance of calcium to phosphate is so disturbed as to favor precipitation of calcium phosphate salts in the tissue. Plaques



FIGURE 20-30 Calcifying panniculitis. This patient with hyperparathyroidism developed erythematous, hemorrhagic, indurated plaques that were cold to the touch.

often are localized at usual sites of subcutaneous injection such as the thighs and abdomen.

Histopathology. The early or minimal lesions of patients with this disorder often have calcification of the media of the medium-sized blood vessels and of the walls of small capillaries in the subcutis (Fig. 20-31). In *calciphylaxis* associated with chronic renal failure, calcification and fibrointimal hyperplasia occlude the lumen of small arteries (148). In severe cases, calcium phosphate crystals form in the small vessels and interspaces between fat cells in the lobules of subcutaneous fat. The affected vessels can undergo thrombosis producing ischemic necrosis of the subcutaneous fat and even the overlying dermis and epidermis.

Pathogenesis. Calciphylaxis is a condition in which the balance of calcium and phosphate favors precipitation of calcium phosphate at the sites of trauma, cold injury, injection of medications containing calcium or phosphate compounds, or in vessel walls. The patients usually have end-stage renal disease and less commonly primary hyperparathyroidism. Case reports indicate that the phenomenon of calcium precipitation can be induced locally by injections of an anticoagulant drug such as calcium heparinate (149), by infusions containing excess phosphate, or for unknown reasons during hemodialysis (150). In young children, extensive subcutaneous calcifications can result from subcutaneous fat necrosis of the newborn. In adults, the differential diagnosis also includes a prior episode of pancreatic fat necrosis or traumatic fat necrosis. Radiologic findings in traumatic fat necrosis are generally a central lucent fat cyst with surrounding curvilinear calcifications, or coarse calcifications, or microcalcifications (151). The extensive calcification of the media of small arterioles is distinctive for calciphylaxis. The concept of calciphylaxis, as introduced by Seyle, has been presented as involving challenge by agents in a setting of hypersensitivity to calcium that led to local calcification. The metastatic calcification in renal disease is due to elevated calcium and phosphate levels and is only vaguely related to the Seyle's presentation of calciphylaxis (152).

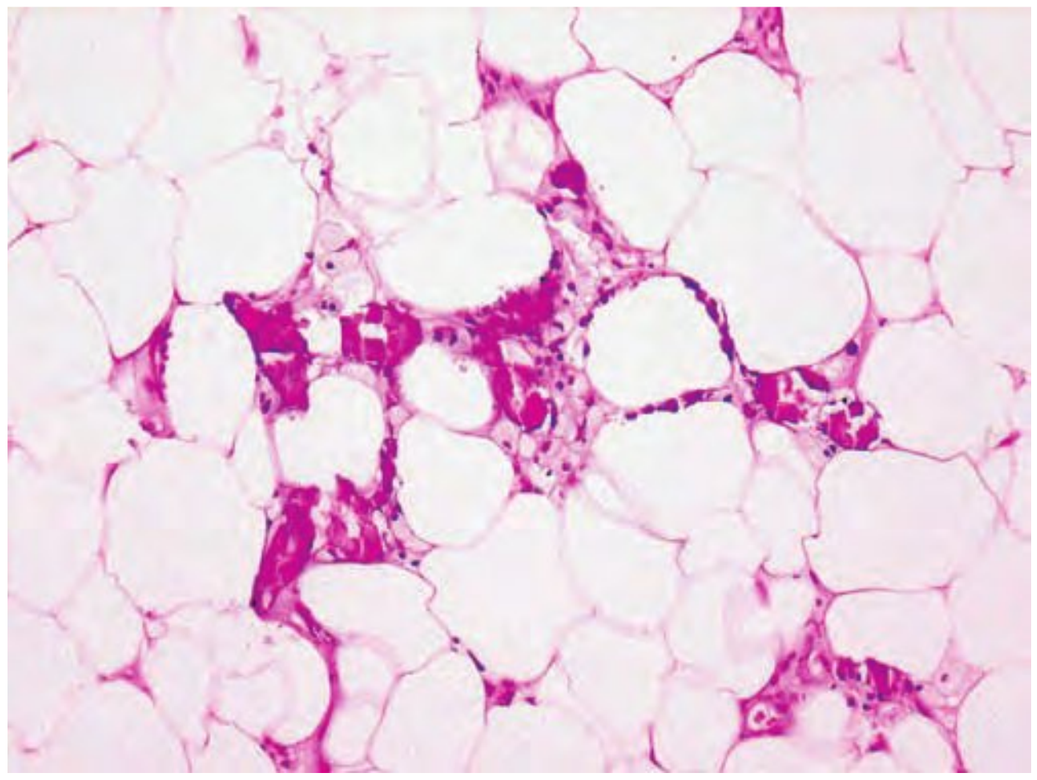


FIGURE 20-31 Calcifying panniculitis. Precipitation of calcium phosphate salts in the blood vessel walls produces a purple-stained deposit. These deposits lead to thrombosis and ischemic necrosis of the adjacent fat and overlying skin.

LIPOMEMBRANOUS CHANGE OR LIPOMEMBRANOUS PANNICULITIS

Clinical Features. Patients with severe stasis, diabetes, and other causes of arterial vascular insufficiency to the lower legs can develop indurated plaques in the subcutis. They are depressed and painful but rarely ulcerate (153–156). The lesions are named *lipomembranous panniculitis* based on the microscopic finding of lipomembranes around fat deposits or "cysts," more properly termed *pseudocysts*. Lipomembranous change has been found also in a number of primary disorders including lupus erythematosus panniculitis, morphea, erythema nodosum, erysipelas, necrobiosis lipoidica, and traumatic panniculitis (157,158). Ischemia and/or stasis can lead to extensive, depressed, hard areas of skin, often on the lower legs and accompanied by hemosiderosis, with epidermal and dermal atrophy, which is a condition named *lipodermatosclerosis* (25).

Histopathology. Biopsies deep into the fat show a lobular panniculitis with focal macrophage infiltration and fibrosis around shrunken lobules. Within the lobules, there are fat pseudocysts that are lined by a thin eosinophilic layer, called a *lipomembrane*, which has fine, feathery projections into the fat cavity (Fig. 20-32A). Spectral imaging shows that the lipomembranes are spectrally distinct from the periphery of surrounding fat cells (Fig. 20-32B). The lipomembrane is positive on PAS stain (Fig. 20-33) and, in late lesions, with elastic tissue stains (158). The lipomembranes are positive for CD68 and lysozyme, suggesting a contribution of these enzymes from the macrophages in the production of lipomembranes. Late or older lesions are only weakly positive or become negative for CD68 and lysozyme (158). Early lesions also have focal areas of fat necrosis, such as those produced by partial ischemia. Lipomembranes

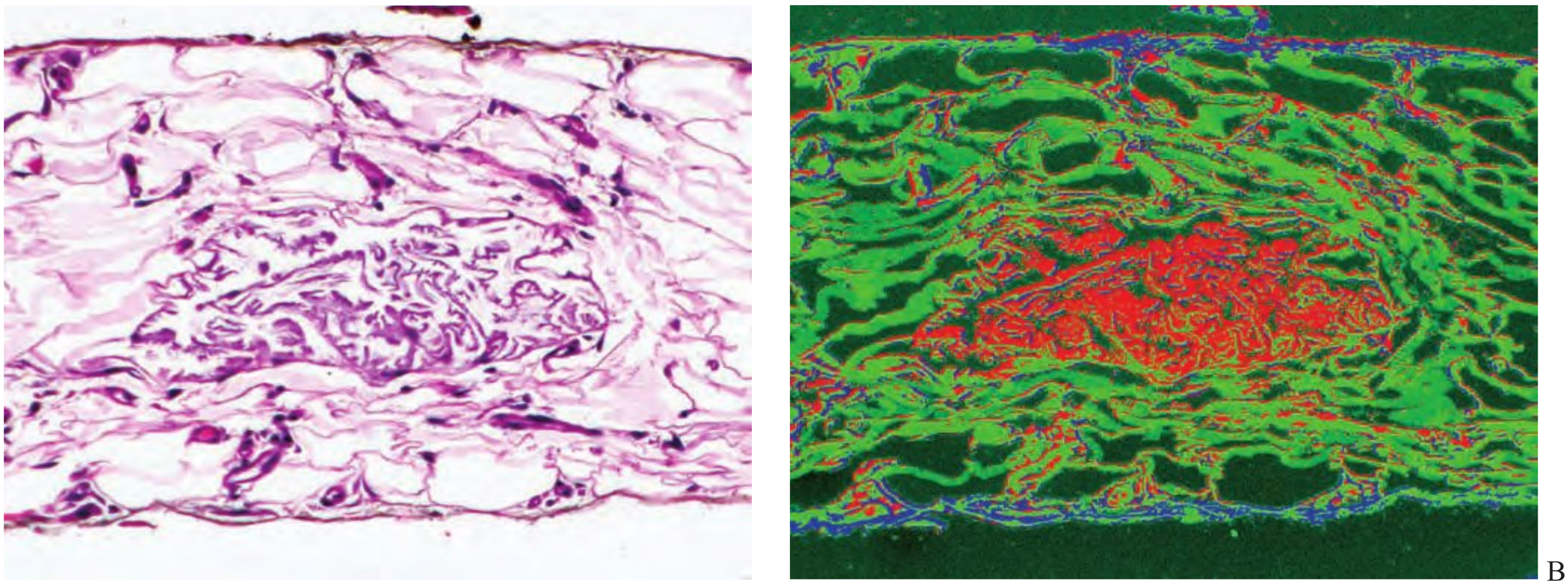


FIGURE 20-32 Lipomembranous panniculitis. A: Necrosis of the fat has produced a layer of pale amphoteric to eosinophilic material, a "lipomembrane" around the periphery of the fat globules. B: Spectral image demonstrating in red that the distinctive spectrum of the lipomembranes is similar to hematoxylin staining of nuclear material. The cytoplasm of adjacent damaged fat cells is shown in green, and the collagen of the septa is in blue.

often can be found in the remaining small fat lobules in late stages of *lipodermatosclerosis*, in which there also is dermal fibrosis with loss of epidermal appendages and fibrous tissue replacement of much of the subcutaneous fat (25).

Differential Diagnosis. This is not a very specific entity and probably reflects the tendency of necrotic fat to accumulate fibrin and lysosomal enzyme containing material from macrophages at the surface of the exposed fat. Although extensive lipomembranous change is rare in uncomplicated traumatic fat necrosis when compared with ischemic panniculitis, a few cases of extensive lipomembranous change have followed minor surgical trauma, possibly related to medications the patient received.

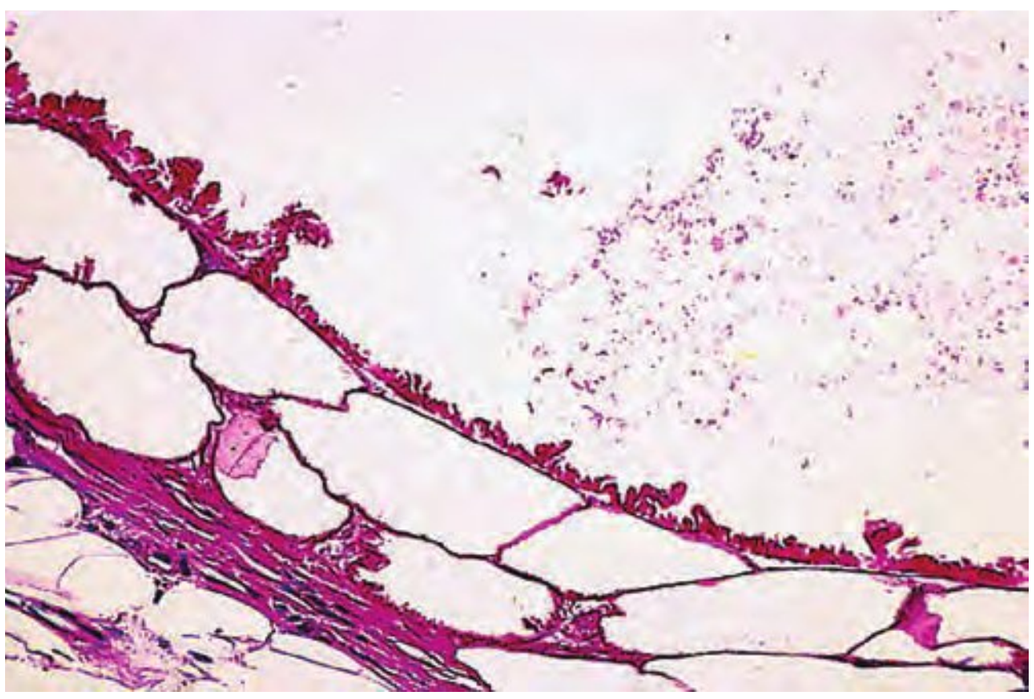


FIGURE 20-33 Lipomembranous panniculitis. Lipomembranes have feathery projections into the fat globules and are PAS positive (PAS stain).

HISTIOCYTIC CYTOPHAGIC PANNICULITIS (SUBCUTANEOUS T-CELL LYMPHOMA WITH HEMOPHAGOCYTIC SYNDROME)

Clinical Features. Histiocytic cytophagic panniculitis is frequently a fatal systemic disease that is characterized by recurrent, widely distributed, painful subcutaneous nodules associated with malaise and fever (90,159–161). The nodules can be hemorrhagic (Fig. 20-34). Ulcers may be present (162).

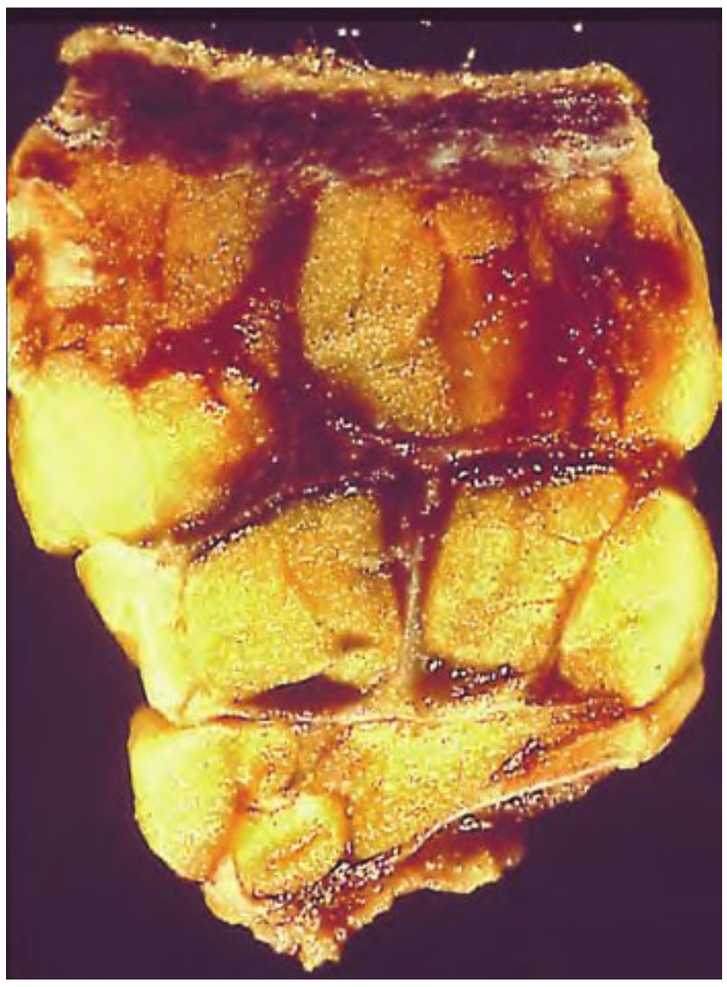


FIGURE 20-34 Histiocytic cytophagic panniculitis. This cross-sectioned skin nodule shows both septal and lobular infiltration and hemorrhage. Note also the dermal hemorrhage.

Hepatosplenomegaly, pancytopenia, and progressive liver dysfunction develop in most cases (163). The patients may follow a long chronic course, or the disease can be fulminant. The patients usually die a hemorrhagic death due to depletion of blood coagulation factors. Aggressive chemotherapeutic intervention, analogous to that used for malignant histiocytosis, has resulted in remission in one patient (164). In some patients, the disease seems limited to the skin and subcutaneous tissue and follows a more benign course (159).

Histopathology. In the subcutis, the inflammation is both septal and lobular (Fig. 20-34). A deep biopsy usually shows both subcutaneous and dermal nodules composed of macrophages and a mixed inflammatory infiltrate. Often, there is necrosis and hemorrhage (Fig. 20-35). The nuclei of the macrophages are within the range of sizes and shapes seen in benign inflammatory disorders. In some cases, lymphocytes infiltrate medium-sized blood vessel walls (Fig. 20-36A). In some areas, the macrophages become so engorged by phagocytosis of erythrocytes, lymphocytes, and cell fragments that they have been called *bean bag cells* (90) (Fig. 20-36B). In

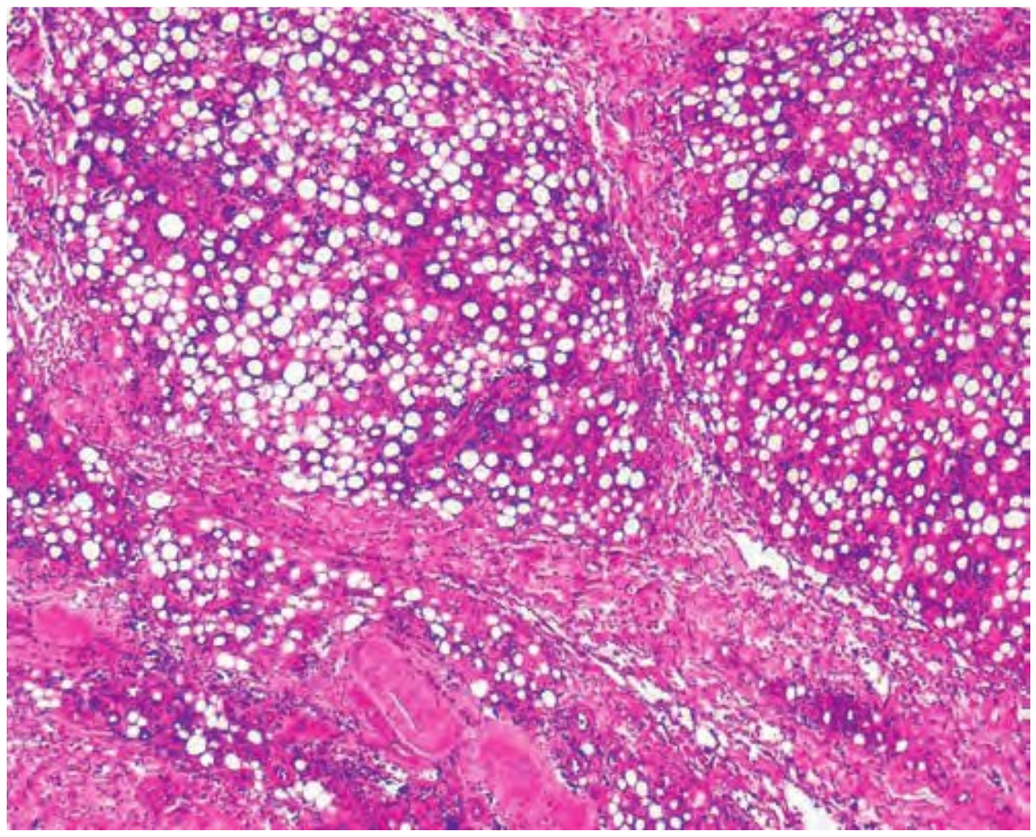
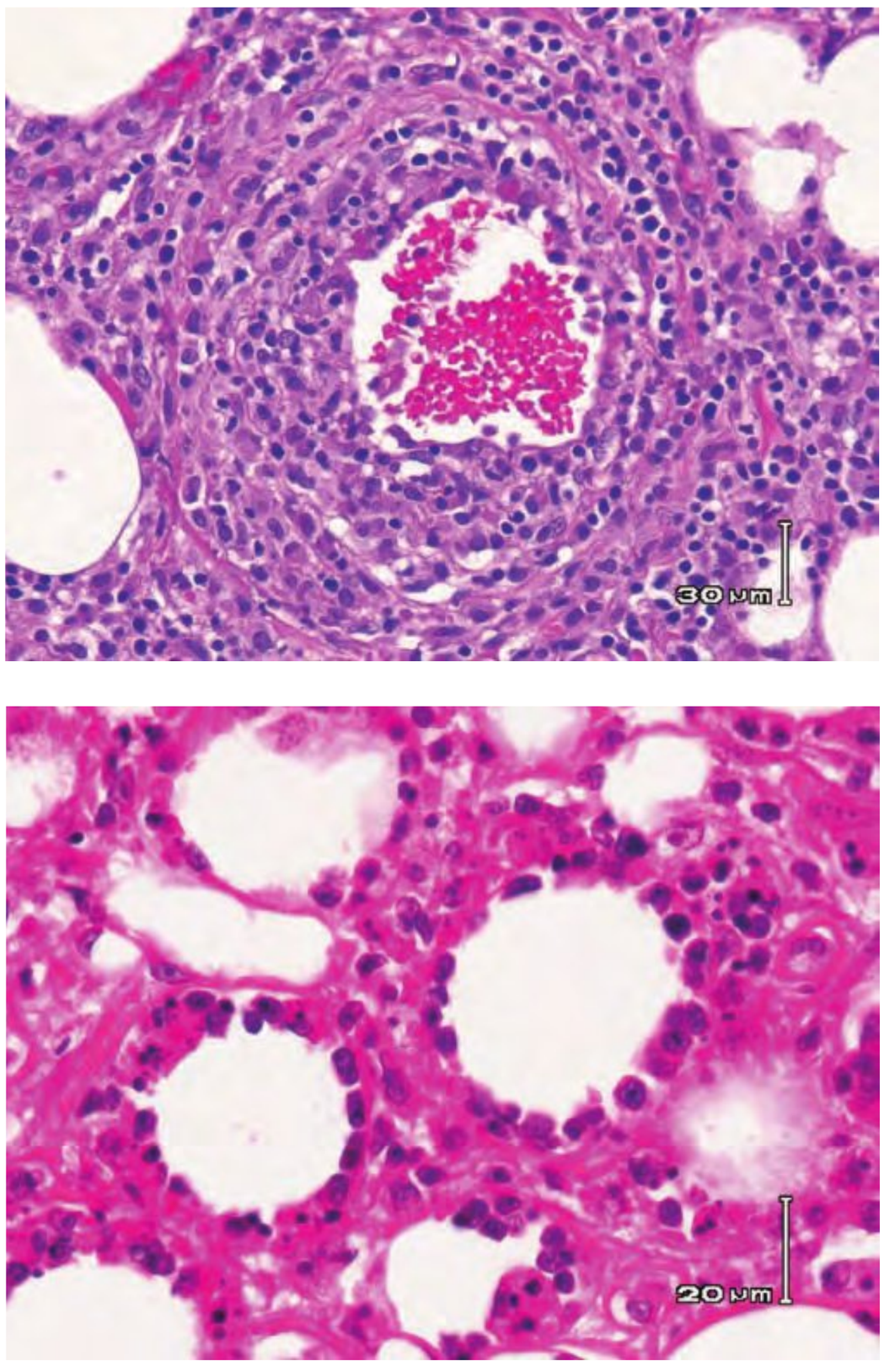


FIGURE 20-35 Histiocytic cytophagic panniculitis. There is hemorrhagic necrosis of the fat with an infiltrate of lymphocytes and macrophages.



A B C

FIGURE 20-36 Histiocytic cytophagic panniculitis. A: Extensive infiltration of blood vessel walls by lymphocytes. B: Characteristic cytophagic histiocytes that have engulfed lymphocytes and erythrocytes to form so-called "bean bag cells." C: Distinctive rings of atypical lymphocytes around fat cells in subcutaneous T-cell lymphoma, which is often a trigger for the cytophagic histiocytic activity.

some patients, early lesions contain a rather dense infiltrate of small lymphocytes and only a few focal areas with cytophagic histiocytes. In some of the cases due to subcutaneous T-cell lymphoma, atypical lymphocytes can be found in rosettes around fat cells (Fig. 20-36C).

The involvement of other organs by similar cytophagic macrophages leads to diffuse infiltration of the liver, bone marrow, spleen, lymph nodes, myocardium, lungs, and gastrointestinal tract (165). The cytophagic macrophages can deplete almost all of the bone marrow elements.

Pathogenesis. When originally described, the disease was differentiated from malignant histiocytosis by the fact that the nuclei of the macrophages in the cytophagic panniculitis were not cytologically atypical. Due to the fulminant course in some patients, the disease initially was considered by some authors to be a variant form of malignant histiocytosis that can remain confined to the skin and subcutis for a protracted period (166). However, more recently, the similarity to terminal hemophagocytic syndromes associated with lymphomas (167,168) has led to consideration that most cases of cytophagic panniculitis result from an abnormal lymphocyte population that has stimulated benign macrophages to engage in fulminant hemophagocytosis (169–173). The patients may have the hemophagocytosis secondary to a T-cell lymphoma of the gamma/delta subtype (which has an associated hemophagocytic syndrome more frequently than the alpha/beta subtype) or an NK/T-cell lymphoma ($CD2^+$ $CD3^-$ $CD8^+$ $CD56^+$) that has also been associated with a hemophagocytic syndrome (79,174). Viral infections that are associated with hemophagocytic syndromes, without lymphoma, usually do not have panniculitis. Benign cytophagic histiocytes can be found in some cases of AAT deficiency panniculitis, ruptured cysts, and infections and can be mimicked by emperipolesis in Rosai-Dorfman disease (4).

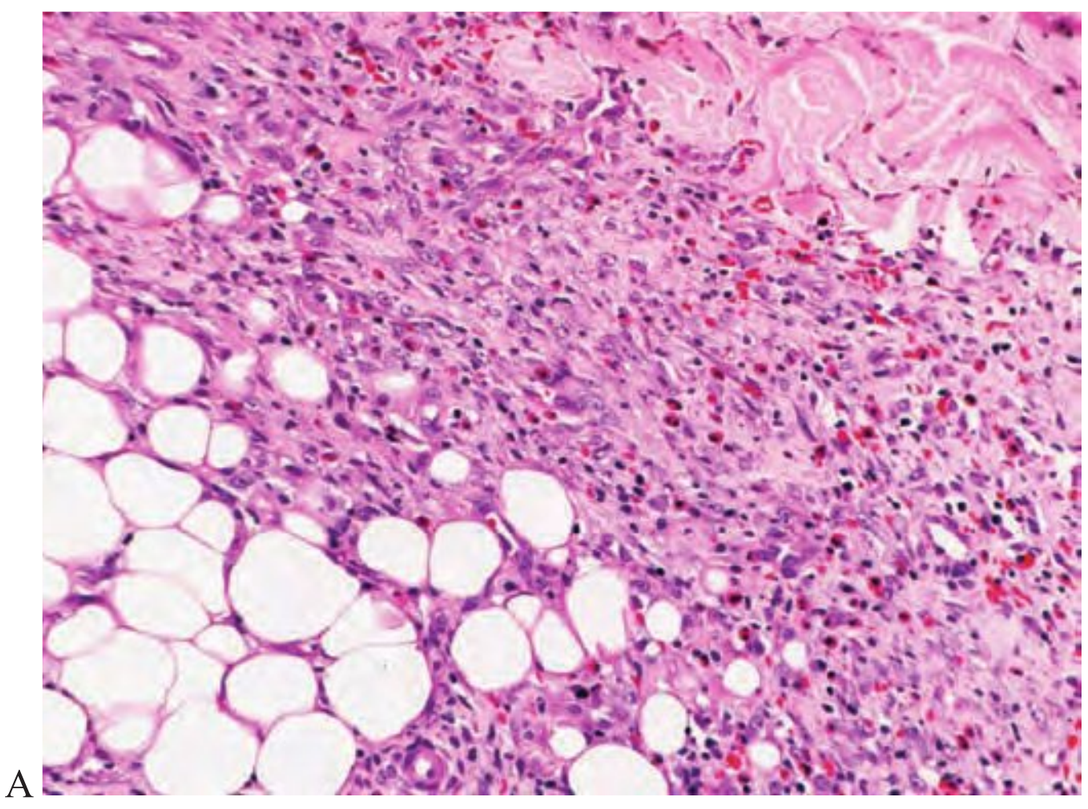
MISCELLANEOUS PANNICULITIS

The administration of bromide and iodide compounds can produce a panniculitis, usually in association with changes in the overlying epidermis and dermis. Due to the decrease in therapeutic use of bromide and iodide compounds, the number of patients with this disorder has decreased dramatically. In reactions to bromides and iodides, there is epidermal hyperplasia that can develop pseudoepitheliomatous features with intraepidermal abscesses of neutrophils and eosinophils. Allergy to potassium bromide has been demonstrated in some patients by a lymphocyte-transformation test (175).

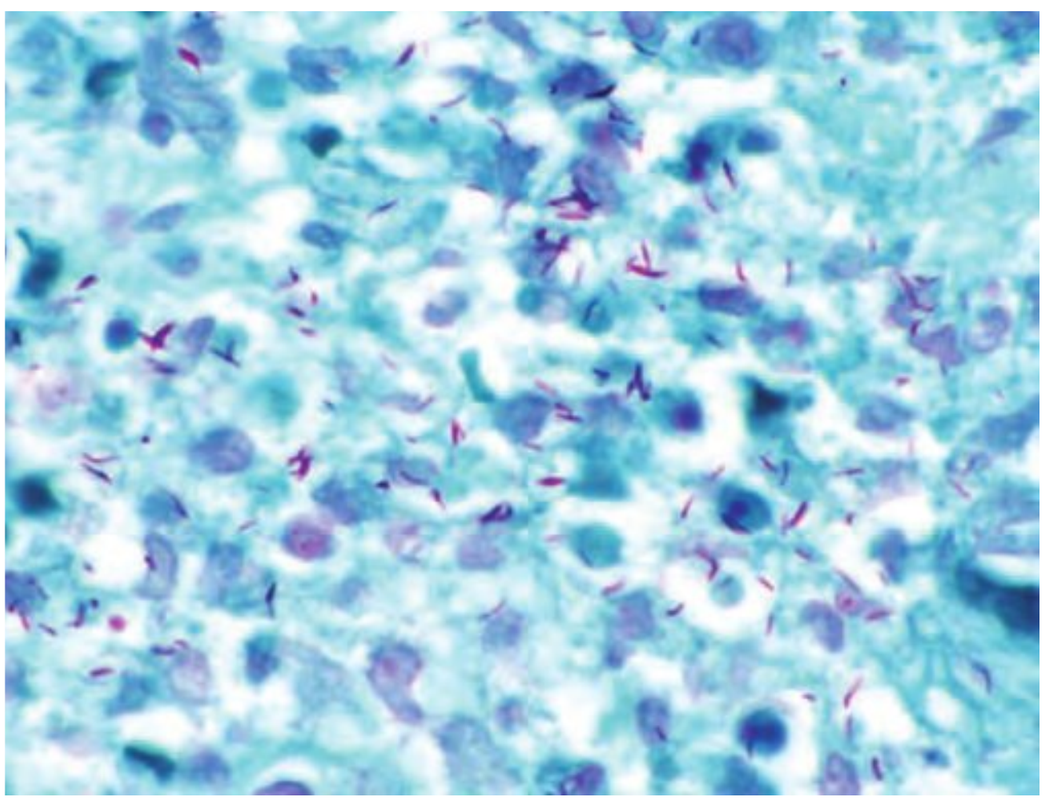
Painful lipomatous masses can develop in severely obese patients with histologic evidence of inflammation of nerves and endocrine abnormalities. This disease, called *adiposis dolorosa* or *Durcum's disease*, is rare, occurs in middle age, and affects females more than males (176,177).

Mycobacterial infection of the fat can produce a *mycobacterial panniculitis* that can mimic erythema nodosum (Fig. 20-37A) as well as erythema induratum (178). Special stains for acid-fast bacteria and cultures are important for the identification of the responsible mycobacteria (Fig. 20-37B). Often, nontuberculous mycobacteria are involved in countries with a low incidence of tuberculosis.

Morphea or scleroderma can produce a panniculitis that has dense infiltrates of lymphocytes and plasma cells at the



A



B

FIGURE 20-37 Mycobacterial panniculitis. Direct M. tuberculosis infection of the panniculus in an HIV-positive patient, which has produced primarily a paraseptal panniculitis with many eosinophils and macrophages adjacent to the septa. A: Erythema nodosum can be mimicked. B: Staining for mycobacteria shows that numerous red, acid-fast bacilli (arrow) are present in this example (AFB stain).

periphery of the fat lobules, particularly at the junction of deep reticular dermis and the subcutis. Characteristically, the septa are widened and have hyalinized sclerotic collagen. Similar changes in the collagen are noted in the overlying dermis in most cases. Some of the changes are similar to those of lupus panniculitis; therefore, immunofluorescence and serologic tests are needed to distinguish them (179–181). Discoid lupus erythematosus with panniculitis has more fibrinoid necrosis of the dermis, which stains more brightly eosinophilic than the staining of the pale sclerotic collagen bundles of morphea or scleroderma panniculitis.

Pyoderma gangrenosum can produce ulcers that are difficult to distinguish from those of an ulcerating primary panniculitis (31,182). However, the gross appearance of pyoderma gangrenosum is characteristic in the irregularity of the ulcers, the usual shallowness, and the undermined violaceous borders. Biopsies taken at the edges of the ulceration may show pustules and lymphocytic inflammation in the dermis with extension of the lymphoid cells into the septa and lobules of the panniculus. The lesions do not have the extensive granulomatous necrosis of the fat that is present in erythema induratum. Acute bullous lupus erythematosus, with its superficial neutrophilic infiltrates, can ulcerate and require immunofluorescence studies to distinguish it from pyoderma gangrenosum. The sterile abscesses of AAT deficiency panniculitis resemble those of pyoderma gangrenosum but extend deeper than pyoderma gangrenosum, which also lacks perilobular subcutaneous abscesses.

SYSTEMIC INTERACTIONS WITH SUBCUTANEOUS FAT

Subcutaneous fat has evolved as an important energy storage system, whose metabolism is set to store energy when food is abundant and to release energy when food is scarce. It also serves for cushioning and maintenance of body temperature. Consequently, pathologic changes in the adipose tissue can have effects on the general metabolic state of the patient. For example, recent studies have revealed a complex interaction between the adipocytes and certain receptors in the hypothalamus that control appetite (183). The protein *leptin* is produced in a constant fashion by adipocytes, with a level that correlates with the size and number of fat cells. When the fat is abundant, leptin levels are increased and normally inhibit the hypothalamus at centers that increase hunger and feeding activity. Children born with a genetic block in the hypothalamus that prevents a response to high blood leptin levels have excessive eating activity that leads to massive obesity. Massive obesity can lead to lymphedema, fat necrosis, and fibrosis, as examples of morphologic impact on the subcutis (184). There are also important systemic complications, including hypertension, and accelerated atherosclerosis. Insulin levels are increased in the blood of such infants, and muscular movement activity levels are low. In obese mice with a defect in leptin production, the administration of synthetic leptin will lead to weight loss. In contrast, in common obesity in adult humans, leptin levels are high in the blood, and the lack of reaction in the hypothalamus prevents a response to synthetic leptin administration. Leptin interaction with the normal hypothalamus can also influence the level of thyroid hormone, decrease reproductive activity, and interfere with inflammatory activity and immune function (185). Leptin-deficient mice (Ob/Ob) with a defective Ob gene are protected in experimental models of inflammation, including autoimmune encephalomyelitis, arthritis, and delayed hypersensitivity reactions. While the hormone production by adipose tissue may be related to increased metabolic energy demand during inflammation, its consequences are at an early level of study. Leptin derived from adipocytes and preadipocytes has been shown to have regulatory activity on Toll-like receptors of the innate immune system. Studies of whole adipose tissue have shown that on stimulation, inflammatory mediators are produced, including tumor necrosis factor (TNF)-alpha, IL-6, and IL-10. TNF-alpha regulates fat mass by decreased lipogenesis, increased lipolysis, and induction of insulin resistance and can initiate apoptosis in adipocytes and preadipocytes. IL-6 increases lipolysis. The balance between preadipocyte differentiation and apoptosis of adipocytes influences the number of adipocytes, even in adults. Apoptosis of adipocytes is likely to play an important role in the lipoatrophy/lipodystrophy syndrome of patients with HIV infection and treatment with protease inhibitors. Adipocytes also secrete the agouti peptide (an antagonist to the melanocortin receptor, with additional multiple paracrine functions). This peptide also functions in the control of peripheral lipid metabolism. Loss of function mutations in the melanocortin receptor gene are a cause of monogenic human obesity (186).

Recent studies have also indicated that cells isolated from adipose tissue, and classified as adipocytes or preadipocytes, express Toll-like receptors, which are the products of evolution based on a need for a very rapid response to certain lethal organisms, for which adaptive immunity may be too slow to save the patient. Approximately 10 Toll-like receptors have been identified, and they recognize different repetitive sequences on the surfaces of bacteria, including mycobacteria, and viruses. Activation of Toll-like receptors can stimulate the production of proinflammatory cytokines and chemokines and the expression of costimulatory molecules necessary for initiating a response of the adaptive immune system. The activation can include the chemoattraction of neutrophils and macrophages to the area. For example, activation of Toll-like receptor TLR-4 leads to activation of the nuclear transcription factor NFkB, which then activates genes that encode for proteins that are involved in the defense against infection. The need for a rapid response system in adipose tissue is most easily understood in the mesenteric fat, which is penetrated by bacterial antigens that filter in from small leaks in the intestinal permeability barrier. Perhaps such reactivity in adipose tissue in other regions, such as the lower legs, has evolved from breaks in the cutaneous permeability barrier (e.g., in the feet and toes). Also low-grade inflammation in the adipose tissue

appears to be important in its correlation with the syndrome of insulin resistance in obese diabetic patients (187). Future research in this area also seems likely to be productive in explaining some of the patterns of inflammation in subcutaneous fat that have been presented in this chapter.

In Memoriam. In July 2007, during the initial phases of this revision of this chapter, Dr. Abelardo Moreno succumbed to a brief illness in Barcelona. His loss is great to us and especially to the young dermatopathologists in training in Spain. His teaching efforts had a worldwide scope, and he pushed us all to do our best work. He remains a coauthor on this chapter in honor of his major contributions to it since the start of our work together.

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CHAPTER 21

Sebastian Lucas

Bacterial Diseases

A wide range of bacteria, including mycobacteria and rickettsia, affect the skin and subcutis. In the ensuing descriptions of the histopathology of most of the cutaneous bacterial infections that may be encountered by the diagnostic pathologists, reference is also made to some epidemiology, clinical features and pathophysiology. The pathogenesis of the skin lesions is multifactorial, including the following:

- Toxin production
- Pyogenic and granulation tissue chemoattractants
- Immunopathology (complement activation and cell-mediated immunity)
- Vasculitis

IMPETIGO

Two types of impetigo occur: impetigo contagiosa, or nonbullous impetigo, usually caused by group A streptococci; and bullous impetigo, including the staphylococcal scalded-skin syndrome, which is caused by *Staphylococcus aureus* (1).

Impetigo Contagiosa

Impetigo contagiosa is primarily an endemic disease of preschool-age children that may occur in epidemics. Very early lesions consist of vesicopustules that rupture quickly and are followed by heavy, yellow crusts. Most of the lesions are located in exposed areas. An occasional sequela is acute glomerulonephritis.

Histopathology. The vesicopustule arises in the upper layers of the epidermis above, within, or below the granular layer. It contains numerous neutrophils (Fig. 21-1). Not infrequently, a few acantholytic cells can be observed at the floor of the vesicopustule. Occasionally, gram-positive cocci can also be found within the vesicopustule, both within neutrophils and extracellularly (2).

The stratum malpighii underlying the bulla is spongiotic, and neutrophils often can be seen migrating through it. The upper dermis contains a moderately severe inflammatory infiltrate of neutrophils and lymphoid cells.

At a later stage, when the bulla has ruptured, the horny layer is absent, and a crust composed of serous exudate and the nuclear debris of neutrophils may be seen covering the stratum malpighii.

Pathogenesis. In the United States, group A streptococci used to be the most frequently recovered organisms in patients with impetigo contagiosa, either alone or in association with *S. aureus.* However, the predominant pathogen responsible for impetigo has changed, and *S. aureus* is the most common organism in the United States and United Kingdom (3).

Differential Diagnosis. Histologic differentiation of impetigo contagiosa from subcorneal pustular dermatosis and from pemphigus foliaceus can be difficult. However, only impetigo shows gram-positive cocci in the bulla cavity. In addition, pemphigus foliaceus usually shows fewer neutrophils, more acantholytic cells, and occasionally some dyskeratotic granular cells.

Bullous Impetigo and Staphylococcal Scalded-Skin Syndrome

Phage group II staphylococci may produce bullous impetigo and the staphylococcal scalded-skin syndrome.

Bullous impetigo occurs mainly in newborns, infants, and young children. Occasionally, it is observed in adults, particularly in those with deficiencies in cell-mediated immunity (4,5). It is characterized by vesicles that rapidly progress to flaccid bullae with little or no surrounding erythema. The contents of the bullae are clear at first; later on, they may be turbid. Bullous impetigo may spread and become generalized, so clinical distinction from staphylococcal scalded-skin syndrome may be impossible (6). An important difference, however, is that cultures from intact bullae of bullous impetigo, unlike those of the staphylococcal scalded-skin syndrome, grow phage group II *S. aureus.*

Staphylococcal scalded-skin syndrome, first described more than 100 years ago and also known as Ritter's disease, occurs largely in the newborn and in children younger than 5 years of age. It rarely occurs in adults or in older children (7–9) except in the presence of a severe underlying disease (10).

The disease begins abruptly with diffuse erythema and fever. Large, flaccid bullae filled with clear fluid form and

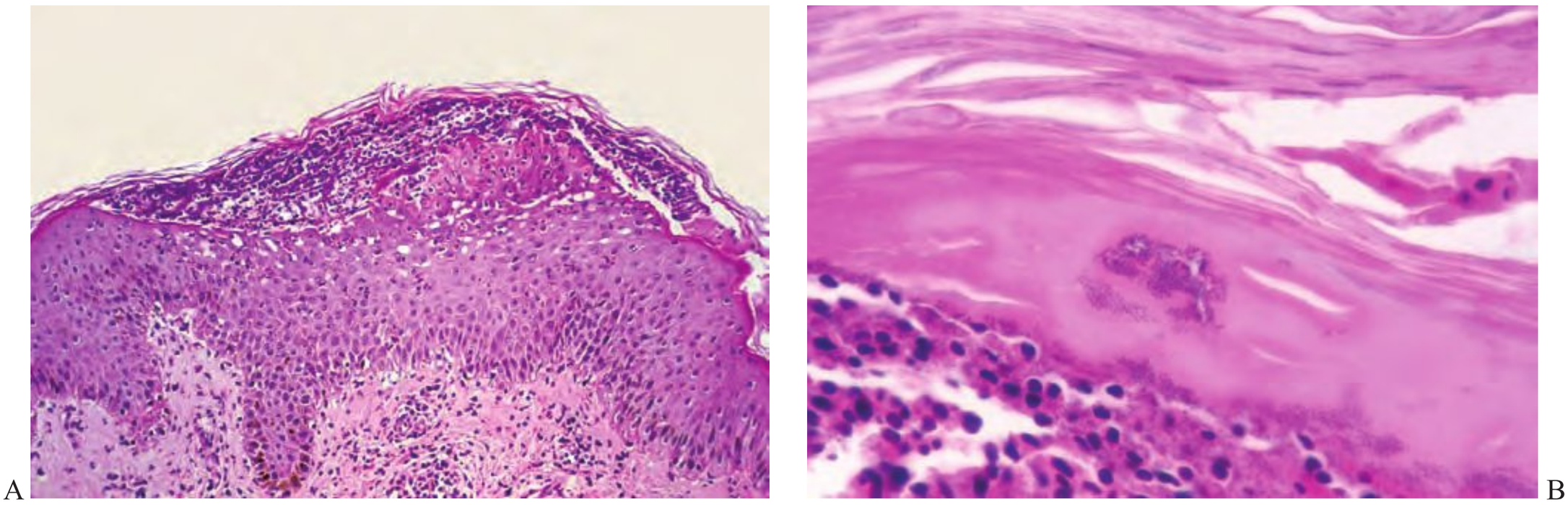


FIGURE 21-1. Impetigo contagiosa. A: In this relatively early lesion, neutrophils are seen in the upper epidermis, forming a subclone pustule. There is a superficial mixed infiltrate within the dermis. B: On closer inspection, neutrophils and bacterial colonies are seen within the stratum corneum. C: Yellow crusted vesiculopustules on the back of the hand of a child. (Part C image courtesy of C. Kovarik.)

rupture almost immediately. Large sheets of superficial epidermis separate and exfoliate. The disease runs an acute course and is fatal in <4% of all cases in children (11). Most fatalities occur in neonates with generalized lesions. In contrast, in the rare cases of staphylococcal scalded-skin syndrome occurring in adults, the prognosis is much worse, with a mortality rate exceeding 50%. Death is usually related to the coexistent disease or to immunosuppressive therapy given for it. Both bullous impetigo and staphylococcal scalded-skin syndrome are transmissible and can cause epidemics in nurseries, where they may occur together (12).

An important difference between the two diseases is that no phage group II staphylococci can be grown from the bullae of the staphylococcal scalded-skin syndrome, in contrast to the bullae of bullous impetigo. The absence of phage group II staphylococci from the bullae of staphylococcal scalded-skin syndrome results from the fact that these staphylococci are present at a distant focus. Usually, the distant focus is extracutaneous and consists of a purulent conjunctivitis, rhinitis, or pharyngitis. Rarely, the distant focus consists of a cutaneous infection or a septicemia.

Histopathology. In both bullous impetigo and staphylococcal scalded-skin syndrome, the cleavage plane of the bulla, like that in impetigo contagiosa, lies in the uppermost epidermis either below or, less commonly, within the granular layer. A few acantholytic cells are often seen adjoining the cleavage plane. However, in contrast to impetigo contagiosa, there are few or no inflammatory cells within the bulla cavity. In bullous impetigo, the upper dermis may show a polymorphous infiltrate, whereas in the staphylococcal scalded-skin syndrome, the dermis is usually free of inflammation.

Pathogenesis. The causative epidermolysins are the exfoliative toxins (ETs) produced by *S. aureus*. There are many strains of these serine protease enzymes. Their target is desmoglein-1, a desmosomal glycoprotein, which has a role in cell-to-cell adhesion in the superficial epidermis (13).

Electron microscopy shows that the cleavage plane of lesions in humans as well as in mice is at the interface between the spinous and granular layers, with some upward extension into the lower granular layer. Splitting occurs without damage to adjacent acantholytic keratinocytes. ET appears to act primarily on the intercellular substance, because in studies carried out on newborn mice, the intercellular spaces widen and microvilli form before the desmosomes separate within their interdesmosomal contact zone (14).

Differential Diagnosis. Both staphylococcal scalded-skin syndrome and severe erythema multiforme of the toxic epidermal necrolysis or Lyell type show clinically extensive detachment of the epidermis and thus may clinically resemble one another. This has resulted in confusion in the past; thus, at one time, both diseases were referred to as *Lyell's disease* or *toxic epidermal necrolysis*. However, the two diseases can be easily differentiated histologically; in severe erythema multiforme, the entire, or nearly the entire, epidermis detaches itself, with considerable necrosis of the epidermal cells, whereas in staphylococcal scalded-skin syndrome, only the uppermost portion of the epidermis becomes detached, with relatively slight damage to the underlying epidermal cells.

ECTHYMA

Ecthyma is essentially ulcerated impetigo contagiosa. It occurs chiefly below the knees as multiple crusted ulcers. It is clearly streptococcal in origin, because skin cultures are nearly always positive for group A streptococci. In addition, coagulase-positive staphylococci as secondary invaders can frequently be cultured from lesions (15).

Histopathology. A nonspecific ulcer is observed with numerous neutrophils both in the dermis and in the serous exudate at the floor of the ulcer.

ERYSIPELAS

Erysipelas is an acute superficial cellulitis of the skin caused by group A streptococci. It is characterized by the presence of a well-demarcated, slightly indurated, dusky red area with an advancing, palpable border. In some patients, erysipelas has a tendency to recur periodically in the same areas. In the early antibiotic era, the incidence of erysipelas appeared to be on the decline, and most cases occurred on the face. More recently, however, there appears to have been an increase in the incidence, and facial sites are now less common whereas erysipelas of the legs is predominant. Potential complications in patients with poor resistance or after inadequate therapy may include abscess formation, spreading necrosis of the soft tissue, infrequently necrotizing fasciitis, and septicemia (16). Nephritic and cardiac complications are rare, because erysipelas is usually produced by nonnephritogenic and nonrheumatogenic strains of streptococci.

Histopathology. The dermis shows marked edema and dilatation of the lymphatics and capillaries. There is a diffuse infiltrate, composed chiefly of neutrophils, that extends throughout the dermis and occasionally into the subcutaneous fat. It shows a loose arrangement around dilated blood and lymph vessels. If sections are stained with the Giemsa or Gram stain, streptococci are found in the tissue and within lymphatics.

In cases of recurring erysipelas, the lymph vessels of the dermis and subcutaneous tissue show fibrotic thickening of their walls with partial or complete occlusion of the lumen.

NECROTIZING FASCIITIS

Necrotizing fasciitis, like erysipelas, is usually caused by group A beta-hemolytic streptococci, and it shows rapidly spreading erythema. However, the erythema is ill-defined and progresses to painless ulceration and necrosis along fascial planes. Whereas erysipelas involves the more superficial layers of the skin, cellulitis extends more deeply into the subcutaneous tissues (17). Although virtually all cases of erysipelas are caused by beta-hemolytic streptococci, primarily group A, the differential diagnosis of cellulitis is much more extensive. In addition to group A streptococci, possible etiologic agents include *S. aureus* and, less frequently, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and (rarely) a laundry list of other organisms including vibrios, gram-negative bacteria such as pseudomonas, areromonas, clostridia, and other anaerobes, legionella, *Erysipelothrix rhusiopathiae,* and *Helicobacter cinaedi*. Minor trauma is frequently a predisposing factor, and there is a significant association with chicken pox in children (18). In these and other patients with necrotizing fasciitis due to group A streptococci, there may be onset of shock and organ failure, which are manifestations of the streptococcal toxic shock syndrome (TSS). Unless treated by wide surgical debridement, necrotizing fasciitis is often fatal (19). Probing of the subcutaneous tissue discloses extensive undermining and a serosanguineous exudate (20).

Histopathology. The histologic picture is characterized by necrosis and variable acute and chronic inflammation (Figs. 21-2 and 21-3). Sometimes, there is minimal inflammation, with only

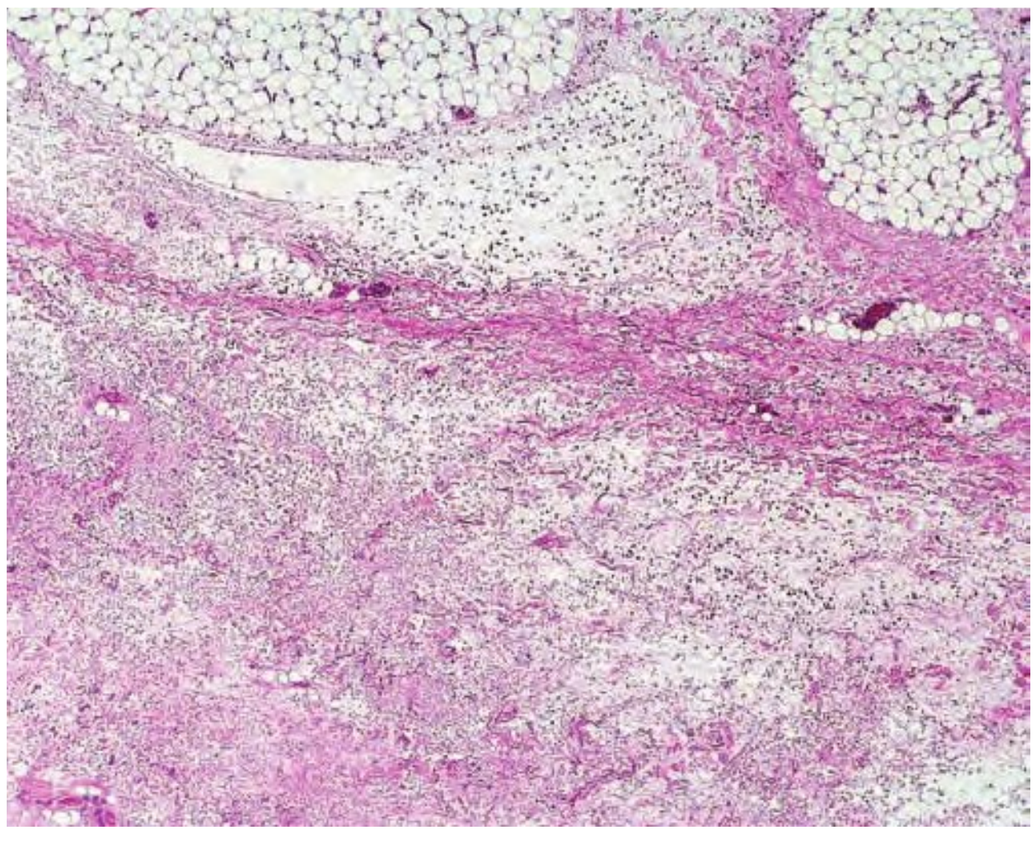


FIGURE 21-2. Necrotizing fasciitis. Subcutis fat with lower zone necrosis and mild inflammatory cells in upper zone (H&E stain).

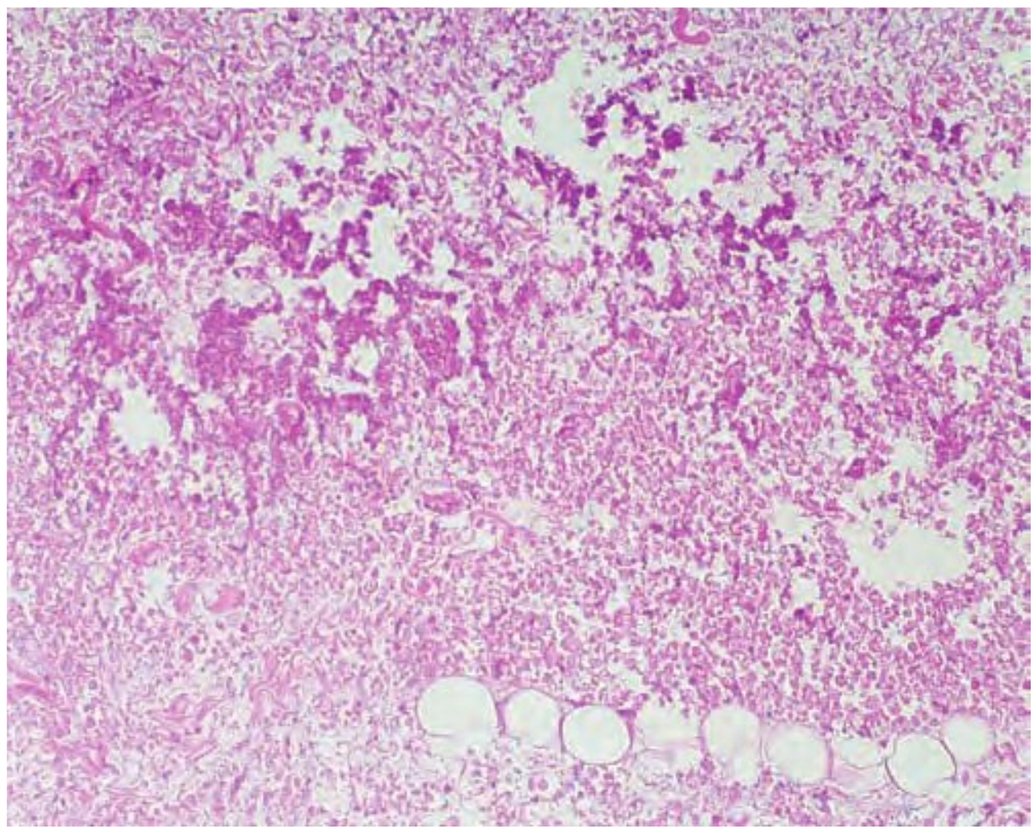


FIGURE 21-3. Necrotizing fasciitis. Higher power view of necrotic subcutis (H&E stain).

necrosis and clusters of bacteria (21). Clumps of gram-positive bacteria are usually present (Fig. 21-4). Often, there is thrombosis of blood vessels as the result of damage to vessel walls from the inflammatory process. The key feature in distinguishing necrotizing fasciitis from a less threatening superficial cellulitis is the location of the inflammation. In the former, the inflammation involves the subcutaneous fat, fascia, and muscle in addition to the dermis. A biopsy may be submitted at the time of surgical debridement for frozen section examination. In an appropriate setting, the presence of edema and neutrophils in these deep locations supports the diagnosis; frank necrosis may not be demonstrable, and bacteria are frequently not evident in an initial biopsy (22).

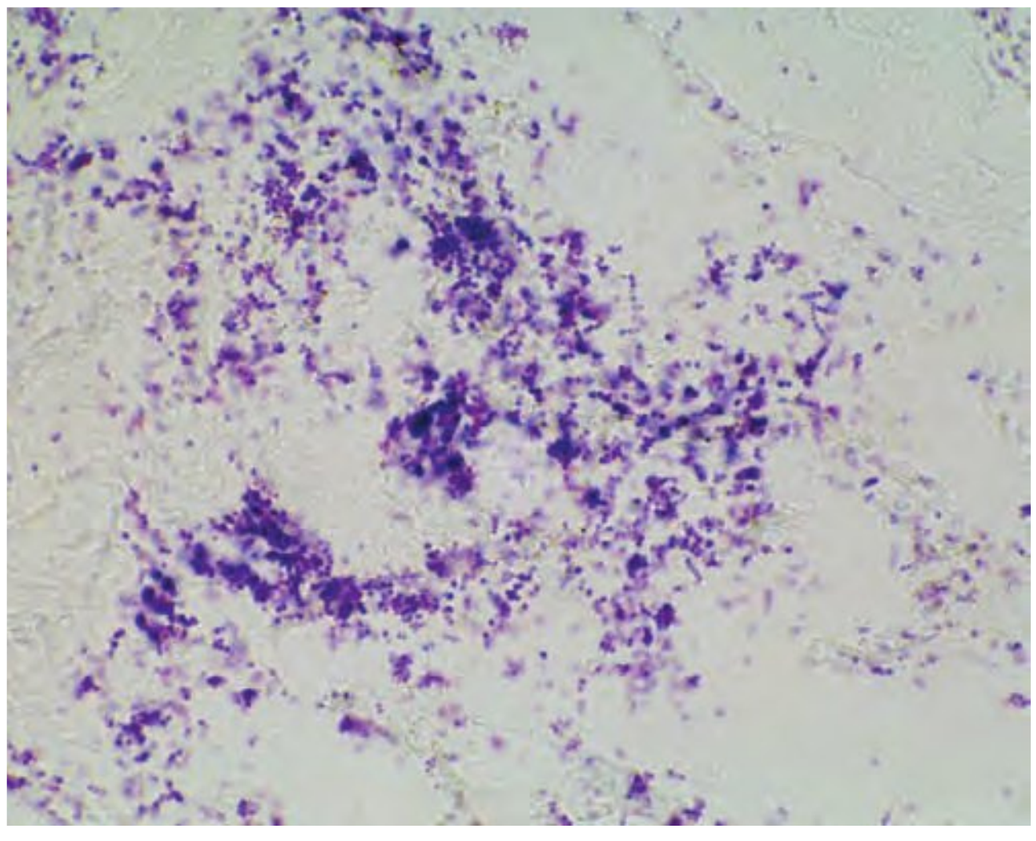


FIGURE 21-4. Necrotizing fasciitis. Clusters of gram-positive streptococci. Note the chains of cocci (Gram stain).

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS SKIN INFECTIONS

Methicillin-resistant *S. aureus* skin infections have been recently reviewed by Cohen (23). Infection caused by community-acquired methicillin-resistant *S. aureus* (CAMRSA) is considered to represent a worldwide epidemic, often presenting as an infectious skin lesion. Athletes, certain ethnic populations, children, homeless persons, homosexual men, household members of infected people, HIV-infected patients, intravenous drug abusers, military personnel, newborns, pregnant and postpartum women, tattoo recipients, and urban dwellers of lower socioeconomic status in crowded living conditions are said to be at increased risk of developing CAMRSA infection. Colonization by *S. aureus* in patients whose skin barrier is disrupted represents a potential reservoir for CAMRSA. In addition, infection-associated risk factors are absent in many individuals who develop cutaneous CAMRSA infection. The most common presentations of CAMRSA infection are abscess, cellulitis, or both, not uncommonly misinterpreted by the patient as spider insect bites. Other manifestations of cutaneous CAMRSA infection are impetigo, folliculitis, and paronychia. Incision and drainage of abscesses, systemic antibacterial therapy, and adjunctive topical antibacterial treatment are the essential components of management of CAMRSA skin infections. The spread of cutaneous CAMRSA infection can potentially be prevented by a combination of personal, environmental, and health care measures directed at eliminating the causes of acquisition and transmission of the bacteria (23).

ACUTE SUPERFICIAL FOLLICULITIS

Folliculitis may involve the superficial, middle, or deep portion of the hair follicle and may be caused by a variety of etiologies, not all infectious. The common staphylococcal superficial folliculitis is the prototype (Figs. 21-5 and 21-6).

Impetigo of Bockhart

Impetigo of Bockhart, caused by staphylococci, is characterized by an eruption of small pustules, many of which are pierced by hairs.

Histopathology. Impetigo of Bockhart presents a subcorneal pustule situated in the opening of a hair follicle. The upper portion of the hair follicle is surrounded by a considerable inflammatory infiltrate composed predominantly of neutrophils.

Pseudomonas Folliculitis

In recent years, patients have exhibited outbreaks of pruritic macules, papules, and follicular pustules after using heated swimming pools, whirlpools, or hot tubs. The eruption



FIGURE 21-5. Acute folliculitis. Multiple follicular pustules on the scalp. Gram-positive cocci were demonstrated in the exudate. (Image courtesy of C. Kovarik.)

usually starts 8 to 48 hours after exposure in a contaminated facility and usually resolves spontaneously within 7 to 10 days (24).

Histopathology. There is distension and disruption of a hair follicle, the pilar canal, of which is filled with a dense infiltrate of neutrophils. There also is a perifolliculitis, and the epithelium of the hair follicle may be disrupted (25).

Pathogenesis. The causative organism is *Pseudomonas aeruginosa*, which is ubiquitous in nature and may be found in soil, in fresh water, and on human skin. Proper chlorination and maintenance of pools decrease the population of *Pseudomonas*.

ACUTE DEEP FOLLICULITIS (FURUNCLE)

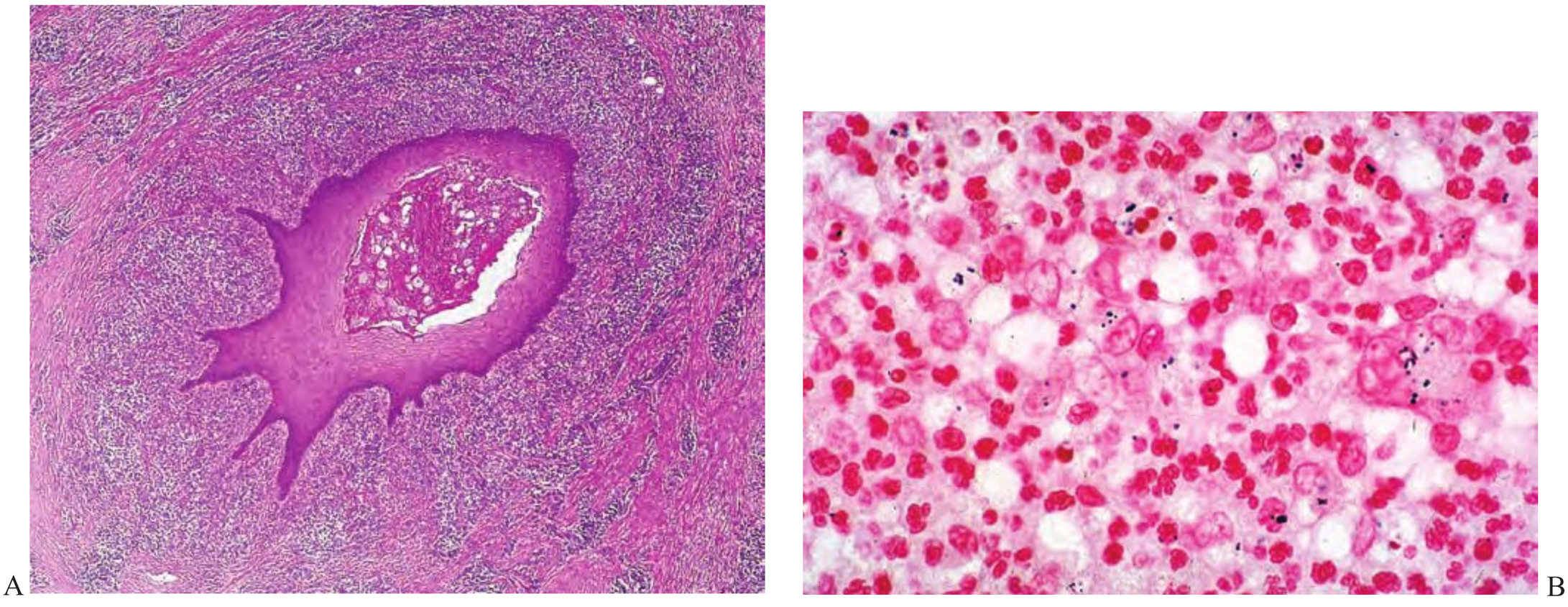
A furuncle is caused by staphylococci and consists of a tender, red, perifollicular swelling terminating in the discharge of pus and of a necrotic plug (Fig. 21-7).

Histopathology. A furuncle shows an area of perifollicular necrosis containing fibrinoid material and many neutrophils. At the deep end of the necrotic plug, in the subcutaneous tissue, is a large abscess. A Gram stain shows small clusters of staphylococci in the center of the abscess (26).

CHRONIC SUPERFICIAL FOLLICULITIS

Acne varioliformis, or acne necrotica, is characterized by recurrent, small, indolent, follicular papules on the forehead and scalp. The lesions undergo central necrosis and usually heal with small, pitted scars (27).

Histopathology. Early lesions show a marked perifollicular lymphocytic infiltrate with exocytosis of lymphocytes into the external root sheath. This is followed by necrosis of the hair follicle and of the perifollicular epidermis. Late lesions have central cores of necrotic tissue.



A B

FIGURE 21-6. Acute folliculitis. A: Hair shaft with early internal inflammation and perifolliculitis (H&E stain). B: Gram-positive cocci visible in the inflammation (Gram stain).



FIGURE 21-7. Furuncle. A deep-seated cutaneous tender, red, perifollicular swelling with a superficial scale, which may terminate in the discharge of pus. (Image courtesy of R. Lee.)

CHRONIC DEEP FOLLICULITIS

Folliculitis barbae is a deep-seated infection of the bearded region in men. There are follicular papules and pustules followed by erythema, crusting, and boggy infiltration of the skin. Abscesses may or may not be present. Scarring and permanent hair loss usually ensue.

Folliculitis decalvans occurs predominantly in men. Scattered through the scalp are bald, atrophic areas showing follicular pustules at their peripheries. In some instances, other hairy areas, such as the bearded and pubic regions and the axillae and the eyebrows and eyelashes, are also involved. Through peripheral spreading, the atrophic areas gradually increase in size (28).

Folliculitis keloidalis nuchae represents a chronic folliculitis on the nape of the neck in men that causes hypertrophic scarring. In early cases, there are follicular papules, pustules, and occasionally abscesses. The lesions are replaced gradually by indurated fibrous nodules.

Histopathology. In early lesions of all three forms of chronic deep folliculitis, a perifollicular infiltrate composed largely of neutrophils but also containing lymphoid cells, histiocytes, and plasma cells is observed. The infiltrate develops into a perifollicular abscess leading to destruction of the hair and hair follicles. Older lesions show chronic granulation tissue containing numerous plasma cells as well as lymphoid cells and fibroblasts. Often, foreign body giant cells are present around remnants of hair follicles, and particles of keratin may be located near the giant cells. As healing takes place, fibrosis is observed. If there is hypertrophic scar formation, as in folliculitis keloidalis nuchae, numerous thick bundles of sclerotic collagen are present.

PSEUDOFOLLICULITIS OF THE BEARD

Pseudofolliculitis of the beard represents a foreign body inflammatory reaction surrounding an ingrown beard hair. It occurs in men with curly hair, especially blacks, who shave closely. Clinically, follicular papules and pustules resembling those of a bacterial folliculitis are observed.

Histopathology. As a result of its curvature, the advancing sharp free end of the hair, as it approaches the skin, causes an invagination of the epidermis accompanied by inflammation and, often, an intraepidermal microabscess. As the hair enters the dermis, a more severe inflammatory reaction develops with downgrowth of the epidermis in an attempt to ensheath the hair. This is accompanied by abscess formation within the pseudofollicle and a foreign body giant cell reaction at the tip of the invading hair (29).

FOLLICULAR OCCLUSION TRIAD (HIDRADENITIS SUPPURATIVA, ACNE CONGLOBATA, AND PERIFOLLICULITIS CAPITIS ABSCEDENS ET SUFFODIENS)

Hidradenitis suppurativa, acne conglobata, and perifolliculitis capitis abscedens et suffodiens, the three diseases included in the follicular occlusion triad, have similar pathogeneses and similar histopathologic findings. Quite frequently, two of the three diseases, and occasionally all three diseases, are encountered in the same patient (30). All three diseases represent a chronic, recurrent, deep-seated folliculitis resulting in abscesses and followed by the formation of sinus tracts and scarring. Although the primary etiology of these conditions is not bacterial, they are discussed in this chapter because the differential diagnosis includes the deep bacterial folliculitides.

In *hidradenitis suppurativa*, the axillary and anogenital regions are affected. Acute and chronic forms can be distinguished (31). The acute form exhibits red, tender nodules that become fluctuant and heal after discharging pus. In the chronic form, deep-seated abscesses lead to the discharge of pus through sinus tracts. Severe scarring results (32).

Acne conglobata, an entity different from acne vulgaris, occurs mainly on the back, buttocks, and chest and only rarely on the face or the extremities. In addition to comedones, fluctuant nodules discharging pus or a mucoid material occur as well as deep-seated abscesses that discharge through interconnecting sinus tracts.

In *perifolliculitis capitis abscedens et suffodiens,* nodules and abscesses as described for acne conglobata occur in the scalp.

Pilonidal sinus is often considered to be a part of this group of disorders ("follicular occlusion tetrad"). Its pathogenesis appears to be similar, and it is often present in patients with one or more of the other members of the group.

Histopathology. Early lesions in all three diseases of the follicular occlusion triad show follicular hyperkeratosis with plugging and dilatation of the follicle. The follicular epithelium may proliferate or be destroyed (Figs. 21-8 and 21-9). At first there is little inflammation, but eventually a perifolliculitis develops with an extensive infiltrate composed of neutrophils, lymphocytes, and histiocytes. Abscess formation results and leads to the destruction first of the pilosebaceous structures and later also of the other cutaneous appendages. Apocrine glands in hidradenitis suppurativa of the axillae or groin regions may be secondarily involved by the inflammatory process. In response to this destruction, granulation tissue containing lymphoid and plasma cells, and foreign body giant cells related to fragments of keratin and to embedded hairs, infiltrates the area near the remnants of hair follicles. As the abscesses extend deeper into the subcutaneous tissue, draining sinus tracts develop that are lined with epidermis. In areas of healing, extensive fibrosis may be observed (30).

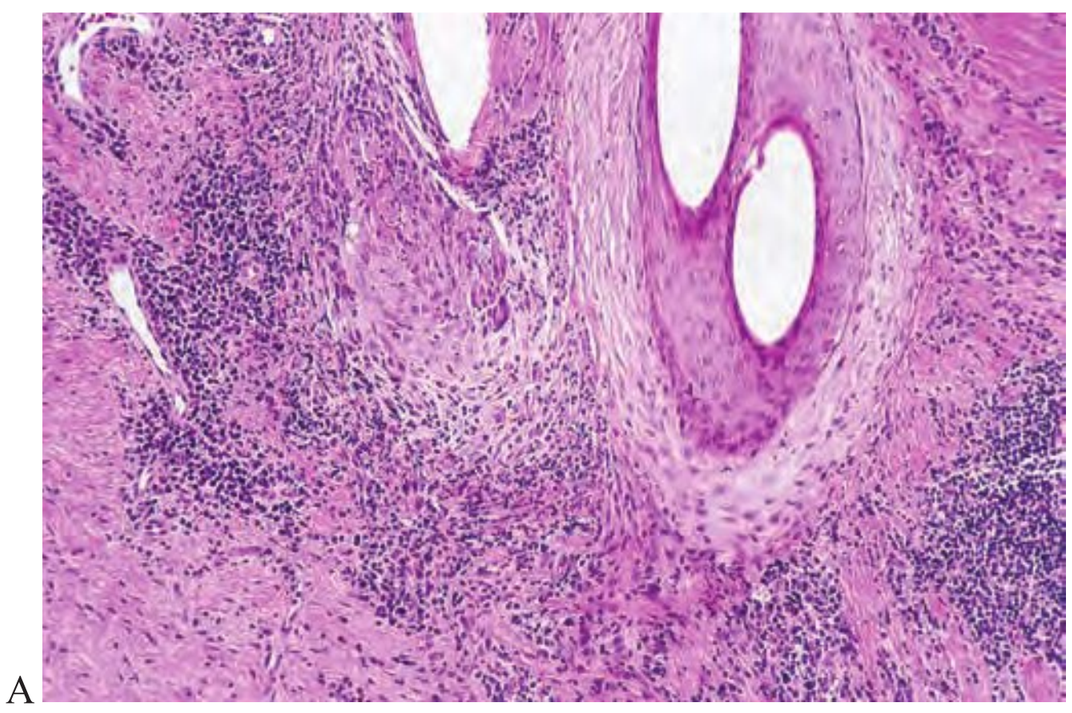
Pathogenesis. The common initiating event in the three diseases of the follicular occlusion triad appears to be follicular hyperkeratosis leading to retention of follicular products. Thus, the designation *hidradenitis suppurativa* is a misnomer, because involvement of apocrine as well as of eccrine glands represents a secondary phenomenon and is the result of extension of the inflammatory process into deep structures.

It appears doubtful that the diseases comprising the follicular occlusion triad are caused primarily by bacterial infection, because cultures from unopened abscesses often are negative (33).

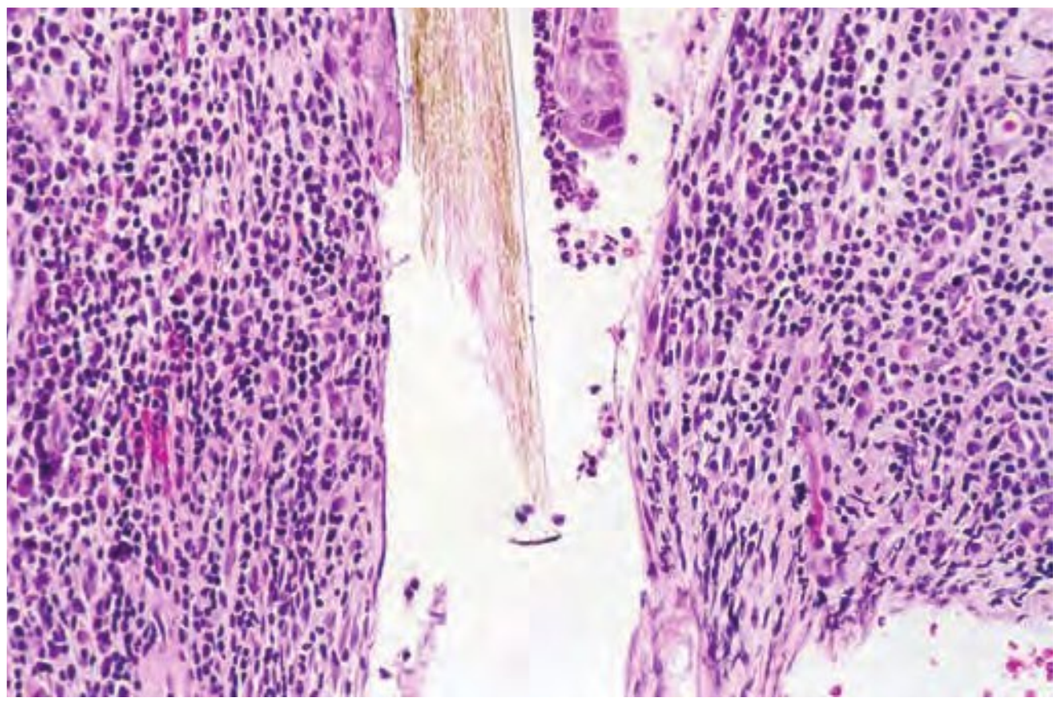


FIGURE 28-8. Follicular occlusion disorder. Dissecting cellulitis of the scalp, low power. Early lesions may show follicular plugging with acute perifollicular inflammation. Eventually, the follicle is destroyed and replaced by dense mixed inflammation. The appearances are indistinguishable from hidradenitis suppurativa.

The beneficial effect of the internal administration of corticosteroid suggests that the three diseases represent antigen-antibody reactions resulting in tissue breakdown. Defects in cell-mediated immunity exist in some patients with hidradenitis suppurativa.



A



B

FIGURE 28-9. Follicular occlusion disorder. A: Dissecting cellulitis of the scalp, medium power. Perifollicular fibrosis ensues and is accompanied by granulomatous inflammation in reaction to follicular contents. Advanced lesions may show sinus tract formation. B. Dissecting cellulitis of the scalp, high power. The follicular epithelium is almost completely destroyed, leaving a hair shaft exposed to the dermis and a mixed infiltrate of neutrophils, lymphocytes, histiocytes, and plasma cells.

BLASTOMYCOSIS-LIKE PYODERMA (PYODERMA VEGETANS)

Two entirely different diseases have been described under the term *pyoderma vegetans* or *pyodermite végétante of Hallopeau*. One disease, now referred to as *pemphigus vegetans of Hallopeau*, shows the typical intercellular immunofluorescence of the pemphigus group on direct immunofluorescence testing. The other disease represents a vegetating tissue reaction, possibly secondary to bacterial infection (34). In order to emphasize the difference between it and pemphigus vegetans of Hallopeau, it is preferable to refer to this disease as *blastomycosis-like pyoderma* rather than *pyoderma vegetans* (35).

Blastomycosis-like pyoderma shows one or multiple large, verrucous, vegetating plaques with scattered pustules and elevated borders. The plaques show considerable resemblance to those observed in fungal blastomycosis. The location of the plaques varies considerably from case to case. In some instances, the face and legs are affected; in others it is the intertriginous areas. Some authors have observed an association with ulcerative colitis (36).

Histopathology. The two major features of blastomycosis-like pyoderma are pseudocarcinomatous hyperplasia and multiple abscesses in the dermis as well as in the hyperplastic epidermis. The abscesses are composed of neutrophils in some cases and of eosinophils in others.

Pathogenesis. Bacteria, most commonly *S. aureus*, can be found regularly in blastomycosis-like pyoderma; however, the presence of several different strains and the variable response of patients to antibiotic therapy suggest that the bacteria are secondary invaders, although they may be responsible for the vegetating tissue reaction. A deficiency in cellular immunity (37) and a decrease in the chemotactic activity of the neutrophils have also been observed.

Differential Diagnosis. In cases with largely eosinophils in the abscesses, pemphigus vegetans must be excluded by direct immunofluorescence. If there is marked pseudocarcinomatous hyperplasia, multiple biopsies may be necessary for differentiation from true squamous cell carcinoma.

TOXIC SHOCK SYNDROME

TSS is an acute febrile illness usually caused by certain toxin-producing strains of *S. aureus*. Occasionally, however, group A beta-hemolytic *Streptococcus* can cause this illness (38). In the initial report in 1978, the disease was described in a series of seven children (39). Although many cases have been associated in recent years with the use of superabsorbent vaginal tampons by menstruating women, additional reported settings for TSS have included surgical wound infections of the skin (40), empyema, fasciitis, osteomyelitis, peritonsillar abscesses, and other infections (41). Fever, hypotension or shock, an extensive rash resembling scarlet fever or sunburn, and involvement of three or more organ systems are the initial defining manifestations, whereas desquamation occurs 1 to 2 weeks after the onset. In rare instances, bullae are also present (42). In addition, there may be a conjunctivitis and an oropharyngitis. Internal organs may be affected by a toxic encephalopathy, thrombocytopenia, renal failure, or hepatic damage. Mortality has been estimated at 5% to 10% (43).

Histopathology. Although in some cases the findings in the skin are not specific, in most instances the histologic findings are quite characteristic, consisting of a superficial perivascular and interstitial mixed-cell infiltrate containing neutrophils and sometimes eosinophils, foci of spongiosis containing neutrophils, and scattered necrotic keratinocytes that sometimes are arranged in clusters within the epidermis (44). If bullae are present, they are subepidermal in location.

Pathogenesis. Even though in rare cases *S. aureus* bacteremia occurs, the cause of TSS is a toxin that is produced locally at the site of a toxigenic staphylococcal infection. Several toxins have been implicated in TSS, including toxic shock syndrome toxin-1 (TSST-1) and the staphylococcal enterotoxins B, C, and F (45). Susceptibility to disease correlates with absence of protective antibodies to the toxin, and cytokine activation may be involved in some aspects of its pathogenesis. Streptococcal TSS has been associated with bacteriemia and extensive necrotizing fasciitis, unlike the staphyloccocal syndrome usually associated with occult or minor focal infections. Streptococcal TSS appears to be caused also by toxins produced by the bacteria, including pyrogenic exotoxin A, that shares some homologies with TSST-1 (46).

ACUTE SEPTICEMIA

Three types of acute fulminating septicemia have cutaneous manifestations that are diagnostically significant. They are those caused by *Neisseria meningitidis*, *Pseudomonas*, and *Vibrio vulnificus*.

Acute Meningococcemia

Fulminating septicemic infections with *N. meningitidis* exhibit extensive purpura consisting of both petechiae and ecchymoses. The centers of the petechiae may show small pustules. In addition, shock, cyanosis, and severe consumption coagulopathy occur (47). Without treatment, death may result within 12 to 24 hours. On autopsy, extensive hemorrhaging is found in many internal organs, especially the lungs, kidneys, and adrenals.

On rare occasions, acute septicemia with purpura can be produced by other organisms, such as *Diplococcus pneumoniae*, *Streptococcus*, or *S. aureus* (48).

Histopathology. The cutaneous petechiae and ecchymoses show, in many dermal vessels, thrombi composed of neutrophils, platelets, and fibrin. In addition, there is an acute vasculitis with considerable damage to the vascular walls resulting in large and small areas of hemorrhaging into the tissue. Neutrophils and nuclear dust are present within and around the damaged vessels. In most instances, many meningococci can be demonstrated in the luminal thrombi, within vessel walls, and around vessels as gram-negative diplococci. They are

present in the cytoplasm of endothelial cells and neutrophils and also extracellularly. Intraepidermal and subepidermal pustules filled with neutrophils may also be observed (49).

Pathogenesis. In the past, vascular collapse and death were attributed to massive bilateral hemorrhaging into the adrenal glands and were known as the *Waterhouse-Friderichsen syndrome*. However, it was then learned that death can occur without significant damage to the adrenals. Therefore, it was assumed that the generalized hemorrhagic diathesis was caused by the consumptive depletion of plasma clotting factors and the resulting disseminated intravascular coagulation (50). It seems likely, however, that there are two distinct pathogenic mechanisms operating in acute meningococcemia (47). First, a shocklike terminal phase is associated with the development of widespread thrombosis of the pulmonary microcirculation. These thrombi, which are caused by meningococcal toxins, are composed of leukocytes and fibrin and often also contain meningococci. They produce severe cor pulmonale, which cannot be prevented by treatment with heparin. Similar microthrombi are found also in the skin, spleen, heart, and liver. Second, a meningococcal endotoxin produces disseminated intravascular coagulation resulting in thrombi composed of fibrin only. These thrombi are found in the capillaries of the adrenal cortex and the kidneys and may cause hemorrhagic infarction of the adrenal glands and renal cortical necrosis. This secondary phase of the disease can be modified with heparin therapy, but its control does not improve survival, because the adrenal and renal lesions are not immediately life threatening, in contrast to the pulmonary lesions, which result in shock and death.

Pseudomonas Septicemia

The classic and diagnostic cutaneous lesions of *P. aeruginosa* or *Pseudomonas cepacia* septicemia are referred to as *ecthyma gangrenosum*. *Pseudomonas* septicemia usually occurs in debilitated, leukemic, or severely burned patients, particularly after they have received treatment with several antibiotics. The cutaneous lesions may be single but usually are multiple. They consist of punched-out ulcers about 1 cm in diameter that have hemorrhagic borders. They usually are preceded by hemorrhagic bullae (51). In Tzanck smears prepared from the bases of the lesions, gram-negative rods can be identified, confirming the diagnosis. In rare instances of *Pseudomonas* septicemia, multiple large, indurated, subcutaneous nodules are observed in addition to the cutaneous ulcers (52,53).

Occasionally, lesions of ecthyma gangrenosum have been observed in immunocompromised patients without bacteremia; these cases have better prognoses (54).

Histopathology. At their bases, the ulcers show a necrotizing vasculitis with only scant neutrophilic infiltration and little nuclear dust. There is, however, extensive bacillary infiltration of the perivascular region and of the adventitia and media of blood vessels. Nevertheless, the intima and the lumen usually are spared (55). *Pseudomonas* bacilli first invade the walls of the deep subcutaneous vessels and then spread along the surfaces of the vessels to the dermis (56). By causing perivascular and vascular necrosis, the bacilli cause extravasation of erythrocytes and the formation of ulcers (Fig. 21-10).

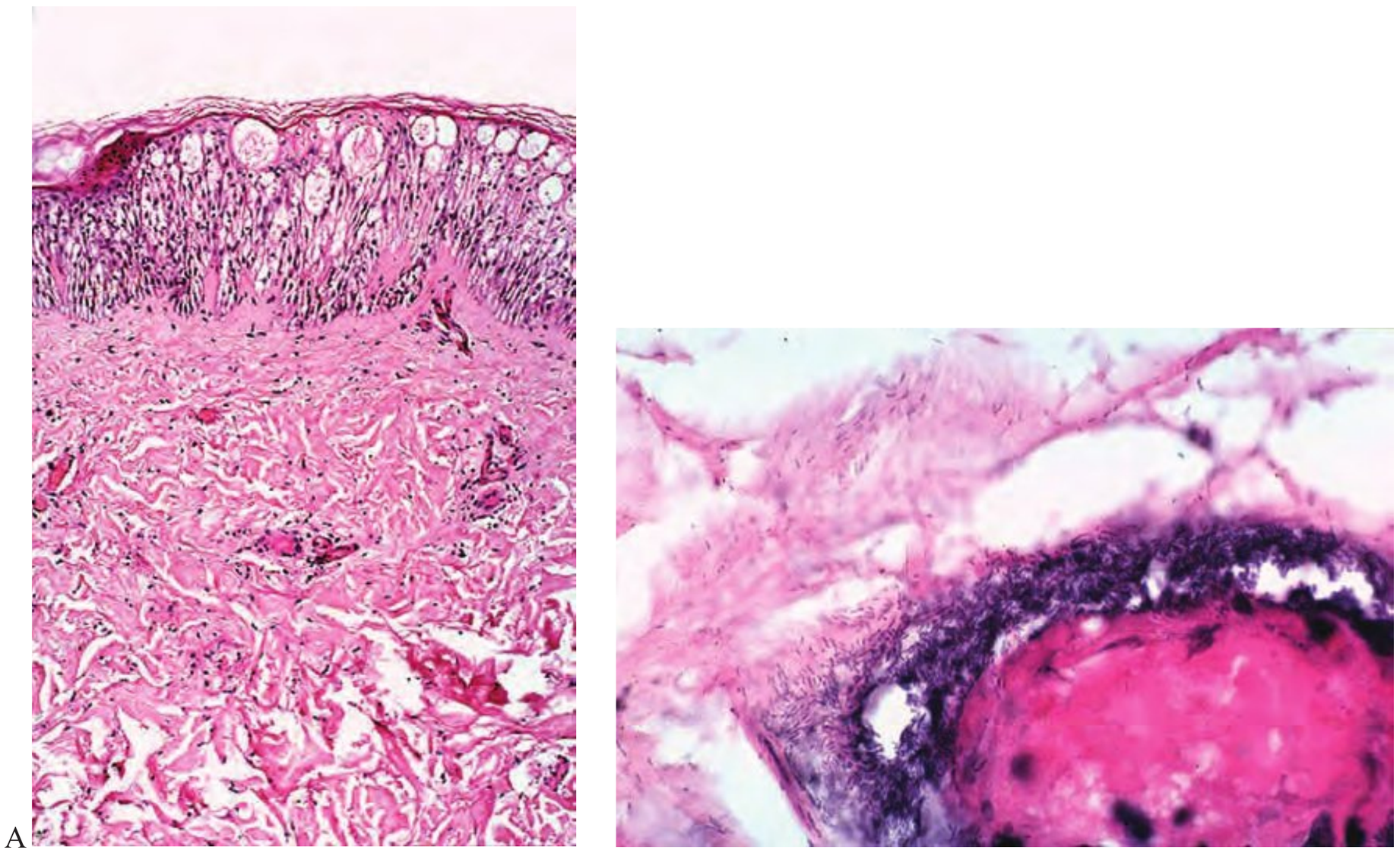


FIGURE 21-10. Pseudomonas septicemia. A: Skin showing infarction of epidermis, with abnormal middermal vessels (H&E stain). In later lesions, a "punched-out" ulcer typically develops. B: Bacilli infiltrating the deep vessel wall and into the surrounding dermis. The lumen is thrombosed. There is no inflammation (H&E stain).

The subcutaneous nodules are the result of cellulitis caused by the presence of large numbers of *Pseudomonas* bacilli (52).

Vibrio Vulnificus Septicemia

V. vulnificus infections occur in coastal regions of the United States. Raw seafood consumption, particularly raw oysters, or wounds acquired in marine environments can cause the infection. *V. vulnificus* is a virulent pathogen, producing significant morbidity and, unless treated, mortality, especially in patients with cirrhosis of the liver.

Striking skin lesions are an early sign of septicemic infection. Indurated plaques show blue discoloration, vesicles, and bullae. Large ulcers may develop (57).

Histopathology. Noninflammatory bullae form as the result of dermal necrosis, which is caused by the extracellular toxin produced by the bacterium. Clusters of bacteria may be seen in dermal vessels without associated dermal infiltrate (58).

Pathogenesis. *V. vulnificus* is a gram-negative rod that is motile by means of a single polar flagellum. It can be isolated from the blood and bullae of patients with this infection.

CHRONIC SEPTICEMIA

Meningococcemia and gonococcemia can occur in association with a chronic intermittent, benign eruption.

Chronic Meningococcemia

In patients with partial immunity to *N. meningitidis*, an infection with this organism produces chronic meningococcemia. This disease is characterized by recurrent attacks of fever, each lasting about 12 hours, associated with migratory joint pains and a papular and petechial eruption. Positive blood cultures are obtained during the febrile attacks.

Histopathology. The cutaneous lesions of chronic meningococcemia, in contrast to those of acute meningococcemia, show no bacteria and no vascular thrombosis or necrosis. Instead, a perivascular infiltrate composed largely of lymphoid cells and only a few neutrophils is observed in popular lesions (59,60). In petechial lesions, in addition to a limited area of perivascular hemorrhage, a fairly high percentage of neutrophils and fibrinoid material in the walls of the vessels may be found; thus, the histologic picture resembles that of a leukocytoclastic vasculitis (Fig. 21-11). The presence of meningococci may be difficult to demonstrate.

Chronic Gonococcemia

Patients with chronic gonococcemia, also referred to as *disseminated gonococcal infection* (61), like those with chronic meningococcemia, have intermittent attacks of fever and polyarthralgia. The cutaneous lesions of the two diseases are also similar, except that those of chronic gonococcemia are few in number and have a predominantly acral distribution. In contrast to chronic meningococcemia, there are often, in addition to papules and petechiae, vesicopustules with hemorrhagic halos and, rarely, hemorrhagic bullae. Blood cultures often are positive for *Neisseria gonorrhoeae*, but only during attacks of fever. A search for gonococci should also be made in possible sites of primary infection.

Histopathology. The capillaries in the upper dermis and middermis are surrounded by an infiltrate of neutrophils and a variable admixture of mononuclear cells and red cells. There often is nuclear dust, as in leukocytoclastic vasculitis. Fibrinoid material may be present in the walls of some vessels, and fibrin thrombi in some lumina (62). Pustular lesions are usually

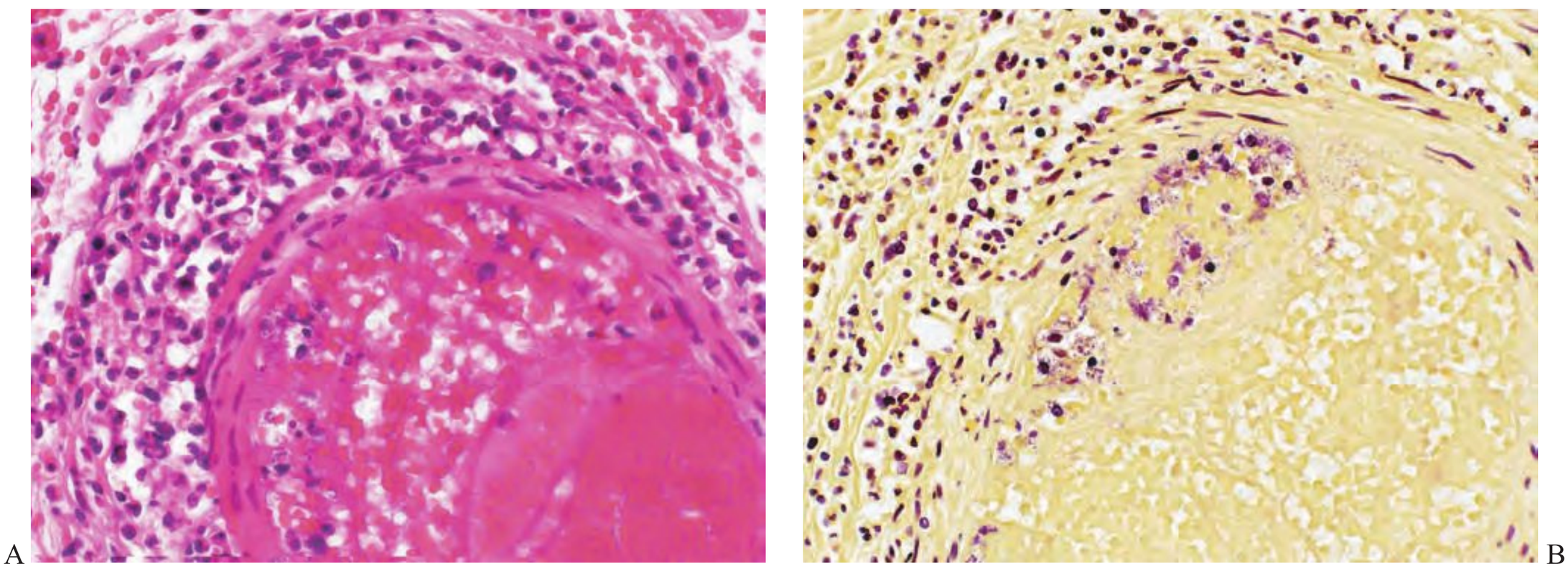


FIGURE 21-11. Meningococcal sepsis. A: Skin vasculitis. Inflamed dermal vessel. B: Skin vasculitis. Brown-Hopps Gram stain showing gram-negative cocci in the monocytes and within the vessel wall.

observed in intraepidermal locations with neutrophils both within them and in the underlying dermis (63). Bullae are subepidermal in location (64).

Gram-negative diplococci are observed in tissue sections only on rare occasions in the walls of blood vessels (65). They are found more readily in direct smears of pus from freshly opened pustules. It is of interest that direct smears reveal gonococci more commonly than cultures (66). However, *N. gonorrhoeae* can frequently be identified in tissue sections by use of fluorescent-antibody techniques (67). For this purpose, fluorescein-labeled antigonococcus globulin is used. Diplococci, as well as single cocci and disintegrated antigenic material, are then observed, largely in perivascular locations. The reason that direct smears are more apt to show diplococci than cultures and that the fluorescent-antibody technique is particularly effective in demonstrating gonococci is that smears and the fluorescent-antibody technique are not dependent on living organisms, as are cultures.

Pathogenesis. Whereas most strains of gonococci are susceptible to the bactericidal action of normal serum, those causing disseminated gonococcal infection are resistant (61).

MALAKOPLAKIA

Malakoplakia may affect various organs, most commonly the urinary tract and the gastrointestinal tract (68). In rare instances, it involves the skin (69,70). The lesions are the result of an inability of macrophages to phagocytose bacteria adequately. The most common organism grown in cultures of tissue material is *Escherichia coli* (71), but in some instances, other bacteria such as *S. aureus*, *Rhodococcus equi*, and nontuberculosis mycobacteria (72) are cultured. Some patients with lesions of malakoplakia have altered immune responsiveness as a result of carcinoma, autoimmune systemic diseases such as systemic lupus erythematosus, or immunosuppressive therapy for lymphoma or for renal transplantation (73).

Cutaneous malakoplakia lesions are chronic and may be associated with internal lesions. The appearance of the cutaneous lesions is nonspecific and variable. Most commonly, a fluctuant area, a draining abscess, draining sinuses, or an ulcer is observed; however, in some patients, a solitary, tender nodule or a cluster of tender papules is observed. The cutaneous disease is benign and self-limited.

Histopathology. There are sheets of large histiocytes containing fine, eosinophilic granules in their cytoplasm. In addition to the granules, many of them contain ovoid or round basophilic inclusions, referred to as *Michaelis-Gutmann bodies*, that vary in size from 5 to 15 μm (70) (Fig. 21-12). These bodies either are homogeneous or have a "target" appearance by showing concentric laminations. The infiltrate may also contain lymphocytes, plasma cells, and polymorphs.

The Michaelis-Gutmann inclusion bodies and the cytoplasmic granules are periodic acid-Schiff (PAS)-positive, diastase resistant, and Alcian blue positive. In addition, the

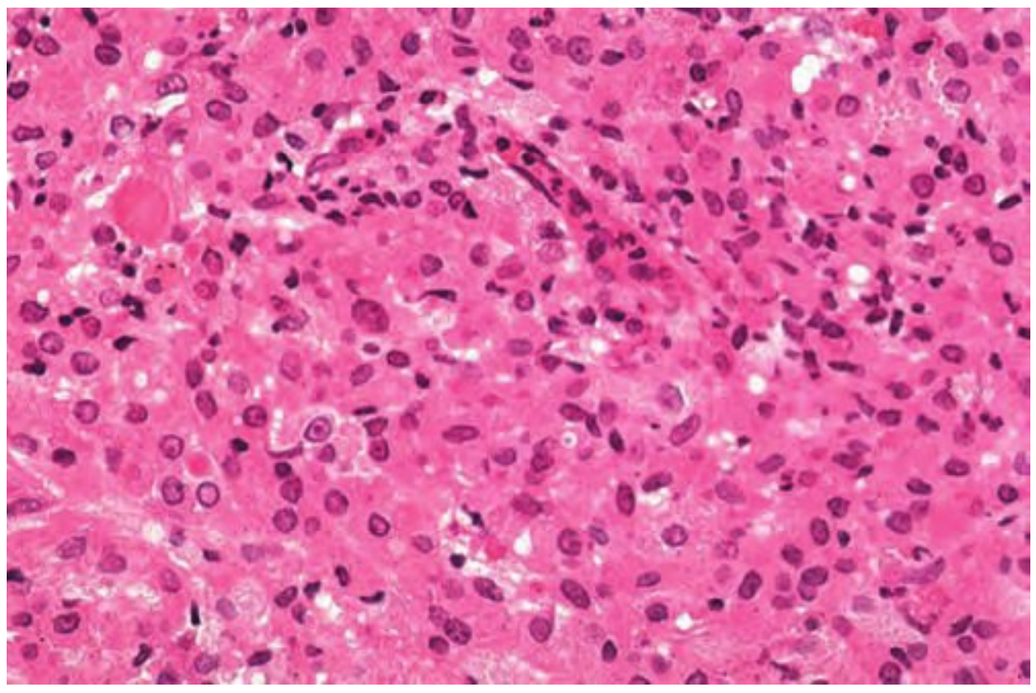


FIGURE 21-12. Malakoplakia. Sheets of macrophages with eosinophilic cytoplasm; several in the center contain Michaelis-Gutmann inclusion bodies (H&E stain).

Michaelis-Gutmann bodies stain with the von Kossa stain for calcium and contain small amounts of iron that may be demonstrated by Perls' stain. With the Gram stain, gram-negative bacteria may be seen in some of the histiocytes, and in the rare case caused by mycobacteria, Ziehl-Neelsen stain reveals the organisms. The bodies may be observed in skin scrapings of lesions (74).

Pathogenesis. Electron microscopic examination reveals that the cytoplasm of the granular cells contains numerous phagolysosomes corresponding to the PAS-positive granules. Some phagolysosomes contain lamellae in a concentric arrangement (70). The Michaelis-Gutmann bodies develop within phagolysosomes by the progressive deposition of electron-dense calcific material on the whorled or concentric lamellae until they are ultimately completely calcified. Bacteria may be observed in the cytoplasm of the granular cells and in various stages of digestion within phagolysosomes (72).

Malakoplakia represents an acquired defect in the lysosomal killing and digestion of phagocytized bacteria. Deficiencies of β-glucuronidase and of 3′,5′ guanosine monophosphate dehydrongenase have been documented (71,75).

MYCOBACTERIAL INFECTIONS

Taxonomically, the mycobacteria are divided into two major groups: the rapid growers and the slow growers in culture. *Mycobacterium leprae* lies outside this scheme because it cannot be cultured *in vitro*. Within each group, the species are organized in subgroups according to certain culture (growth requirement) and biochemical characteristics. Among the infections to be considered in this chapter, the important slow growers are the *Mycobacterium tuberculosis* complex, including bacille Calmette-Guérin (BCG); the *Mycobacterium avium* complex, including *M. avium* and *M. avium-intracellulare*; the

Mycobacterium kansasii complex; the complex that includes *Mycobacterium marinum* and *Mycobacterium ulcerans*; and mycobacteria with special growth requirements, such as *Mycobacterium haemophilum*. Rapid growers that affect the skin include the *Mycobacterium fortuitum* complex, which also includes *Mycobacterium chelonei* (76). Many other mycobacteria can occasionally cause skin lesions (77–79). In a recent series of 25 cases from Israel, there were 16 cases with *M. marinum*, 3 of atypical *Mycobacterium* without species identification, and 1 each with *M. chelonae*, *Mycobacterium xenopi*, *Mycobacterium abscessus*, *Mycobacterium gordonae*, and *M. fortuitum*, and it was emphasized that absence of a pathognomonic clinical picture and variable histologic findings often delay diagnosis of these nontuberculous mycobacteria (NTM)-induced cutaneous infections. The diagnosis of NTM should be confirmed by histology and bacteriology studies of tissue cultures. However, strong clinical suggestion of *M. marinum* infection may warrant initial empirical treatment to prevent progression to deep infection (80).

Tuberculosis and leprosy bacilli are intracellular parasites that are found in the tissues of humans and occasionally animals. Transmission requires exposure to infected people. The other mycobacteria are abundant in nature in both soil and water, and exposure to infection occurs throughout life, although usually without significant clinical disease.

Mycobacteria are bacilli that are weakly gram positive and are classically identified in histologic sections by stains that exploit their resistance to decoloration by acid—that is, acid-fast bacilli (81). All mycobacteria apart from the leprosy bacillus (see section Leprosy beginning on page 558) are well stained by the standard Ziehl-Neelsen technique.

TUBERCULOSIS

Until recently tuberculosis was considered to be a diminishing clinical problem in industrialized nations while remaining a dominant public health problem in resource-poor countries. However, there is a global resurgence of tuberculosis because of a combination of factors, including immigration from endemic countries (particularly in Asia and Africa), increased movement of refugees, the HIV pandemic, and poverty (82). As a result, cutaneous tuberculosis remains a clinical and diagnostic problem (83,84).

Infection of the skin and subcutis by *M. tuberculosis* occurs by three routes: (a) by direct inoculation into the skin (causing a primary chancre, or tuberculosis verrucosa cutis, or tuberculosis cutis orificialis lesions); (b) by hematogenous spread from an internal lesion (causing lupus vulgaris, miliary tuberculosis, and tuberculous gumma lesions); and (c) from an underlying tuberculous lymph node by direct extension (causing scrofuloderma). For descriptive purposes, these different tuberculous dermatitides are delineated (a modified "Beyt classification" is used) (78). But in clinical practice, many cases do not readily fit into these clinical and histologic categories (79,85,86). In a recent study of cutaneous tuberculosis infections in a pediatric population from India, with histopathologic evaluation there was a large spectrum of clinical patterns. The different patterns of cutaneous tuberculosis seen were scrofuloderma (37%), lichen scrofulosorum (33%), lupus vulgaris (21%), tuberculosis verrucosa cutis (4%), papulonecrotic tuberculid (4%), and erythema nodosum (3%). Systemic associations were seen in 53%, namely tuberculosis lymphadenitis (30%), pulmonary tuberculosis (13%), abdominal tuberculosis (6%), and tuberculosis arthritis (6%) (87).

The basic reaction of human tissues to tuberculous bacilli is a sequence, first of acute nonspecific inflammation during which the bacilli multiply and cannot be phagocytosed and killed by neutrophil polymorphs. Macrophages then phagocytose the organisms, but their efficacy in killing them depends crucially on enhanced activation. T-cell mediated allergy to tuberculous antigens induces secretion of cytokines that recruit and activate macrophages, which become epithelioid cells. Some will fuse to form giant cells, the typical form of which in tuberculosis is the Langhans giant cell with the nuclei arranged around the periphery of the cytoplasm. As delayed hypersensitivity increases, there is caseation necrosis within the granuloma, caseation being a homogeneous eosinophilic infarct-like necrotic process whereby the macrophages die. It is probably mediated by cytokines (such as tumor necrosis factor) and the macrophage proteases. This necrotic process inactivates or kills many of the mycobacteria in the lesion, but it does not eliminate them (88,89).

The necrotic granuloma is thus typical of tuberculosis and other mycobacterial infections, but it is not specific, being seen in numerous other infections that involve this type of cell-mediated immunity (e.g., histoplasmosis, syphilis, and leishmaniasis).

The determinants of what happens in tuberculosis infection therefore include the virulence of the organism (tuberculosis is more virulent than most of the nontuberculosis mycobacteria), the size of the inoculum, the route of infection, and the immune status of the patient. It is evident that if cell-mediated immunity is impaired, the T-cell/macrophage system will not operate to contain the infection. The resulting pathology is generally less granulomatous (fewer activated macrophages) and has a higher density of mycobacteria. Such conditions are HIV infection with its sequel of AIDS, steroid therapy, and cytotoxic drugs.

Primary Tuberculosis

Primary infection with tuberculosis occurs only rarely on the skin. Children or adults may acquire it following minor trauma or contact with infected material—as a result, for instance, of mouth-to-mouth artificial respiration (90), inoculation during an autopsy (91), needle-stick injury (92), or inoculation during tattooing (93). Usually, the cutaneous lesion arises within 2 to 4 weeks after the inoculation. It consists of an asymptomatic crust-covered ulcer referred to as *tuberculous chancre*. The regional lymph nodes become enlarged and tender and may suppurate and produce draining sinuses.

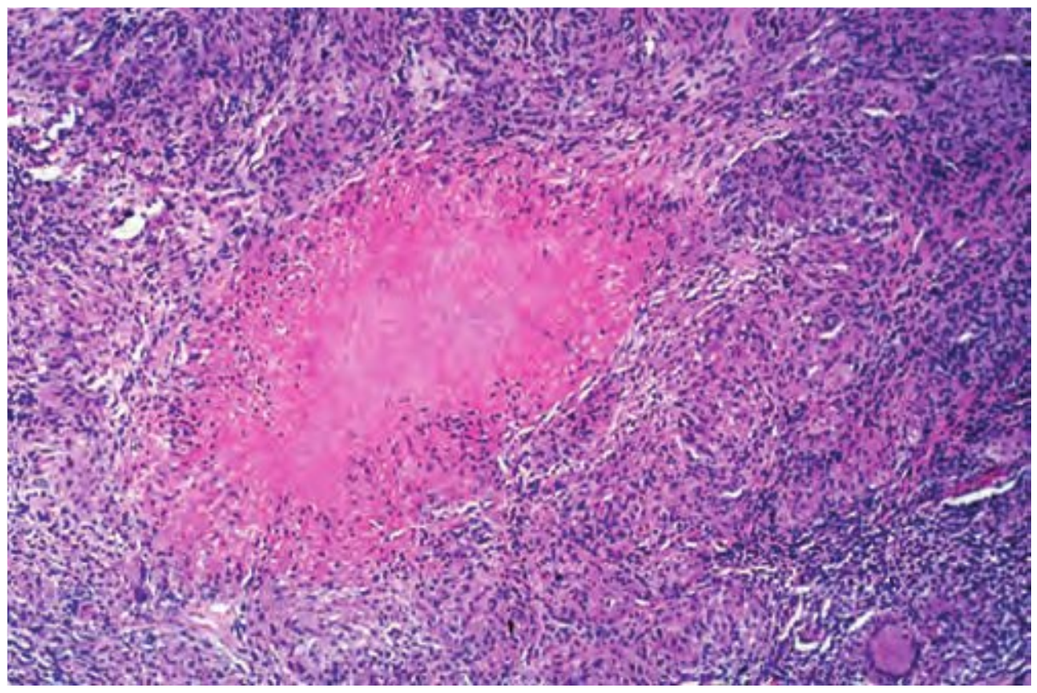


FIGURE 21-13. Tuberculosis. A prosector's wart following inoculation of the finger from a tuberculous cadaver. There is central caseation necrosis with dense macrophage and lymphocyte surround (H&E stain).

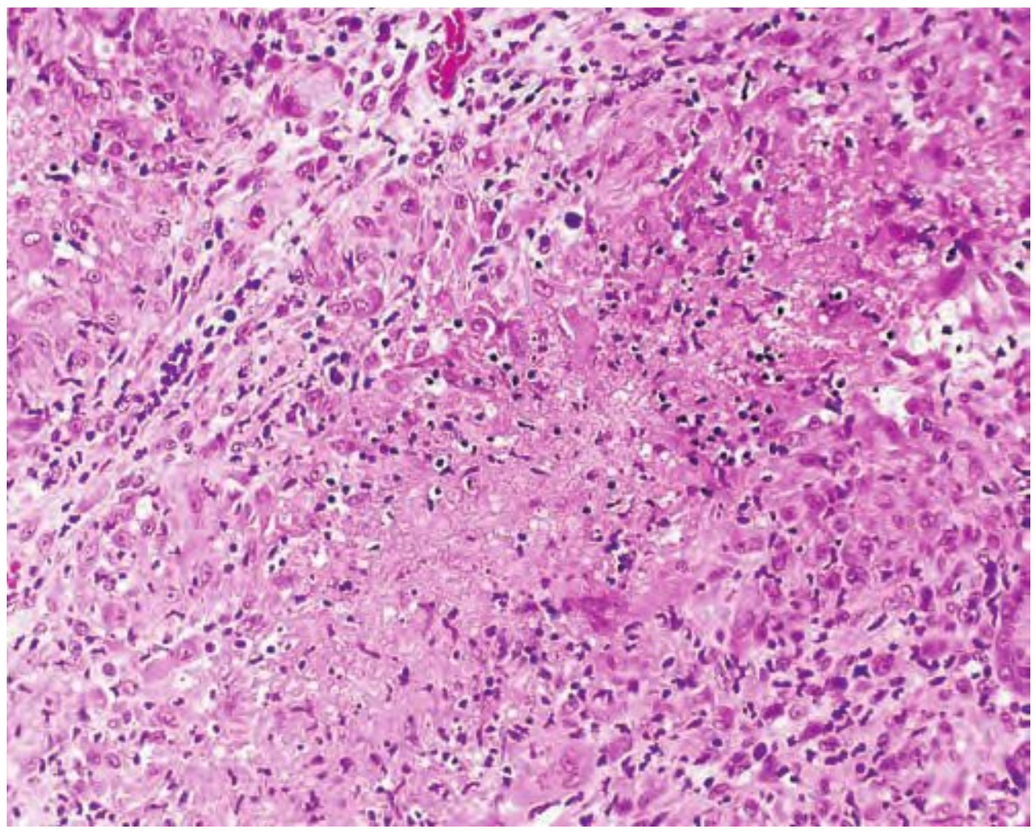


FIGURE 21-14. Tuberculosis. An epithelioid cell granuloma and caseation (H&E stain).

Histopathology. The histologic development of the lesion is very much like that observed in experimental cutaneous inoculation of the guinea pig. In the earliest phase, the histologic picture is that of an acute neutrophilic reaction, with areas of necrosis resulting in ulceration. Numerous tubercle bacilli are present, particularly in the areas of necrosis (91). After 2 weeks, monocytes and macrophages predominate. Three to 6 weeks after onset, epithelioid cells and giant cell granulomas develop, followed by caseation necrosis within the granuloma mass (Fig. 21-13). In time, the necrosis lessens, and the number of tubercle bacilli decreases until it is so greatly reduced that the bacilli may be impossible to demonstrate in histologic sections. Simultaneous with the decrease in the number of tubercle bacilli in the lesion, the tuberculin test with purified protein derivative (PPD), previously negative, becomes positive. The draining lymph nodes receive tubercle bacilli and enlarge through developing caseating granulomas, parallel to a primary infection in the lung.

Tuberculosis Verrucosa Cutis

Tuberculosis verrucosa cutis represents an inoculated exogenous infection of the skin in persons with a degree of immunity—that is, previous exposure to tuberculosis. In tuberculosis verrucosa cutis, a single lesion presenting as a verrucous plaque with an inflammatory border and showing gradual peripheral extension is usually observed. The verrucous surface exhibits fissures from which pus often can be expressed. The most common sites are the hands and, in children, the knees, buttocks, and thighs.

Histopathology. The histologic picture includes hyperkeratosis and acanthosis. Beneath the epidermis, there is an acute inflammatory infiltrate. Abscess formation may be observed in the upper dermis or within downward extensions of the epidermis. In the middermis, tuberculoid granulomas with a moderate amount of necrosis are usually present (Fig. 21-14). Tubercle bacilli are more numerous in this disease than in lupus vulgaris and occasionally can be demonstrated histologically.

Miliary Tuberculosis of the Skin. Involvement of the skin with miliary tuberculosis is rare in the immunocompetent, occurring mostly in infants and only occasionally in adults. Usually, internal involvement is widespread as a result of hematogenous dissemination, and the cutaneous eruption is generalized, consisting of erythematous papules and pustules 2 to 5 mm in diameter (94). The tuberculin test generally is negative. The disease has a high fatality rate.

However, a milder form of hematogenous dissemination of tubercle bacilli exists in neonates born of tuberculous mothers. This form shows limited visceral involvement and only a few scattered erythematous papules with central crusts (95).

Histopathology. In severe cases, the center of the papule shows a microabscess containing neutrophils, cellular debris, and numerous tubercle bacilli. This is surrounded by a zone of macrophages with occasional giant cells. In the milder form, the histologic picture in the skin is similar, except that the Ziehl-Neelsen stain is negative for acid-fast organisms.

Lupus Vulgaris

The lesions of lupus vulgaris are usually found on the head or neck. The skin of and around the nose is frequently involved (96). The lesions consist of one or a few well-demarcated, reddish-brown patches containing deep-seated nodules, each about 1 mm in diameter. If the blood is pressed out of the skin with a glass slide, these nodules stand out clearly as yellow-brown macules, referred to, because of

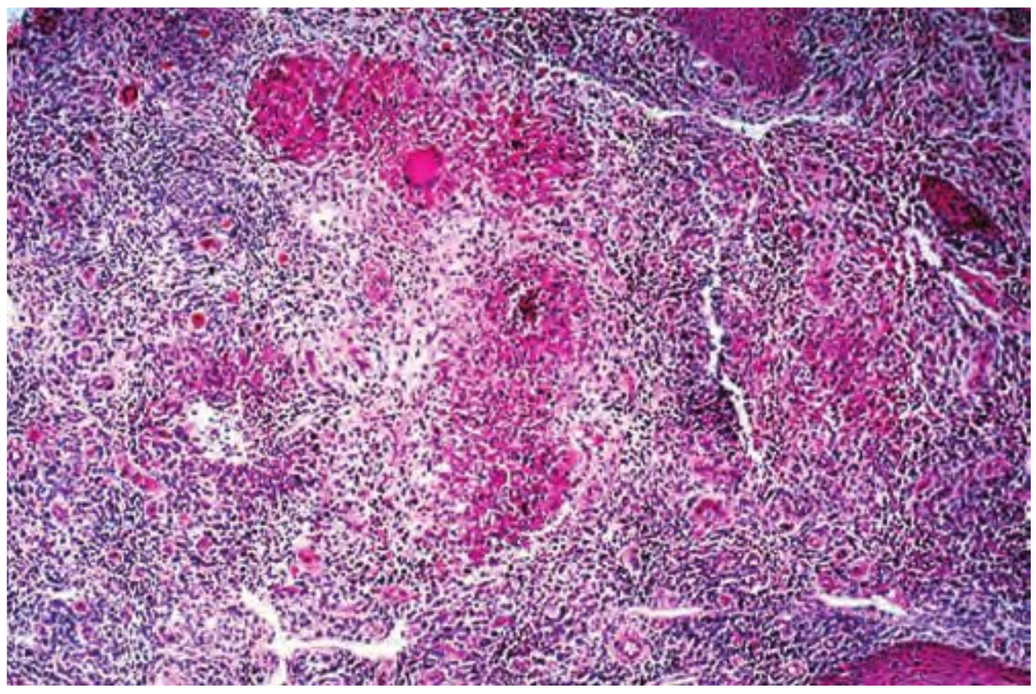


FIGURE 21-15. Tuberculosis. Epithelioid cell granulomas with central acute inflammation ("mixed" granuloma). Scanty acid-fast bacilli were seen in this case (H&E stain).

their color, as *apple-jelly nodules*. The disease is very chronic, with slow, peripheral extension of the lesions. Over time, the affected areas become atrophic, with contraction of the tissue. It is a characteristic feature of lupus vulgaris that new lesions may appear in areas of atrophy. Superficial ulceration or verrucous thickening of the skin occurs occasionally. Squamous cell carcinoma develops at the margins of ulcers in rare instances.

Histopathology. Tuberculoid granulomas composed of epithelioid cells and giant cells are present. Caseation necrosis within the tubercles is slight or absent (97). Although the giant cells usually are of the Langhans type, with peripheral arrangement of the nuclei, some can be of the foreign body type, with irregular arrangement of the nuclei. There is an associated infiltrate of lymphocytes (Figs. 21-15 and 21-16). Sometimes, this may be so prominent that the granulomatous component is obscured. The inflammation is most pronounced in the upper dermis, but in some areas, it may extend into the subcutaneous layer. Tuberculoid granulomas cause destruction of the cutaneous appendages. In areas of healing, extensive fibrosis may be present.

Secondary changes in the epidermis are common. The epidermis may undergo atrophy and subsequent destruction, causing ulceration, or it may become hyperplastic, showing acanthosis, hyperkeratosis, and papillomatosis. At the margins of ulcers, pseudoepitheliomatous hyperplasia often exists. Unless a deep biopsy is done in such cases, only the epithelial hyperplasia and a nonspecific inflammation may be seen, and the diagnosis may be missed. In rare instances, squamous cell carcinoma supervenes (98).

Tubercle bacilli are present in such small numbers that they can very rarely be demonstrated by staining methods. Polymerase chain reaction (PCR) detection of mycobacterial DNA is more often positive (99). In some instances of lupus vulgaris when an old focus of primary infection cannot be detected, a positive tuberculin test and the response to antituberculous therapy must suffice as proof of a tuberculous etiology.

Pathogenesis. Lupus vulgaris is a form of secondary or reactivation tuberculosis developing in previously infected and sensitized persons. Hypersensitivity to PPD tuberculin is high. Although the mode of infection often is not apparent, the disease rarely seems to be the result of an exogenous reinfection of the skin; usually it results from hematogenous spread from an old, reactivated focus in the lung or from lymphatic extension from a tuberculous cervical lymphadenitis (78).

Scrofuloderma

Scrofuloderma represents a direct extension to the skin of an underlying tuberculous infection present most commonly in a lymph node or a bone. The lesion first manifests itself as a blue-red, painless swelling that breaks open and then forms an ulcer with irregular, undermined, blue borders.

Histopathology. The center of the lesion usually exhibits nonspecific changes, such as abscess formation or ulceration. In the deeper portions and at the periphery of the lesion, if the biopsy specimen is adequate, tuberculoid granulomas with a considerable amount of necrosis and a pronounced inflammatory reaction usually are seen. Often, the number of tubercle bacilli is sufficient for them to be found in histologic sections.

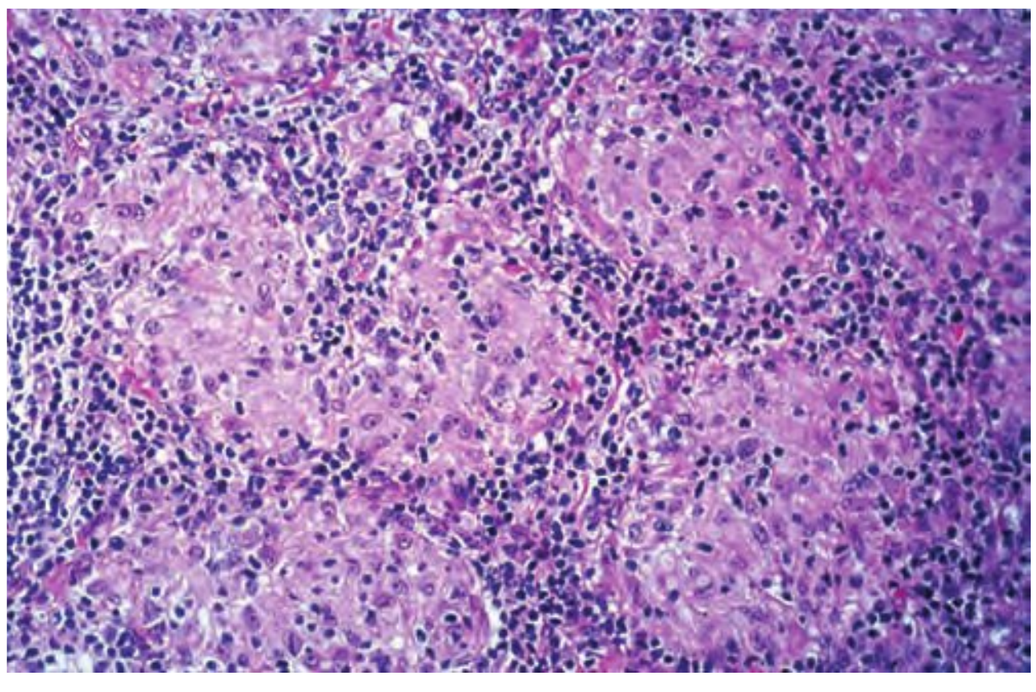


FIGURE 21-16. Lupus vulgaris. Near-confluent nonnecrotizing epithelioid cell granulomas in the dermis (H&E stain).

Tuberculous Gumma

Hematogenous infection of the skin from an internal lesion may result in a large dermal or subcutaneous nodule that is necrotic and ultimately ulcerates the epidermis.

Histopathology. Most of the lesion is caseation necrosis with a rim of epithelioid cells and giant cells (Figs. 21-17 and 21-18). Acid-fast bacilli are scanty.

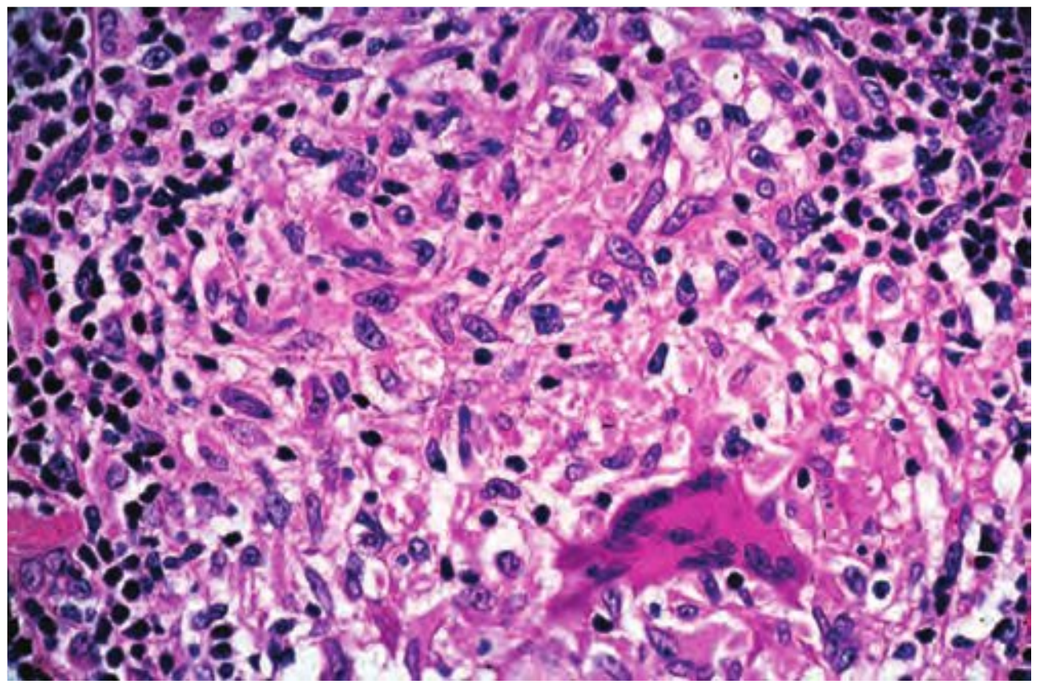


FIGURE 21-17. Lupus vulgaris. Same lesion as in Figure 21-16, showing an epithelioid cell granuloma and Langhans giant cell (H&E stain).

Tuberculosis Cutis Orificialis

The lesions of tuberculosis cutis orificialis are shallow ulcers with a granulating base occurring singly or in small numbers on or near the mucosal orifices of patients with advanced internal tuberculosis. The infection has spread by direct contamination from an internal lesion that is excreting bacilli. Most patients have a low degree of immunity. The ulcers, which are often very tender, may occur inside the mouth, on the lips, around the anus, or on the perineum (100). In the case of genitourinary tuberculosis, ulcers may occur on the vulva.

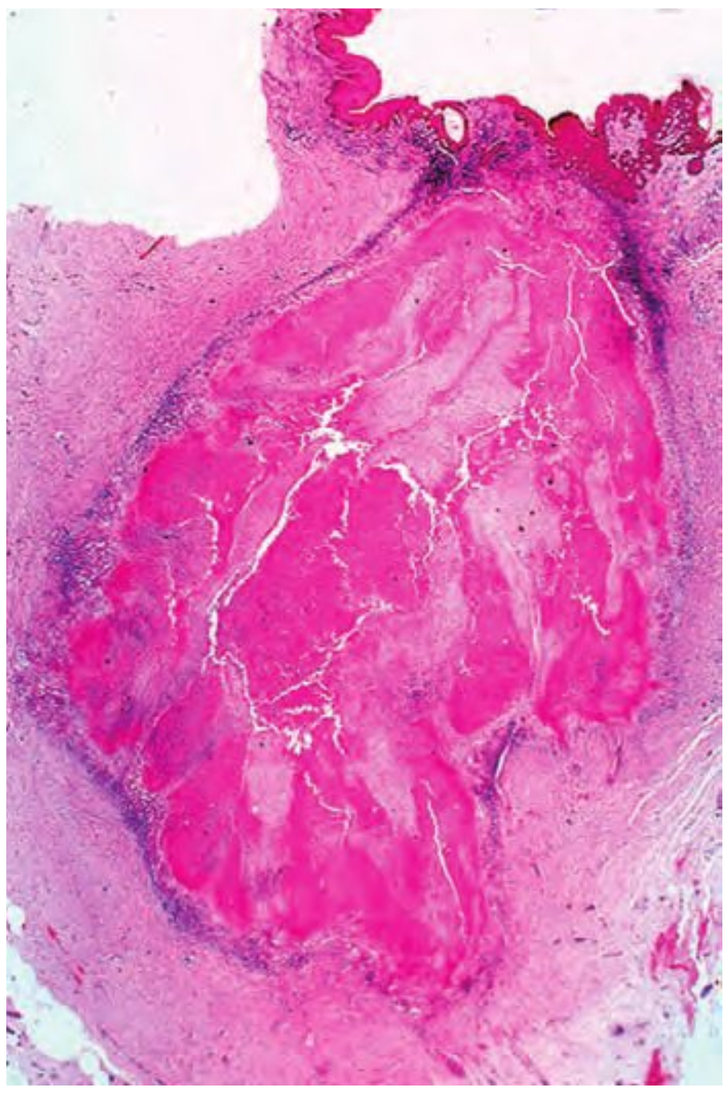


FIGURE 21-18. Tuberculosis. A tuberculoma-like appearance with much caseation necrosis in the dermis (H&E stain).

Histopathology. The histologic picture may show merely an ulcer surrounded by a nonspecific inflammatory infiltrate. In most instances, tuberculoid granulomas with pronounced necrosis are found deep in the dermis. Tubercle bacilli are usually readily demonstrated in the sections, even when the histologic appearance is nonspecific.

Differential Diagnosis of Cutaneous Tuberculosis

Because tuberculosis can produce such a wide variety of inflammatory reactions—nonnecrotic granulomas, necrotic granulomas, nonspecific acute inflammation, and epithelial hyperplasia—it is not surprising that many other lesions have similar histologic appearances. These other lesions include sarcoidosis, mycoses, leishmaniasis, nontuberculosis mycobacterioses and leprosy, syphilis, foreign body implantation reactions, Wegener's granulomatosis, and rosacea.

Sarcoidosis usually has little lymphocytic reaction around the granulomas, unlike most forms of granulomatous tuberculosis. When necrosis occurs in a sarcoid, it is usually fibrinoid in type rather than caseating. A thorough search for acid-fast bacilli, a search for fungal infection with PAS and Grocott stains, and the use of polarizing light to exclude foreign material are obviously important in arriving at a diagnosis. Clinical data and the result of a tuberculin test are also significant. Culture of a lesion should establish the diagnosis in most cases. Recently, the use of PCR technology on paraffin sections to detect specific mycobacterial DNA has proved useful in confirming tuberculosis in the absence of evident organisms in sections (101). In a recent review, the utility of a PCR test versus other laboratory tests was studied in 37 skin biopsies from patients with different variants of cutaneous tuberculosis. The PCR test showed the maximum positivity of 79% followed by histopathology (73%), BACTEC culture (47%), LJ media culture (29%), and smear examination (6%). Using culture as the gold standard, the sensitivity and specificity of PCR testing were 95.2% and 100.0%, respectively. The mean times to a positive result in different tests were $<$24 hours for smear examination, 1 day for the PCR test, and 23 to 38 days for different culture methods, demonstrating that PCR is a rapid and sensitive test for diagnosis of cutaneous tuberculosis using skin biopsy samples (102).

Tuberculids

The *tuberculids*, a term first proposed in 1896 (103), according to some authors comprise two types of dermatoses: papulonecrotic tuberculids and lichen scrofulosorum (104,105). Cases of nodular vasculitis, when associated with tuberculosis, are included within the group of tuberculids and are called *erythema induratum* (Bazin's disease; see Chapters 8 and 20).

Tuberculids are skin lesions in patients with tuberculosis, often occult, elsewhere in the body. The most common sites of infection are lymph nodes (106). By definition, stains for acid-fast bacilli and culture for mycobacteria are negative; delayed hypersensitivity skin tests for tuberculosis are positive, and the lesions

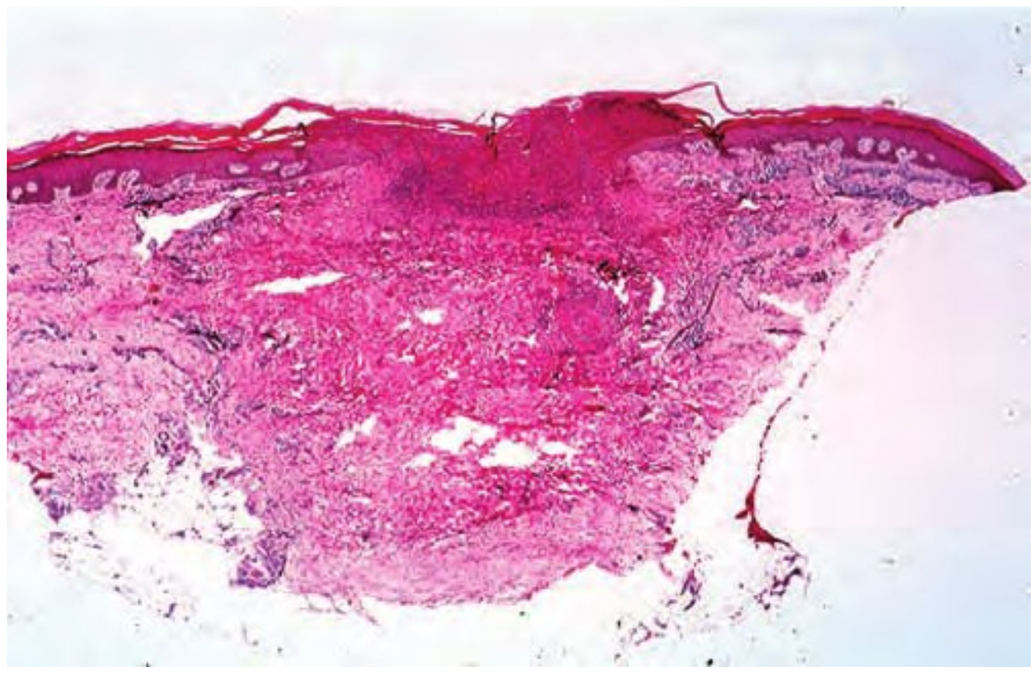


FIGURE 21-19. Papulonecrotic tuberculid. Wedge-shaped infarction of the dermis and epidermis caused by vasculitis (H&E stain).

heal on antituberculous therapy. Recently, using the PCR technique, mycobacterial DNA has been identified in some lesions (107). This supports the concept of tuberculids as immunologic reactions to degenerate dead bacilli or antigenic fragments thereof that have been deposited in the skin and subcutis.

Papulonecrotic Tuberculids

Papulonecrotic lesions are erythematous papules that usually develop on the limbs in a symmetrical distribution (108). They ulcerate and heal, leaving depressed scars. These tuberculids often recur until treated. Occasionally, they may develop into lupus vulgaris.

Histopathology. Vascular involvement is observed in early lesions. It may consist of a leukocytoclastic vasculitis or a lymphocytic vasculitis. In either case, it is associated with fibrinoid necrosis and thrombotic occlusion of individual vessels (109). Subsequently, a wedge-shaped area of necrosis forms, with its broad base toward the epidermis (108) (Figs. 21-19 and 21-20). As this wedge is gradually cast off, epithelioid and giant cells gather around its periphery, although focal granuloma formation is poor. Follicular necrosis or suppuration may occur, although diffuse acute inflammatory cells are infrequent. Ziehl-Neelsen stains are, of course, negative.

Differential Diagnosis. Numerous conditions may be confused clinically or histopathologically with papulonecrotic tuberculids. They include pityriasis lichenoides acuta, syphilides, miliary tuberculosis, perforating granuloma annulare, and suppurative folliculitis (108).

Lichen Scrofulosorum

Lichen scrofulosorum consists of yellow or brown follicular papules, 0.5 to 3.0 mm in diameter, on the trunk. They heal without scarring.

Histopathology. Superficial dermal granulomas are observed, usually in the vicinity of hair follicles or sweat ducts. The granulomas are composed of epithelioid cells, with some Langhans giant cells and a narrow margin of lymphoid cells at the periphery (Fig. 21-21). Generally, caseation necrosis is absent.

Differential Diagnosis. Distinction of lichen scrofulosorum from sarcoidosis may be impossible on histologic grounds alone.

Pathogenesis. The histogenesis of tuberculids is still unclear. Tubercle bacilli are absent in tuberculids, either because they have arrived hematogenously in fragmented form or because they have been destroyed at the sites of the tuberculids by immunologic mechanisms. Mycobacterial DNA is, however, demonstrable in many cases (107,110). The reaction in the papulonecrotic

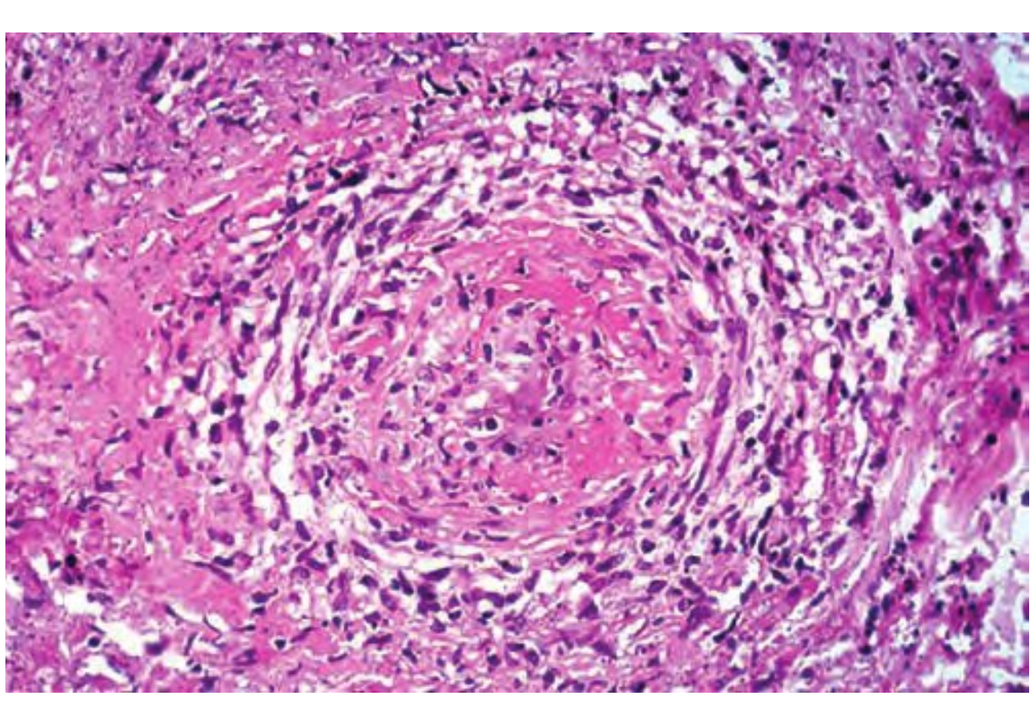


FIGURE 21-20. Papulonecrotic tuberculid. Necrotizing vasculitis of a dermal artery with granulomatous surround (H&E stain).

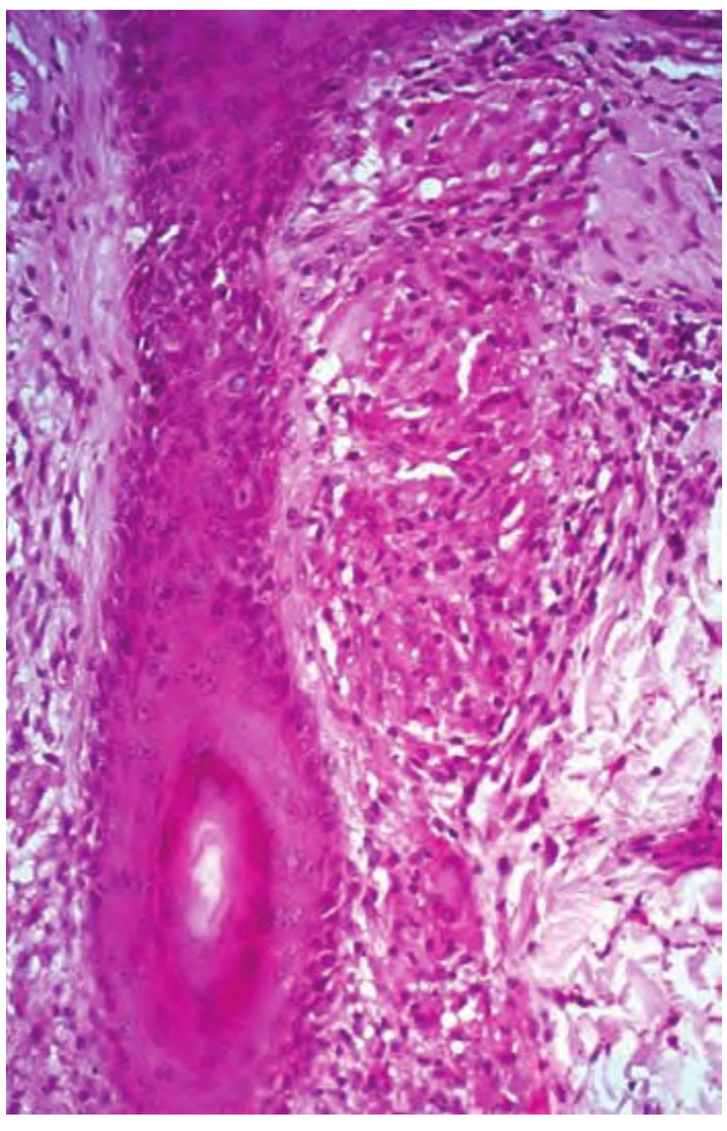


FIGURE 21-21. Lichen scrofulosorum. Nonnecrotizing epithelioid cell granulomas alongside a hair shaft (H&E stain).

tuberculid consists of an Arthus reaction with vasculitis followed by a delayed hypersensitivity response with granuloma formation. In the case of lichen scrofulosorum, there is only a delayed hypersensitivity reaction resulting in granuloma formation (105).

Tuberculid-type reactions are also described with nontuberculosis mycobacteria (*Mycobacterium bovis* and *M. avium*) (111,112).

INFECTIONS WITH NONTUBERCULOSIS MYCOBACTERIA

Among the nontuberculosis, nonleprosy mycobacterial infections of the skin, those caused by *M. marinum* are the most common among nonimmunosuppressed people (113). Unlike *M. tuberculosis*, which is transmitted from person to person, nontuberculosis mycobacteria are abundant in nature, in soil and water, and contact is frequent in most zones of the world (77,114).

These skin infections may be acquired by direct inoculation into the skin or by hematogenous spread from a visceral focus. Increased use of immunosuppression in medicine (e.g., for transplantation and cancer chemotherapy) and the pandemic of HIV/AIDS have resulted in many more mycobacterial skin infections. The cell-mediated immune system is a major defense against such organisms and is affected or destroyed during the course of these immunosuppressive conditions. The clinical and histopathologic patterns are also altered, with organisms being found in greater density than in immunocompetent persons.

The histopathologic picture in nontuberculosis mycobacterioses is just as variable as the clinical picture and may present nonspecific acute and chronic inflammation, suppuration and abscess formation, or tuberculoid granulomas with or without caseation (85,115). In some instances, both tissue reactions occur concurrently. The presence or absence of acid-fast bacilli depends on the tissue reaction. In suppurative lesions, numerous acid-fast bacilli often can be found.

Infection with Mycobacterium Kansasii

M. kansasii is usually a lymph node and pulmonary infection, and skin lesions are unusual. Implantation causes a chronic cutaneous nodule and sometimes ulceration (77). The lesions are often crusted. There may be sporotrichoid lymphatic spread of lesions up the extremity (113). In immunocompromised patients, such as those with HIV infection, there may be multiple visceral lesions (lung and bone) with hematogenous dissemination to skin. The skin lesions are acute abscesses with large numbers of acid-fast bacilli (Fig. 21-22).

Infection with Mycobacterium Avium-intracellulare

M. avium complex infection is a common cause of cervical lymph node mycobacteriosis in normal children and of pulmonary disease in previously damaged lungs (77). Prior to the HIV pandemic, skin infections were rare, with hematogenously borne lesions in skin and subcutis observed in patients usually with immunosuppressing diseases (78).

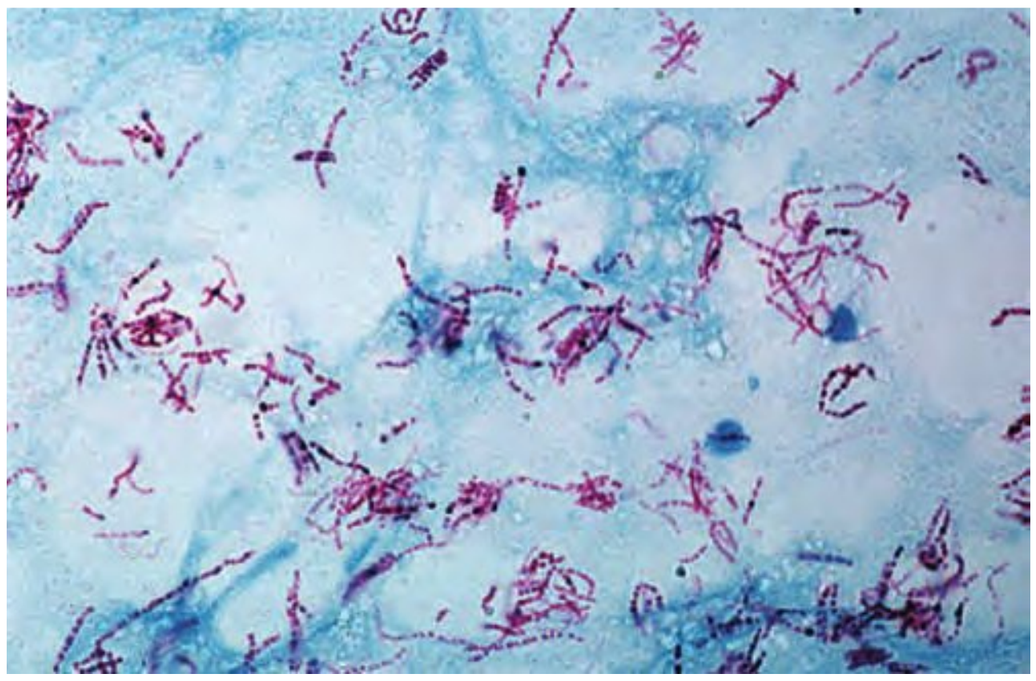


FIGURE 21-22. Mycobacterium kansasii infection. Needle aspirate of a skin lesion on an immunocompromised patient. Abundant elongated and beaded acid-fast bacilli typical of M. kansasii (Ziehl-Neelsen stain).

Severely immunocompromised patients, such as those with HIV infection, have a very high prevalence of *M. avium-intracellulare* bacteremia (116), and many show one or more cutaneous papules and nodules (117,118). Steroid therapy also predisposes to skin lesions. The histology may be granulomatous or mixed acute and chronic inflammatory, as with tuberculosis (77). Sometimes, there is a histology resembling that of lepromatous leprosy (Figs. 21-23 to 21–25). Macrophages contain large numbers of bacilli without necrosis, and a spindle cell transformation of macrophages, forming a histoid-like lesion (as in leprosy), can occur (119,120).

Infection with Mycobacterium Marinum

Infections with *M. marinum* can be contracted through minor abrasions incurred while bathing in swimming pools or in ocean or lake water or while cleaning home aquariums (121). Infected swimming pools have caused epidemics, the largest of

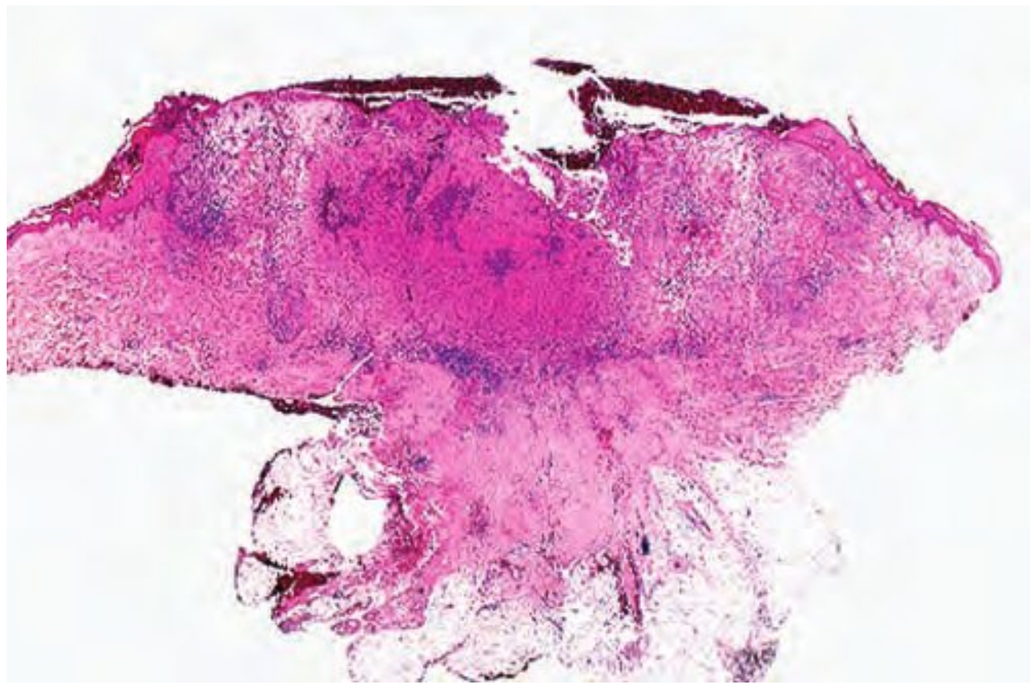


FIGURE 21-23. Mycobacterium avium-intracellulare infection. Discrete inflammatory lesion in an elderly female (H&E stain).

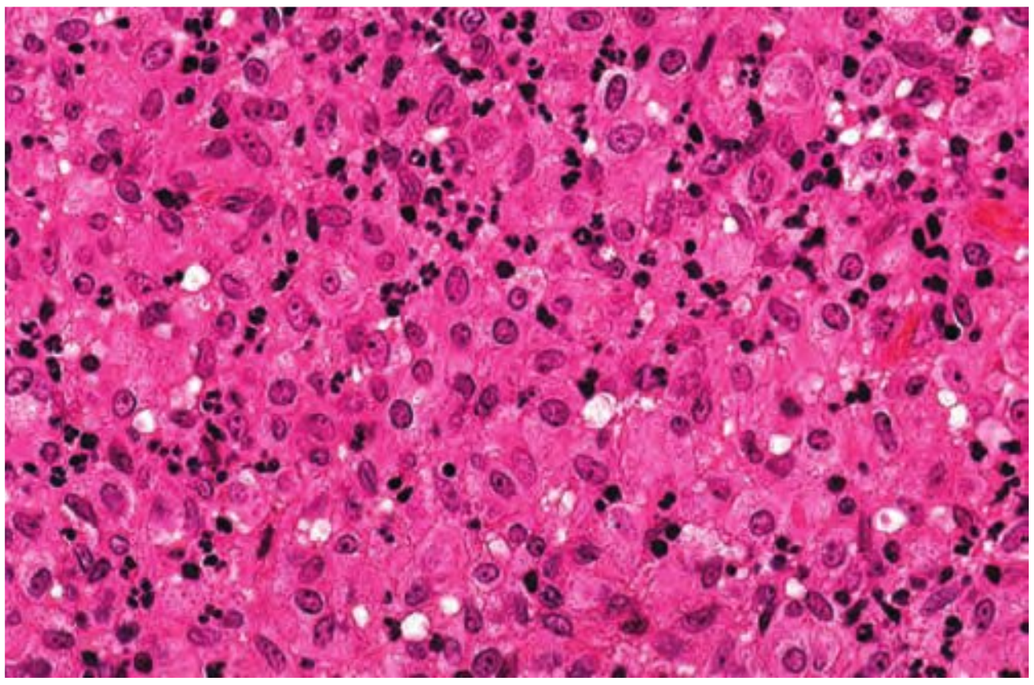


FIGURE 21-24. Mycobacterium avium-intracellulare infection. Same lesion as Figure 21-23. Unactivated macrophages with eosinophilic cytoplasm (H&E stain).

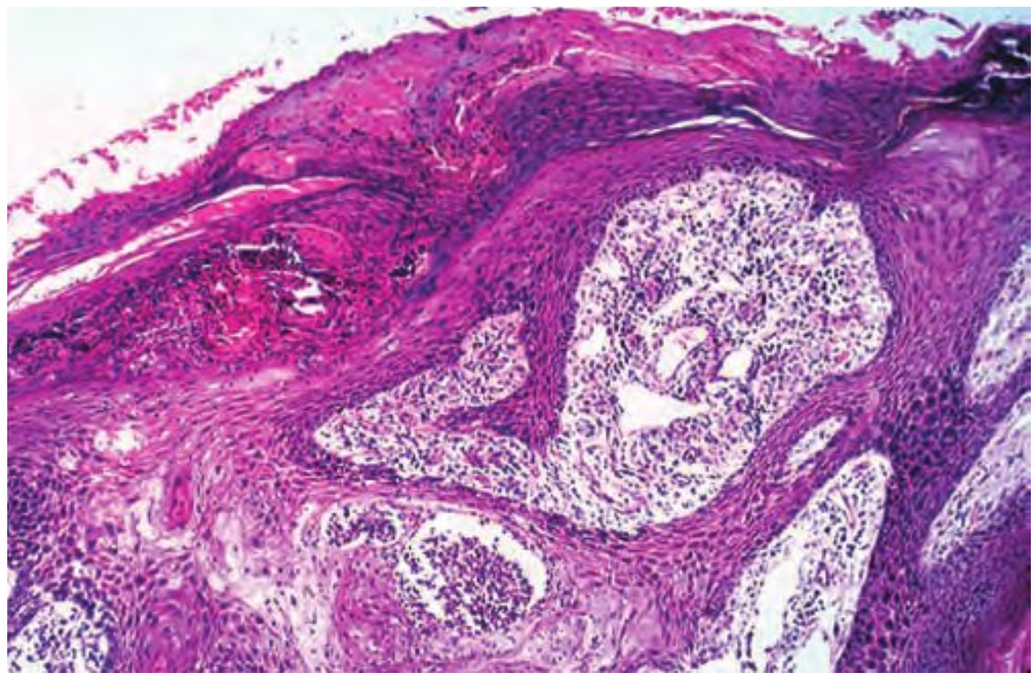


FIGURE 21-26. Mycobacterium marinum infection. A marked pseudoepitheliomatous epidermal hyperplasia, with acute inflammatory foci within the epidermis (H&E stain).

which affected 290 persons (122). The period of incubation usually is about 3 weeks but may be longer (113).

Clinically, most of the lesions caused by *M. marinum* are solitary and consist of indolent, dusky red, hyperkeratotic, papillomatous papules, nodules, or plaques. Superficial ulceration is occasionally observed. The fingers, knees, elbows, and feet are most commonly affected. In some instances, satellite papules arise and ascending sporotrichoid spread occurs (123). Lesions may form at different sites in the case of multiple injuries. Although spontaneous healing usually takes place within a year, the lesions persist in some patients for many years. A few HIV-associated cases have been reported (124). Fatal disseminated *M. marinum* infection is rare (125).

Histopathology. Early lesions no more than 2 or 3 months old show a nonspecific inflammatory infiltrate composed of neutrophils, monocytes, and macrophages. In lesions about 4 months old, a few multinucleated giant cells and a few small epithelioid cell granulomas usually are present, and in lesions 6 months old or older, typical tubercles or tuberculoid structures may be seen (126). Areas of necrosis are only occasionally present in the centers of the granulomas. The epidermis often shows marked hyperkeratosis with an acute inflammatory infiltrate and ulceration (Fig. 21-26).

Acid-fast bacilli usually can be identified in histologic sections of early lesions that show a nonspecific inflammatory infiltrate. In contrast, tuberculoid granulomas generally no longer show acid-fast organisms unless areas of central necrosis are present. Although primary lesions usually require a few months for the formation of tuberculoid granulomas, the sporotrichoid nodules that arise later show tuberculoid granulomas and a lack of acid-fast bacilli even when they have been present for only a few weeks.

Differential Diagnosis. The granulomatous reaction produced by *M. marinum* is similar to that observed in tuberculosis verrucosa cutis or lupus vulgaris. The pattern of pseudoepitheliomatous hyperplasia with granulomas and polymorphonuclear neutrophil infiltrate is also seen in several cutaneous mycoses (e.g., sporotrichosis and chromoblastomycosis), so fungal stains need to be examined alongside Ziehl-Neelsen stains. For definitive identification, culture may be necessary.

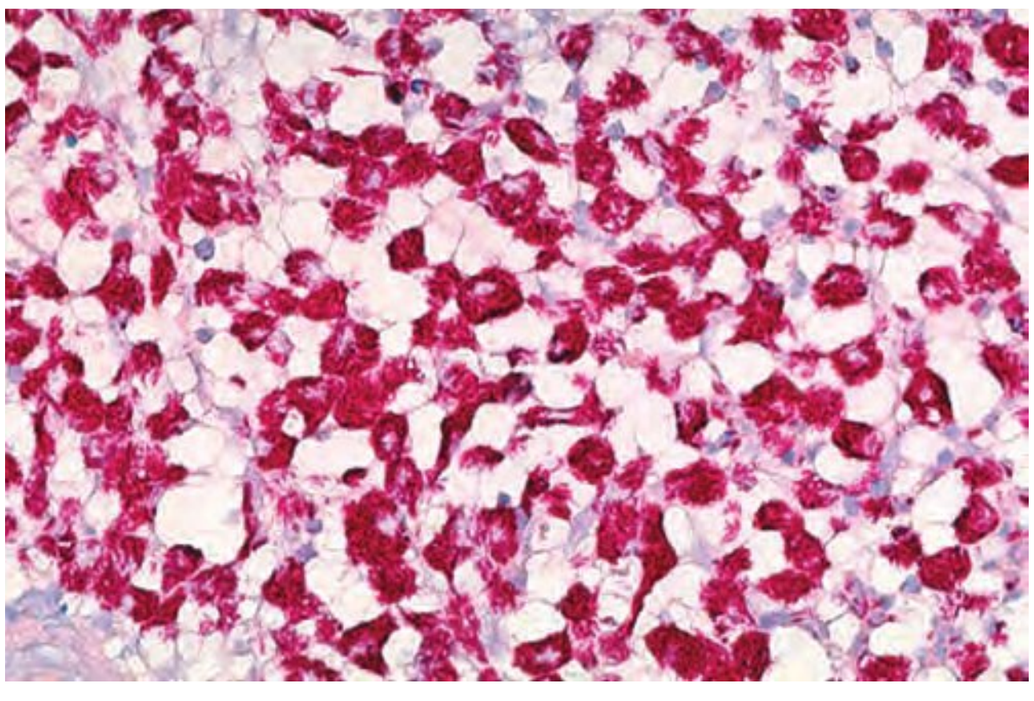


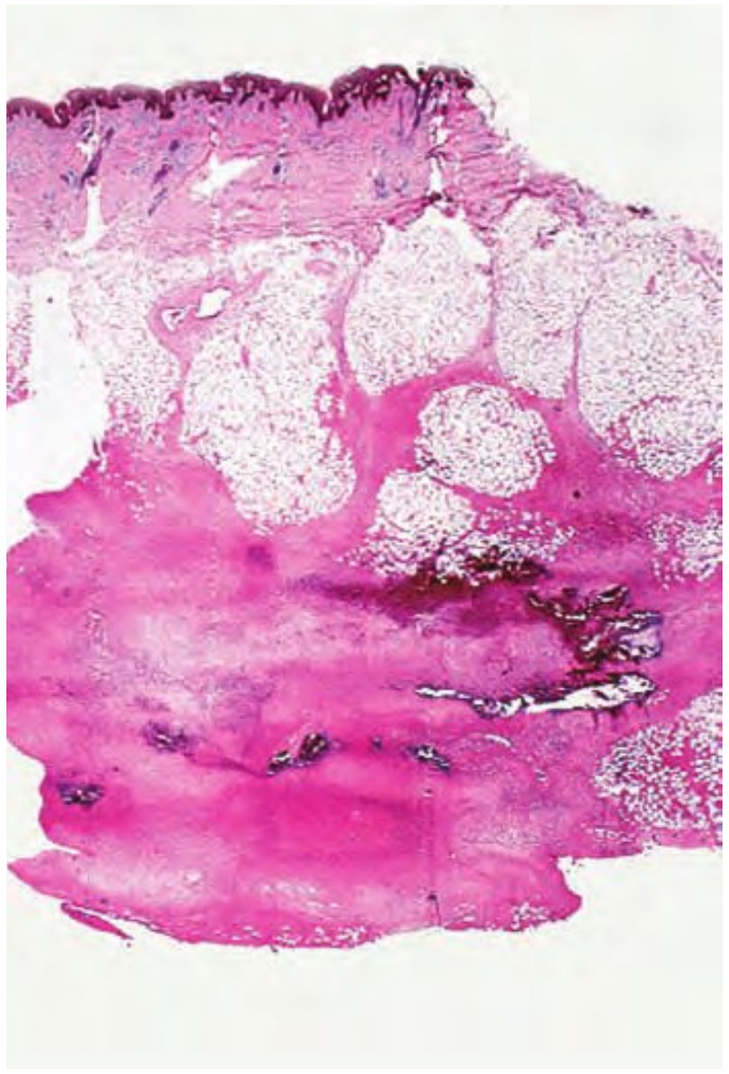
FIGURE 21-25. Mycobacterium avium-intracellulare infection. Same lesion as in Figure 21-23, showing abundant acid-fast bacilli, similar to lepromatous leprosy (Ziehl-Neelsen stain).

Buruli Ulcer (Mycobacterium ulcerans)

Buruli ulceration, an infection caused by a nontuberculosis mycobacterium, *M. ulcerans*, is endemic in West and Central Africa, Central America, and South Australia (127–129). The organism is now identified in nature, near inland water and rivers, and is directly implanted or follows an aquatic insect bite. The infection commences as a palpable cutaneous nodule. In some cases, this may heal but more usually progresses to ulceration of the skin with extensive undermining of the epidermis and extension of the necrosis down to fascia and even bone (130). These painless ulcers are usually located on extremities and buttocks, but trunk and facial ulcers also occur.



A



B

FIGURE 21-27. Buruli ulcer (M. ulcerans infection). A: An evolving ulcer with undermined edge. B: Early, preulcerating lesion, with deep dermal and subcutaneous fat necrosis (H&E stain).

Histopathology. The infection begins as a subcutaneous nodule exhibiting "ghost" ischemic-type dermal collagen and fat necrosis with deposition of fibrin and hematoxyphilic extracellular clumps of mycobacteria. Ulceration proceeds as the epidermis loses its vascular supply. Ziehl-Neelsen stains reveal vast numbers of acid-fast bacilli in the necrotic fat (Figs. 21-27 to 21-29); their distribution is often irregular. A variable degree of neutrophil infiltration and thrombosis of vessels are also observed. In time, a nonspecific granulation tissue or a granulomatous reaction commences from the depth and sides of the ulcer; healing and re-epithelialization take place with considerable scarring. Acid-fast bacilli decline rapidly in number during healing (128,131). The histopathologic case definition for Buruli ulcer, useful for research studies, is (a) the typical pattern of infarctive-like necrosis of deep dermal collagen and fat and (ideally, but not always found in limited samples) (b) nearby clusters of acid-fast bacilli.

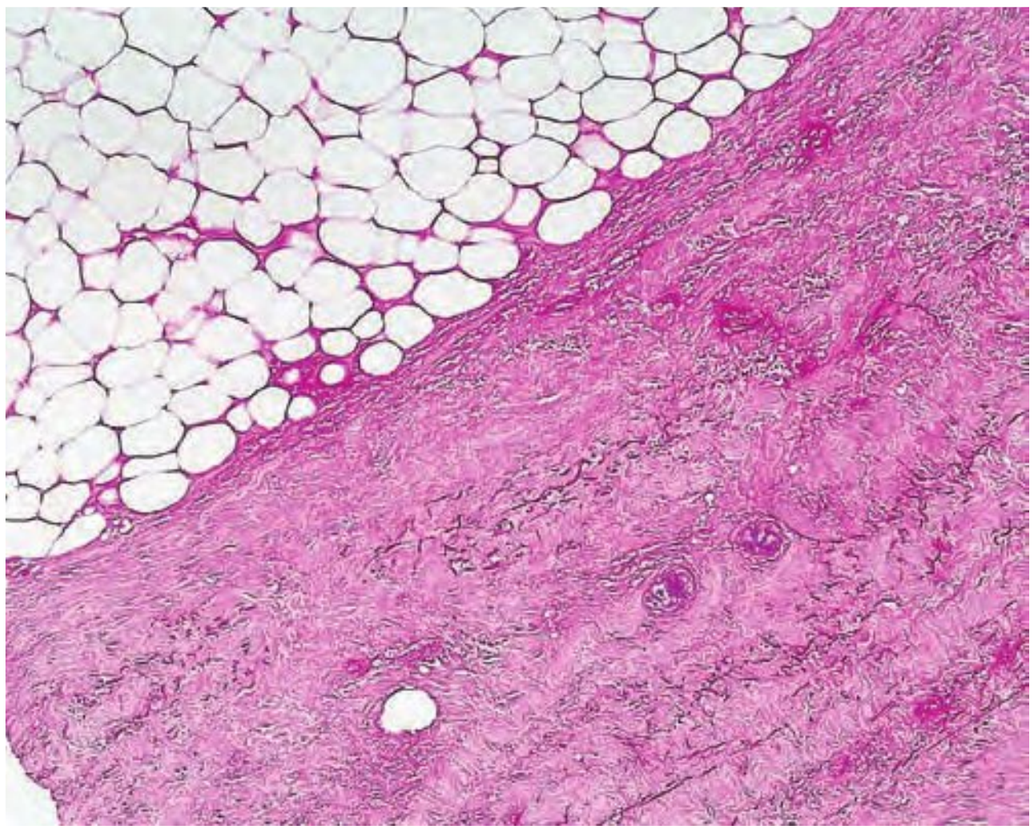


FIGURE 21-28. Buruli ulcer. The ischemic-type fat and collagen necrosis without cellular reaction; the hematoxyphilic clusters are mycobacteria (H&E stain).

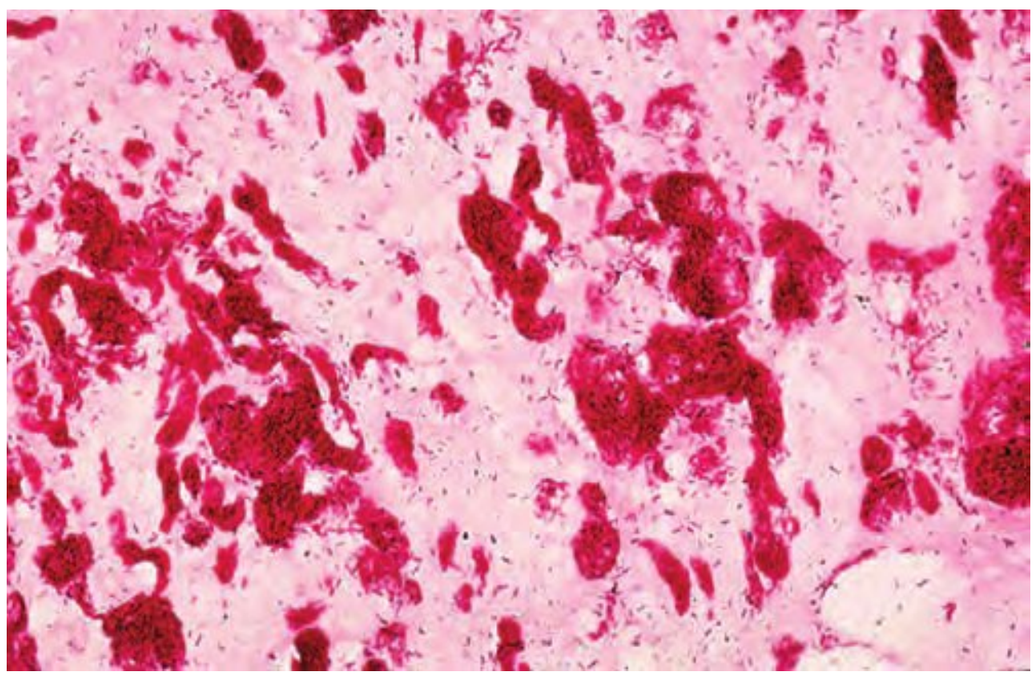


FIGURE 21-29. Buruli ulcer. Clumps of acid-fast bacilli within the fat necrosis (Ziehl-Neelsen stain).

Pathogenesis. The widespread necrosis of subcutaneous tissue is caused by a toxin secreted by *M. ulcerans*, a pathogenesis unique to this species of mycobacteria. It is polyketide mycolactone, and strain and geographical differences in mycolactone virulence are already described (the disease is less severe in Australia than in central Africa, related to different mycolactone strains). This toxin causes necrosis when inoculated into guinea pig skin and into macrophages in tissue culture (127). Like *M. marinum*, *M. ulcerans* shows optimal cultural growth at 30° to 33°C.

PCR technology has been used to track the distribution of *M. ulcerans* in Buruli ulcer lesions and to compare the mycobacterial burden with histopathologic changes (132). While peaks of mycobacterial DNA and histopathologically recognized acid-fast bacilli in the necrotic base of the ulcers marked the position of the primary infection focus, mycobacterial DNA (and sometime microcolonies) was also present in samples from the periphery of the ulcers and occasionally from macroscopically and histologically healthy-looking excised tissue margins and in sites where satellite lesions were developing. Even when granulomas provided evidence for the development of cell-mediated immunity, development of satellite lesions by contiguous spreading was not completely prevented.

Healing of Buruli ulcer coincides with development of delayed hypersensitivity to the mycobacterium, possibly contingent on the cessation of mycolactone production. In a recent study, expression of cytokines was correlated with the inflammatory response evaluated by histopathology (133). All of the cases showed extensive necrosis and chronic inflammation. The most important feature correlating with chronicity was considered to be the presence or absence of granulomas coexisting with a mixed proinflammatory/antiinflammatory cytokine balance. Granulomas were absent from relatively early ulcerative lesions, which contained more bacilli and little interferon (IFN)-gamma, suggesting that at this stage of the disease strong suppression of the protective cellular immune response facilitates proliferation of bacilli. When granulomas were present, significantly higher expression of IFN-gamma was seen as well as lower bacillary counts.

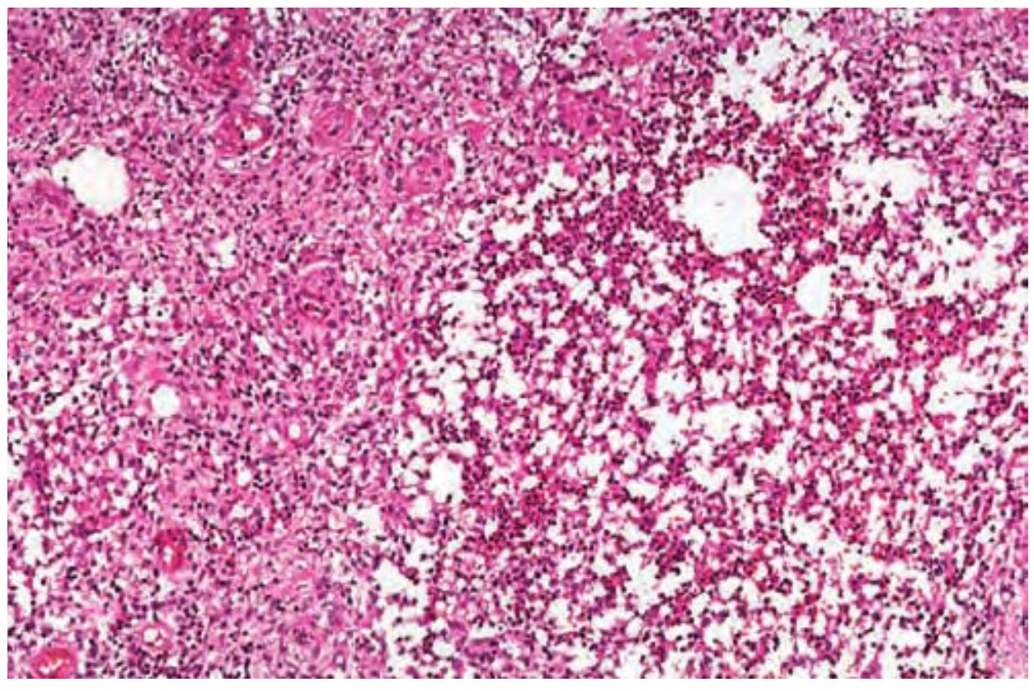


FIGURE 21-30. Mycobacterium fortuitum injection abscess. Dermal mixed granulomatous and acute inflammation (H&E stain).

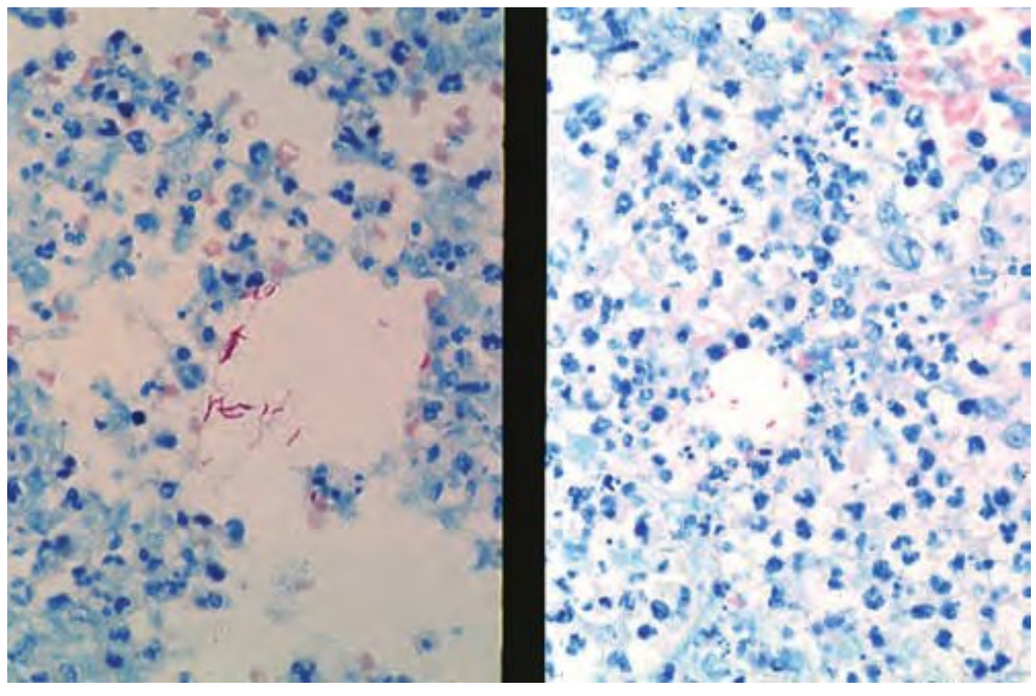


FIGURE 21-31. Mycobacterium fortuitum injection abscess. Clusters of acid-fast bacilli within a fat vacuole (Ziehl-Neelsen stain).

Other Nontuberculosis Mycobacterioses

Infections in the skin and subcutis caused by the rapid growers *M. chelonei*, *M. fortuitum*, and *M. abscessus* are associated with medical injections through unsterile contaminated needles and cannulas (77,134). Sporotrichoid spread can occur with *M. chelonei* (135). The inflammatory reaction is usually a mixed acute (neutrophilic) and chronic (granulomatous) response, with acid-fast bacilli visible on sections (77) (Figs. 21-30 and 21-31). Localized and disseminated *M. haemophilum* infection is reported in patients with HIV and other causes of immunosuppression (136–138).

BCG is the most commonly used vaccine, yet it rarely results in significant cutaneous lesions. Persisting ulcerating lesions may be observed. Histologically, these lesions are caseating granulomas in the dermis, as seen in tuberculosis, but acid-fast bacilli are rarely observed. In immunocompromised patients, there may be generalized cutaneous nodules, and histology shows abundant bacilli, poorly formed bacilli, and variable or no necrosis (139).

LEPROSY

Leprosy is caused by *M. leprae* and predominantly affects the skin and peripheral nerves. The disease is endemic in many tropical and subtropical countries but is declining in prevalence as a result of multidrug therapy. The Indian subcontinent, Southeast Asia, sub-Saharan countries in Africa, and Brazil comprise the areas most affected at present (140,141). The mode of transmission of leprosy is unknown, but it is probably inhalation of bacilli, which may be excreted from the nasal passages of a multibacillary patient or possibly implanted from organisms in the soil. Direct person-to-person infection by means of the skin occurs rarely if at all. After inhalation, it is likely that bacilli pass through the blood to peripheral and cutaneous nerves, where infection and host reaction commence.

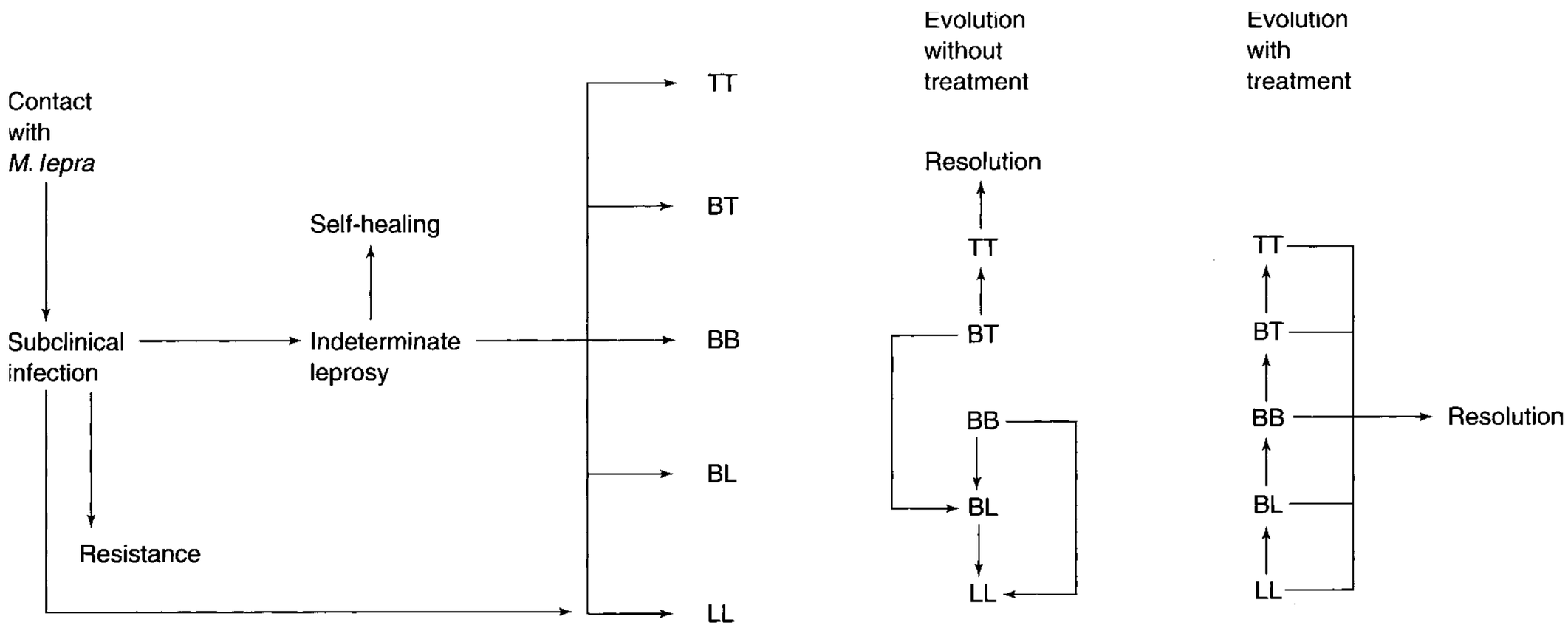


FIGURE 21-32. Leprosy. The sequence of events that may follow infection with M. leprae. (TT, tuberculoid; BT, borderline tuberculoid; BB, midborderline; BL, borderline lepromatous; LL, lepromatous.)

Immunopathologic Spectrum of Leprosy

The sequence of disease pathogenesis is complex, is very chronic, and depends on host-parasite immunologic responses. The leprosy bacillus is nontoxic, and clinicopathologic manifestations are the result of immunopathology and/or the progressive accumulation of infected cells. Leprosy is the best example of a disease showing an immunopathologic spectrum whereby the host immune reaction to the infective agent ranges from apparently none to marked, with a consequent range of clinicopathologic manifestations (142,143). Tuberculoid leprosy indicates a high cellular immune response (i.e., T cells and macrophage activation) and few bacilli in tissues; at the opposite pole, lepromatous leprosy indicates an absent cellular immune response to *M. leprae* antigens, with no macrophage activation and abundant bacilli in tissues. The spectrum of leprosy is a continuum, and patients may move in either direction according to host response and treatment. The standard delineation follows that of Ridley and Jopling, with categories defined along the spectrum by a combination of clinical, microbiologic, histopathologic, and immunologic indices: TT (tuberculoid), BT (borderline tuberculoid), BB (midborderline), BL (borderline lepromatous), and LL (lepromatous). The term *borderline* is used to denote patterns that share some features of both tuberculoid and lepromatous leprosy (141,142).

TT and LL patients are stable, the former often self-healing and the latter remaining heavily infected unless given appropriate chemotherapy. Patients presenting at the BT point will often downgrade toward BL leprosy in the absence of treatment. The central point of the spectrum (BB) is the most unstable, with most patients downgrading to LL if not treated. The term *indeterminate leprosy* is used to describe patients presenting with very early leprosy lesions that cannot be categorized definitely along the immunopathologic spectrum (e.g., cannot be determined as BT or LL).

It is likely that in endemic zones, a high proportion of people are infected by *M. leprae* but either have full immunity and no disease or have developed one or a few lesions that have self-healed without significant morbidity. The progression of infection and disease is summarized in Figure 21-32. Patients with determined leprosy are most numerous at the BT and LL points of the spectrum.

Staining of Mycobacterium leprae Bacilli

The classical method for demonstrating leprosy bacilli in lesions is a modified Ziehl-Neelsen stain, where the degree of acid and alcohol removal of carbol fuchsin is less than in the methods used for identifying other mycobacteria. The Fite methods are the most commonly used (143). Methanamine silver stains are also useful in detecting fragmented acid-fast bacilli. The sensitivity of detection of acid-fast bacilli by histologic means remains poor, because about 1,000 bacilli per cubic centimeter of tissue must be present in order to detect 1 bacillus in a section. For lesions where bacilli are scanty, it is recommended that at least six sections be examined before declaring them negative (144). The standard enumeration of leprosy bacilli in lesions—the bacterial index (BI)—follows Ridley's logarithmic scale (which applies to both skin biopsies and slit skin smears).

- BI = 0: no bacilli observed
- BI = 1: 1 to 10 bacilli in 10 to 100 high-power fields (hpf, oil immersion)
- BI = 2: 1 to 10 bacilli in 1 to 10 hpf
- BI = 3: 1 to 10 bacilli per hpf
- BI = 4: 10 to 100 bacilli per hpf
- BI = 5: 100 to 1,000 bacilli per hpf
- BI = 6: >1,000 bacilli per hpf

Solid-staining bacilli indicate that the organisms are capable of multiplication. Fragmented (beaded) and granular acid-fast

bacilli indicate that they are dead. Patients with no bacilli detectable in lesions are termed *paucibacillary*; those with some or many bacilli are *multibacillary* (this distinction is important in determing the duration of chemotherapy) (145).

Immunocytochemical methods for demonstrating mycobacterial antigens have a limited role. The most frequently used is a polyclonal anti-BCG antibody (146). In untreated lesions, it will not detect small numbers of bacilli if ordinary histochemical methods have proved negative. However, immunocytochemistry does have a role in demonstrating the presence of leprosy antigen after the bacilli have fragmented, been partly digested by macrophage enzymes, and lost their acid-fast staining quality (see page 562).

Clinical Pathology of Leprosy

For general discussions of clinical leprosy and leprosy pathology, the reader is referred to Job (147) and Britton and Lockwood (141).

Early, Indeterminate Leprosy

Many patients present with obvious or advanced skin and peripheral nerve lesions (the latter are primarily nerve enlargement and the consequences of anesthesia). These patients have "determined leprosy." However, the earliest detectable skin lesion comprises one or a few hypopigmented macules with variable loss of sensation. Any part of the body may be affected.

Histopathology. There is mild lymphocytic and macrophage accumulation around neurovascular bundles, the superficial and deep dermal vessels, sweat glands, and erector pili muscle; focal lymphocytic invasion into the lower epidermis and into the dermal nerves may be observed. No formed epithelioid cell granulomas are present (if they were, it would not be indeterminate leprosy but a tuberculoid leprosy). Schwann cell hyperplasia is a feature, but it is highly subjective. Not all of these features are present in every case. The diagnosis hinges on finding one or more acid-fast bacilli in the sites of predilection: in nerve, in erector pili muscle, just under the epidermis, or in a macrophage about a vessel. Without demonstrating bacilli, the diagnosis can only be presumptive (Figs. 21-33 and 21-34).

Lepromatous Leprosy

Lepromatous (LL) leprosy initially has cutaneous and mucosal lesions, with neural changes occurring later. The lesions usually are numerous and symmetrically arranged. There are three clinical types: macular, infiltrative-nodular, and diffuse. In the macular type, numerous ill-defined, confluent, either hypopigmented or erythematous macules are observed. They are frequently slightly infiltrated. The infiltrative-nodular type, the classical and most common variety, may develop from the macular type or arise as such. It is characterized by papules, nodules, and diffuse infiltrates that are often dull red. Involvement of the eyebrows and forehead often results in a leonine facies, with a loss of eyebrows and eyelashes. The lesions themselves are not notably hypoesthetic, although through involvement of the large peripheral nerves, disturbances of sensation and nerve paralyses develop. The nerves that are most commonly involved are the ulnar, radial, and common peroneal nerves.

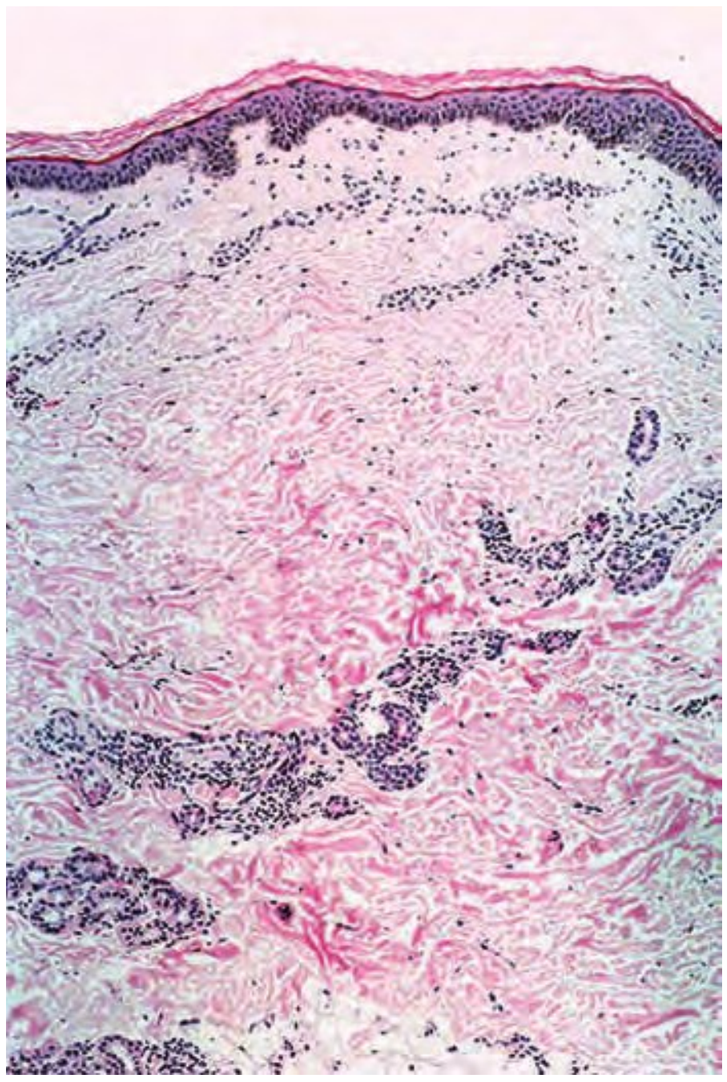


FIGURE 21-33. Indeterminate leprosy. Slight pandermal perineurovascular and periappendageal chronic inflammation (H&E stain).

The diffuse type of leprosy, called *Lucio leprosy*, which is most common in Mexico and Central America, shows diffuse infiltration of the skin without nodules. This infiltration may be quite inconspicuous except for the alopecia of the eyebrows and eyelashes it produces. Acral, symmetric anesthesia is generally present (148).

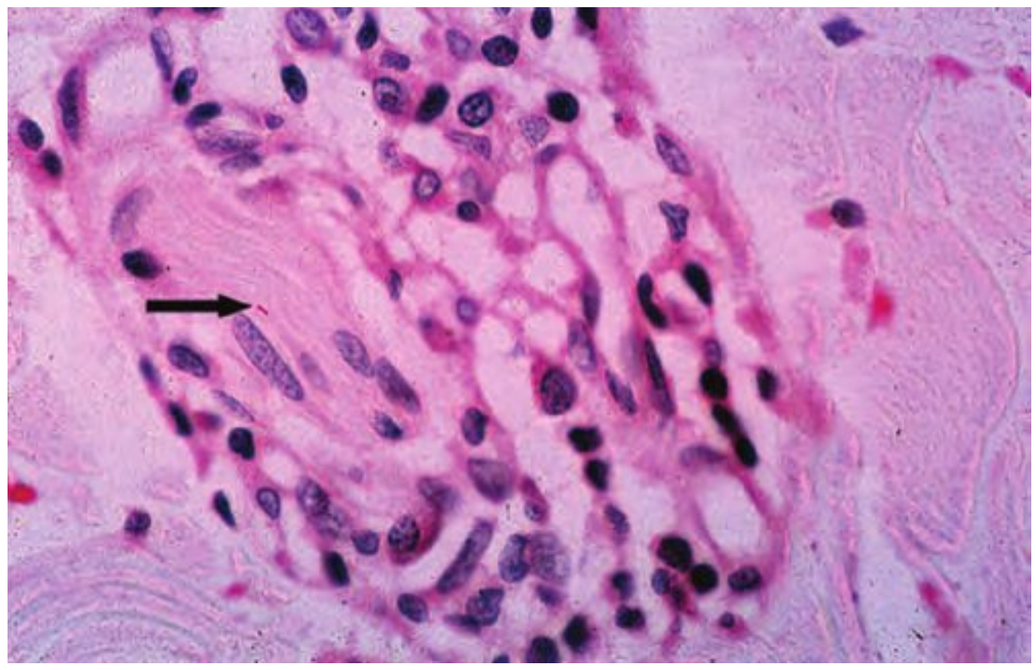


FIGURE 21-34. Indeterminate leprosy. High-power view of a small dermal nerve with surrounding lymphocytes and an intraneural acid-fast bacillus (arrow). There is no granuloma formation (Wade-Fite stain).

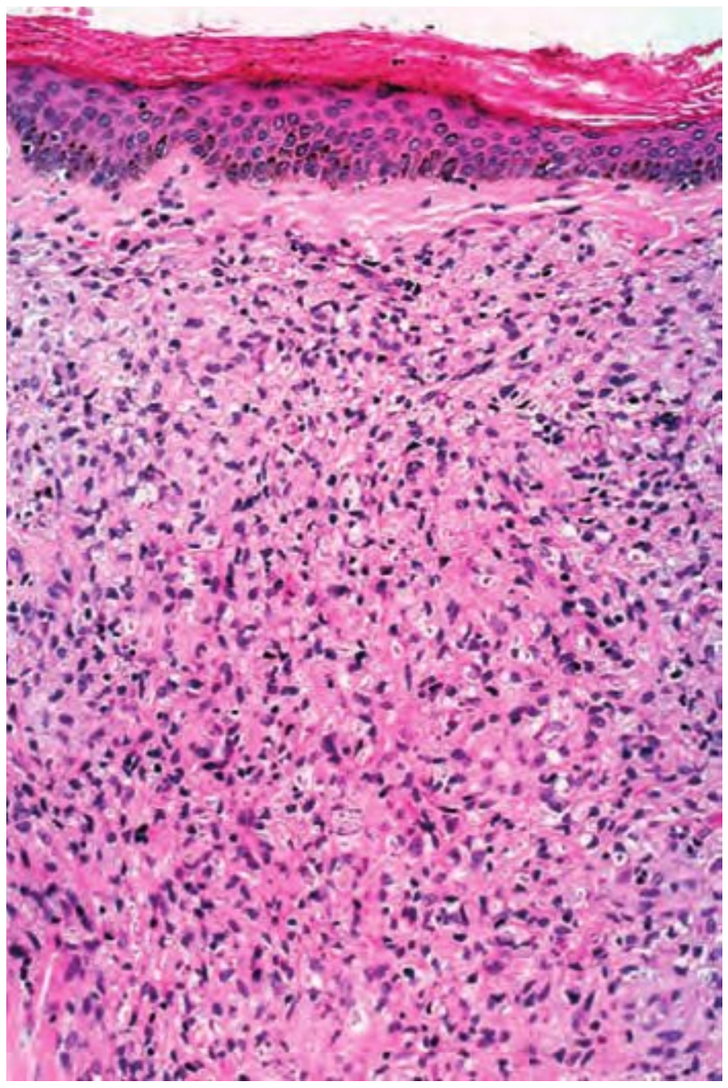


FIGURE 21-35. Lepromatous leprosy. Skin in multibacillary leprosy with a mass of macrophages in the dermis (no granuloma formation), leaving a clear grenz zone under the epidermis (H&E stain).

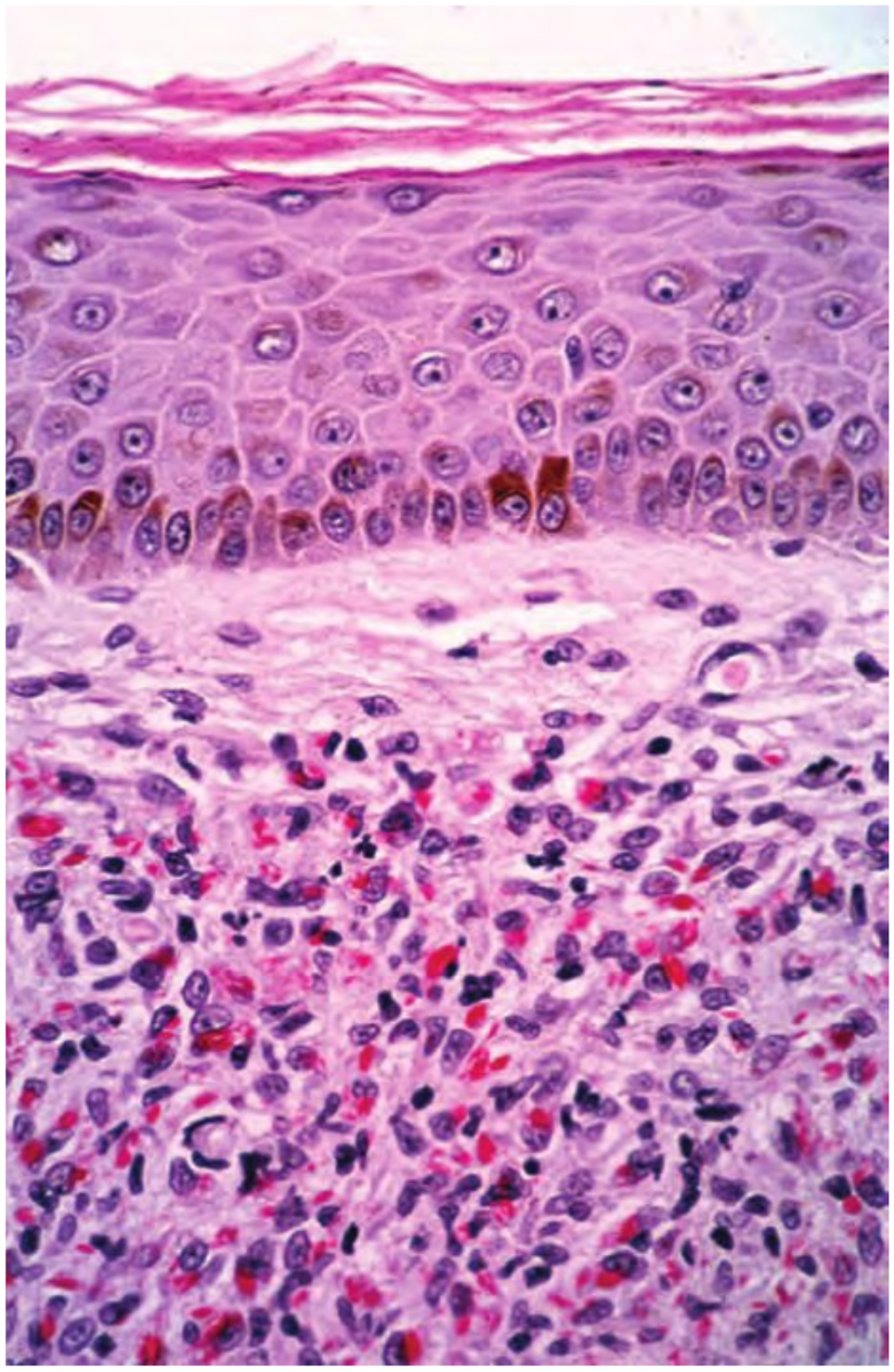


FIGURE 21-36. Lepromatous leprosy. Same case as Figure 21-35. Acid-fast bacilli, mostly solid, in large numbers (Wade-Fite stain).

A distinctive variant of lepromatous leprosy, the histoid type, first described in 1963 (149), is characterized by the occurrence of well-demarcated cutaneous and subcutaneous nodules resembling dermatofibromas. It frequently follows incomplete chemotherapy or acquired drug resistance, leading to bacterial relapse.

Rarely, lepromatous leprosy can present as a single lesion rather than as multiple lesions (150).

Histopathology. Lepromatous leprosy, in the usual macular or infiltrative-nodular lesions, exhibits an extensive cellular infiltrate that is almost invariably separated from the flattened epidermis by a narrow grenz zone of normal collagen (Figs. 21-35 and 21-36). The infiltrate causes the destruction of the cutaneous appendages and extends into the subcutaneous fat. In florid early lesions, the macrophages have abundant eosinophilic cytoplasm and contain a mixed population of solid and fragmented bacilli (BI = 4 or 5) (Figs. 21-33). The bacilli, on Wade-Fite staining, can be seen to measure about 5.0 by 0.5 μm and if solid may be packed like cigars. Bacilli are commonly observed in endothelial cells as well (Fig. 21-37). There is no macrophage activation to form epithelioid cell granulomas. Lymphocyte infiltration is not prominent, but there may be many plasma cells.

In time, and with antimycobacterial chemotherapy, degenerate bacilli accumulate in the macrophages—the so-called lepra cells or Virchow cells—which then have foamy or vacuolated cytoplasm (Fig. 21-38). They resemble xanthoma cells and, on staining with fat stains, are shown to contain lipid—largely neutral fat and phospholipids—rather than cholesterol. The Wade-Fite stain reveals that the bacilli are fragmented or granular and, especially in very chronic lesions, disposed in large basophilic clumps called *globi*. In lepromatous leprosy, in contrast to tuberculoid leprosy, the nerves in the skin may contain considerable numbers of leprosy bacilli but remain well preserved for a long time and slowly become fibrotic.

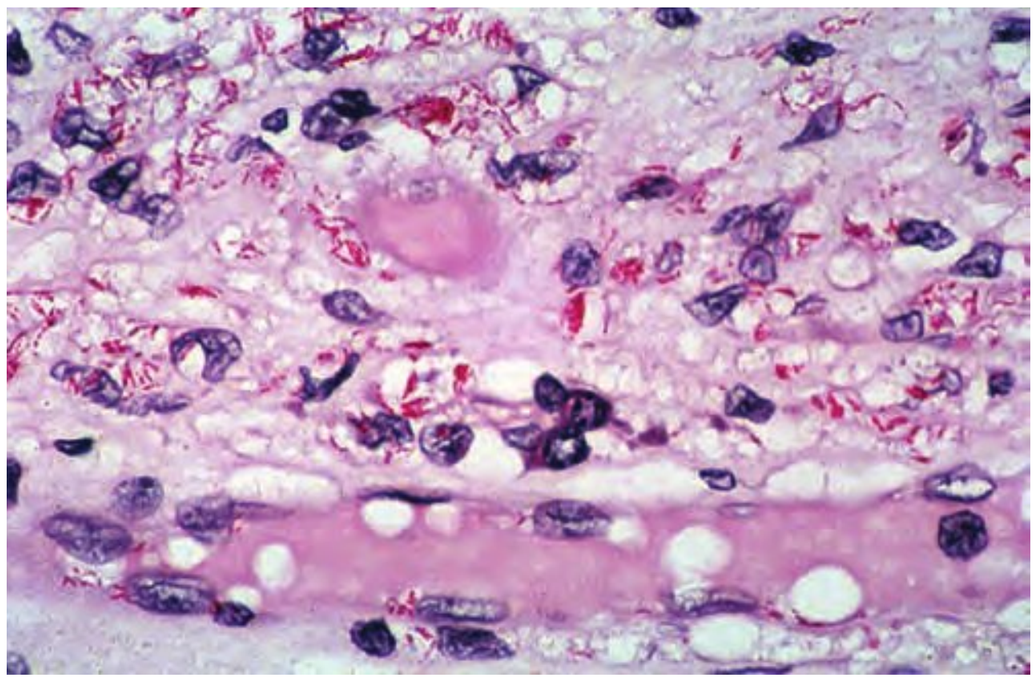


FIGURE 21-37. Lepromatous leprosy. Macrophages and endothelial cells of the capillary contain solid acid-fast bacilli (Wade-Fite stain).

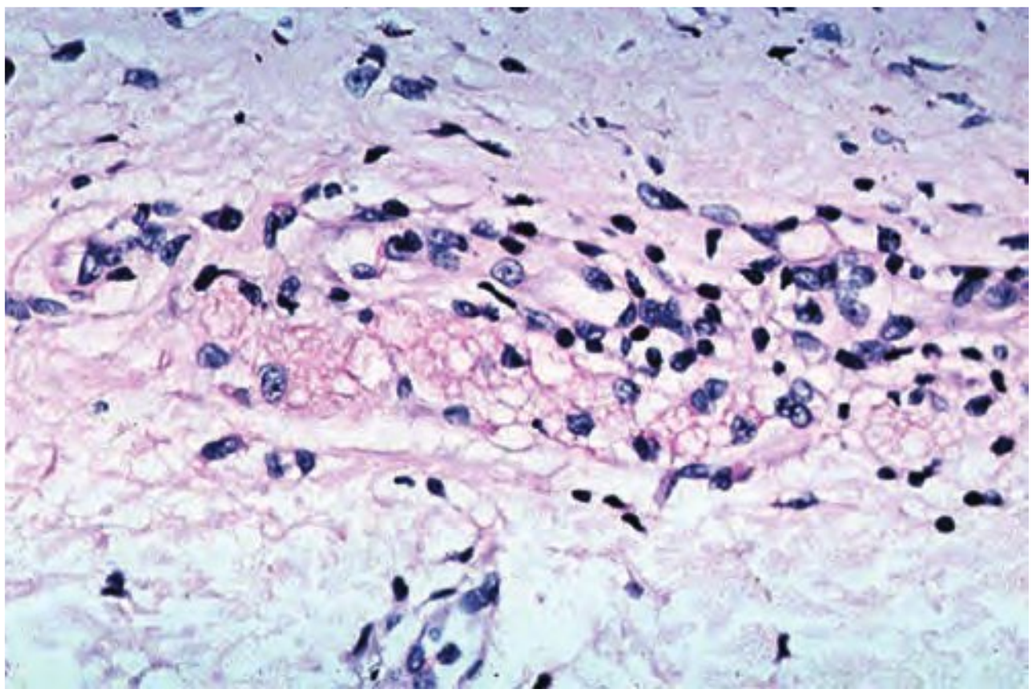


FIGURE 21-38. Lepromatous leprosy. Old, treated lesion, with large foamy macrophages and no identifiable bacilli (Wade-Fite stain).

When lepromatous leprosy is treated, the bacilli die rapidly and become fragmented within weeks or months. However, it can take several years for the bacterial debris to be cleared by host macrophages. The *M. leprae* antigen may persist even longer and can be demonstrated by immunocytochemical stains (Wade-Fite or silver) even when no bacilli are evident (Fig. 21-39).

The histopathology of Lucio (diffuse) leprosy is similar but with a characteristic heavy bacillation of the small blood vessels in the skin (148).

Histoid Leprosy

Histoid leprosy shows the highest loads of bacilli (frequently, the BI is 6), and the majority are solid staining, arranged in clumps like sheaves of wheat. The macrophage reaction is unusual in that the cells frequently become spindle shaped and oriented in a storiform pattern, similar to those of a fibrohistiocytoma (Fig. 21-40). The epidermis may be stretched over such dermal expansile nodules.

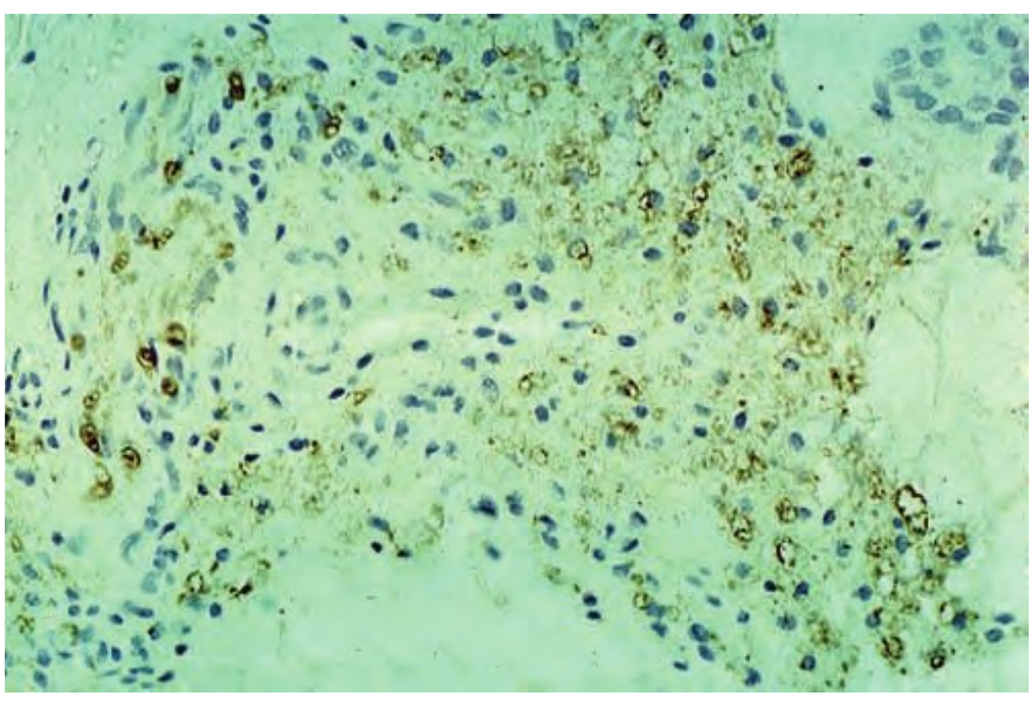


FIGURE 21-39. Lepromatous leprosy. Old, treated lesion; foamy macrophages remain but no acid-fast bacilli visible. However, an antimycobacterial immunocytochemical stain reveals persistent leprosy antigen (anti-BCG stain).

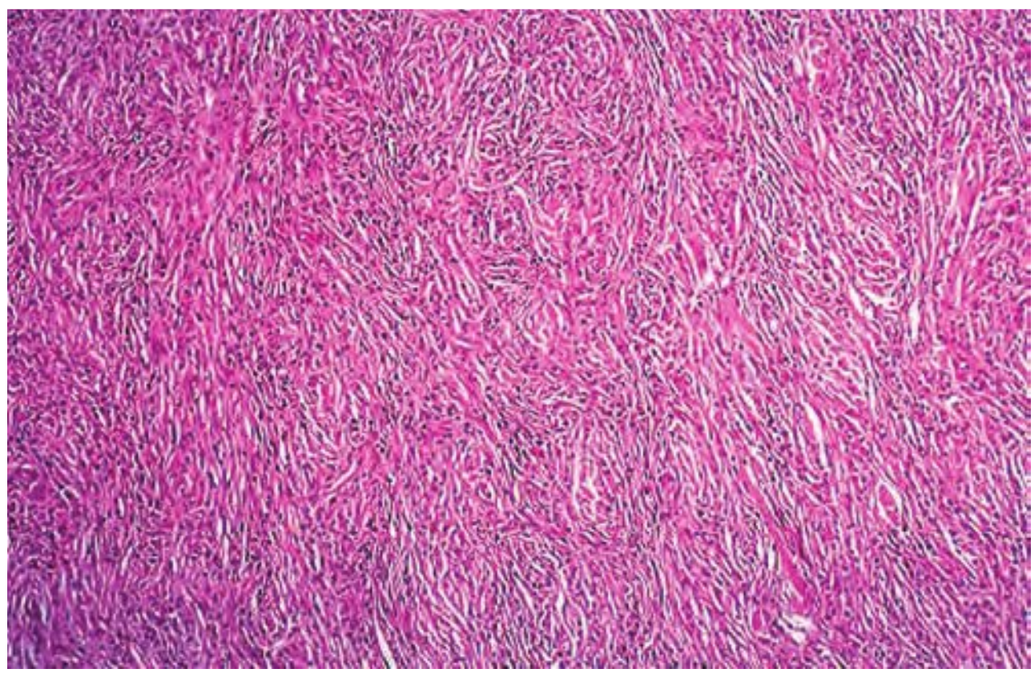


FIGURE 21-40. Lepromatous leprosy. A histoid lesion, with spindle cell proliferation of macrophages, resembling a storiform tumor. The acid-fast bacillus stain showed larger numbers of bacilli (H&E stain).

Borderline Lepromatous Leprosy

The lesions of borderline lepromatous (BL) leprosy are less numerous and less symmetrical than LL lesions and often display some central dimples.

Histopathology: The important difference between LL and BL leprosy histology is that in BL, the lymphocytes are more prominent and there is a tendency for some activation of macrophages to form poorly to moderately defined granulomas. Perineural fibroblast proliferation, forming an "onion skin" in cross-section, is typical. Foamy cells are not prominent, and globi do not usually accumulate; the BI ranges from 4 to 5.

Midborderline Leprosy

In midborderline (BB) leprosy, the skin lesions are irregularly dispersed and shaped erythematous plaques with punched-out centers. There may be small satellite lesions. Edema is prominent in the lesions.

Histopathology: In BB leprosy, the macrophages are uniformly activated to epithelioid cells but are not focalized into distinct granulomas, and lymphocytes are scanty. There are no Langhans giant cells. The BI ranges from 3 to 4. Dermal edema is prominent between the inflammatory cells.

Borderline Tuberculoid Leprosy

In borderline tuberculoid (BT) leprosy, the lesions are asymmetrical and may be scanty. They are dry, hairless plaques with central hypopigmentation. Nerve enlargement is usually found, and the lesions are usually anesthetic.

Histopathology: Granulomas with peripheral lymphocytes follow the neurovascular bundles and infiltrate sweat glands and erector pili muscles. Langhans giant cells are variable in number

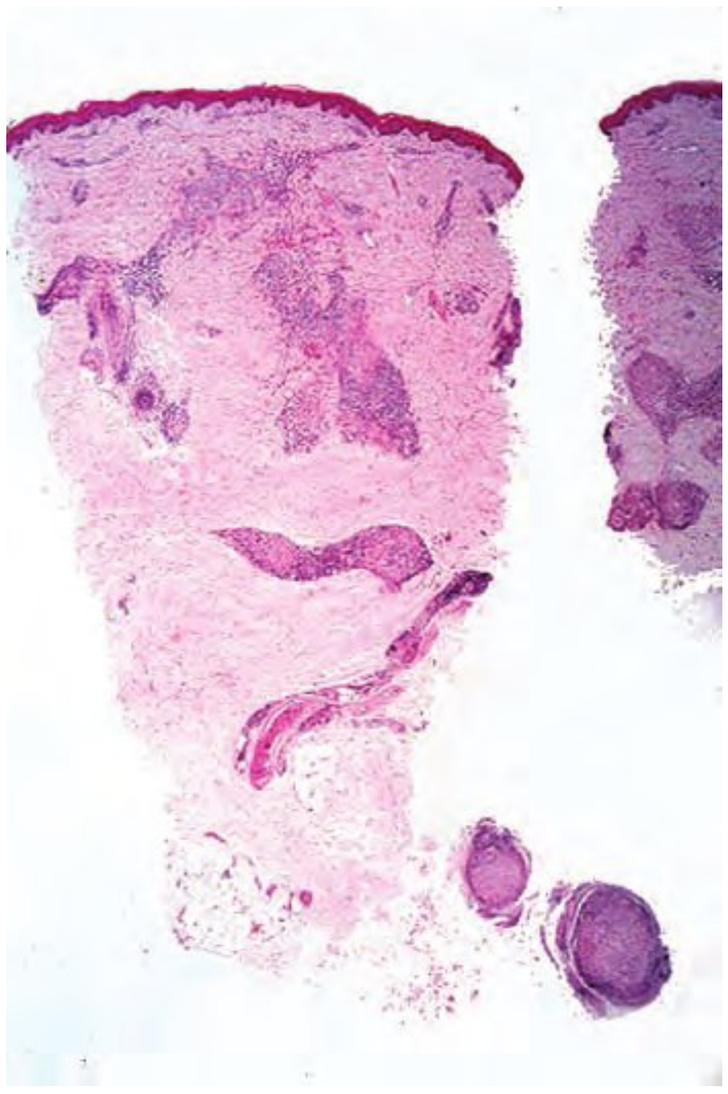


FIGURE 21-41. Tuberculoid leprosy. A typical lesion, showing pandermal perineurovascular granulomas and lymphocytes (H&E stain).

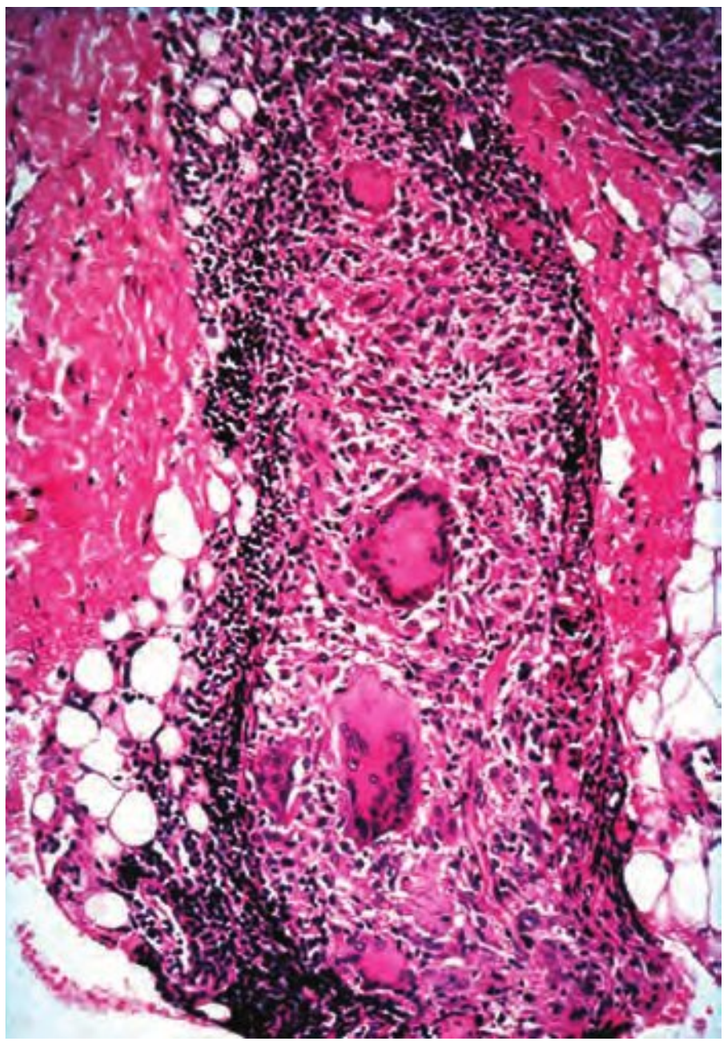


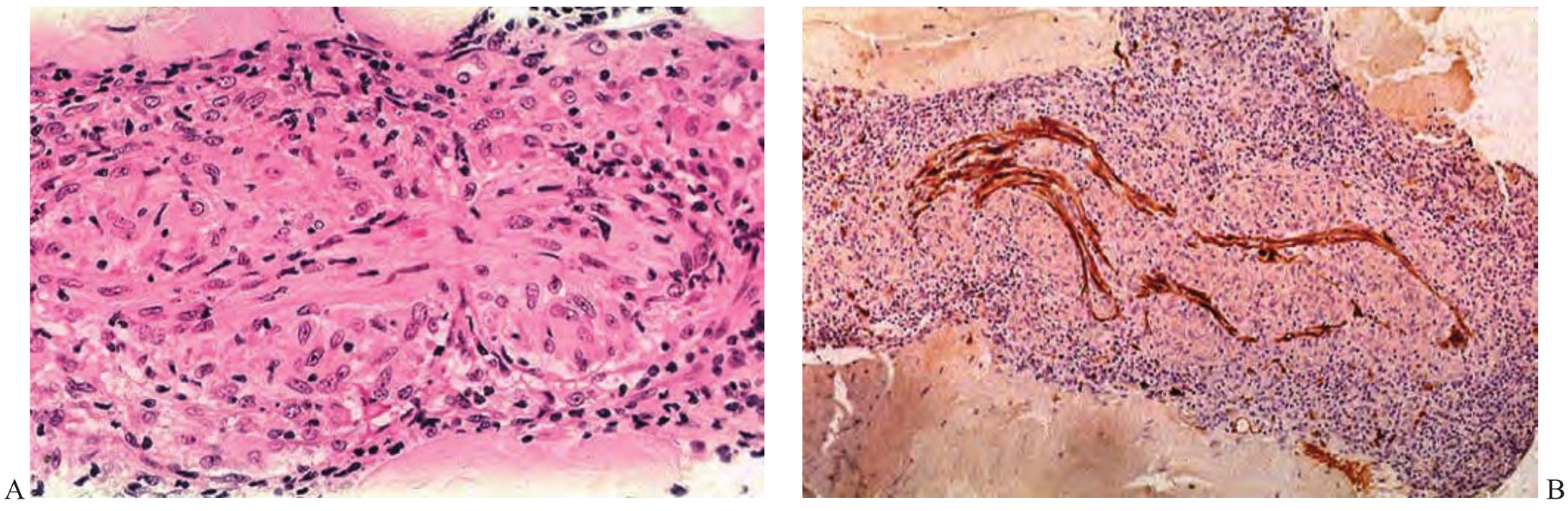
FIGURE 21-42. Tuberculoid leprosy. Granulomatous neuritis; dense lymphocytosis surrounding and eroding into the deep dermal nerve with giant cells (H&E stain).

and are not large in size. Granulomas along the superficial vascular plexus are frequent, but they do not infiltrate up into the epidermis. Nerve erosion and obliteration are typical (Figs. 21-41 to 21-43). Acid-fast bacilli are scanty (BI ranges from 0 to 2) and most readily found in the Schwann cells of nerves. Immunocytochemical staining for S-100 protein often demonstrates the perineural and intraneural granuloma well (Fig. 21-43B).

Tuberculoid Leprosy

The skin lesions of tuberculoid (TT) leprosy are scanty, dry, erythematous, hypopigmented papules or plaques with sharply defined edges. Anaesthesia is prominent (except on the face). The number of lesions ranges from one to five. Thickened local peripheral nerves may be found. The lesions heal rapidly on chemotherapy.

Histopathology. Primary TT leprosy has large epithelioid cells arranged in compact granulomas along with neurovascular bundles, with dense peripheral lymphocyte accumulation. Langhans giant cells are typically absent. Dermal nerves may be absent (obliterated) or surrounded and eroded by dense lymphocyte cuffs. Acid-fast bacilli are rarely found, even in nerves. A second pattern of TT leprosy is found in certain reactional states (see next page).



A B

FIGURE 21-43. Tuberculoid leprosy. A: Typical endoneuritis with granulomas eroding into the nerve (H&E stain). B: Granulomatous neuritis; granulomas within the dermal nerve disrupting the Schwann cells and axons (S100 immunoperoxidase stain).



A B

FIGURE 21-44. Leprosy reversal reaction. A: Pretreatment BL leprosy. B: Three months posttreatment, with enlargement of the skin lesions due to increased inflammation.

Peripheral Nerves

In all of these patterns of leprosy, the major peripheral nerves are often undergoing parallel pathologies. The inflammation is similar, and the same classification system is applied. However, the density of acid-fast bacilli is often a logrithm higher than in the nearby skin (151).

Leprosy Reactions

Leprosy reactions are classified into two main types (1 and 2). A third reaction is specific to Lucio multibacillary leprosy (152).

Type 1 Reactions

Because the immunopathologic spectrum of leprosy is a continuum, patients may move along it in both directions. Should such shifts be rapid, they induce an inflammatory reaction with edema that results in enlargement of lesions with more erythema (Fig. 21-44). Shifts toward the tuberculoid pole are called *upgrading* or *reversal reactions*; shifts toward the lepromatous pole are termed *downgrading reactions*. Both are aspects of delayed hypersensitivity, or type 1, leprosy reactions. TT patients are stable. BT patients may downgrade without treatment. Multibacillary patients, particularly those at the BL point, frequently upgrade on chemotherapy, and about one quarter of them will exhibit significant reactions. BB patients are most unstable and will move either way depending on therapy, often with reactions. The most important aspect of type 1 reactions is not the skin but the condition of the peripheral nerves, in which a similar inflammatory process is going on; reaction induces increased intraneural inflammation and edema, which is damaging. At worst, there is caseous necrosis of large peripheral nerves resulting from upgrading reactions.

Histopathology: The histopathology of type 1 reactions has still not been well evaluated (153). The distinction between upgrading and downgrading reactions is difficult to make and may require serial examinations. Typically, there is edema within and about the granulomas and proliferation of fibrocytes in the dermis. In upgrading reactions, the granuloma becomes more epithelioid and activated, and Langhans giant cells are larger (Fig. 21-45); there may be erosion of granulomas into the lower epidermis, and there may be fibrinoid necrosis within granulomas and even within dermal nerves. In downgrading reactions, necrosis is much less common, and over time the density of bacilli increases. Multibacillary leprosy patients who upgrade on therapy show old foamy macrophages and degenerate bacilli admixed with new epithelioid cell granulomas.

Type 2 Reaction: Erythema Nodosum Leprosum

Erythema nodosum leprosum (ENL) occurs most commonly in LL leprosy and less frequently in BL leprosy. It may be observed not only in patients under treatment but also in untreated patients. Clinically, the reaction has a greater resemblance to erythema multiforme than to erythema nodosum.

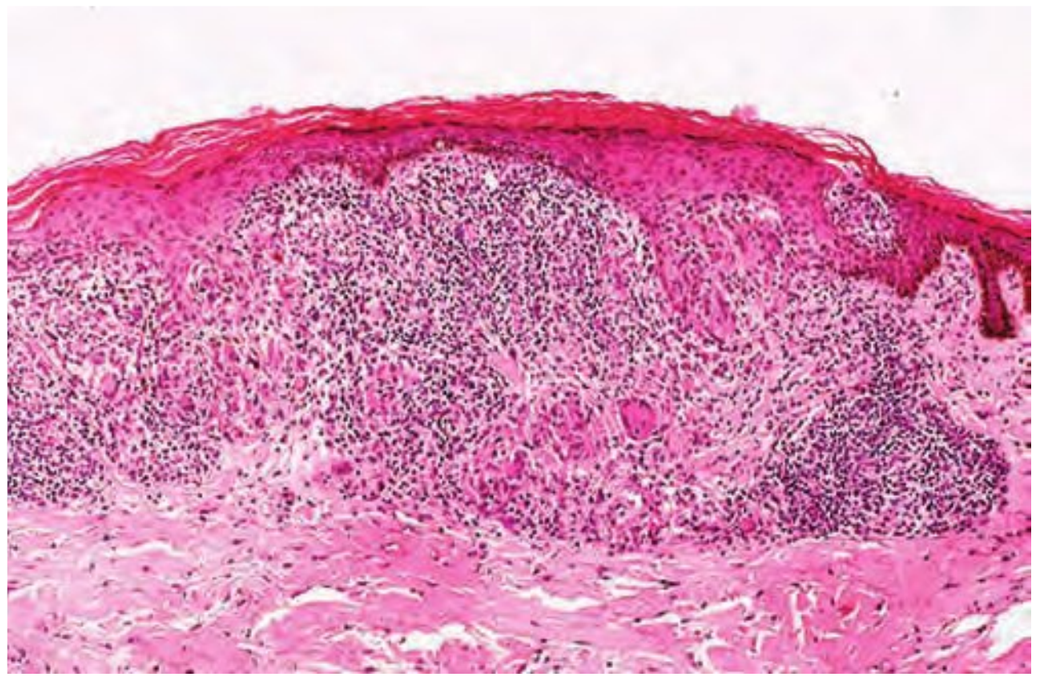


FIGURE 21-45. Leprosy: type 1 reaction (delayed hypersensitivity). Granulomatous erosion of the epidermis; this feature is not usually encountered in nonreacting leprosy (H&E stain).

On the skin, tender, red plaques and nodules together with areas of erythema, and occasionally also purpura and vesicles, are observed. Ulceration, however, is rare. The eruption is widespread and accompanied by fever, malaise, arthralgia, and leukocytosis. New lesions appear for only a few days in some cases but for weeks and even years in others. This is the only type of reactional leprosy that responds to treatment with thalidomide.

Histopathology. In ENL, the lesions are foci of acute inflammation superimposed on chronic multibacillary leprosy (Fig. 21-46). Polymorph neutrophils may be scanty or so abundant as to form a dermal abscess with ulceration (154). Whereas foamy macrophages containing fragmented bacilli are usual, in some patients no bacilli remain and macrophages have a granular pink hue on Wade-Fite staining, indicating mycobacterial debris. An antimycobacterial immunocytochemical stain (e.g., anti-BCG) will indicate abundant antigen. A necrotizing vasculitis affecting arterioles, venules, and capillaries occurs in some cases of ENL; these patients may have superficial ulceration.

Lucio Reaction

The Lucio reaction occurs exclusively in diffuse lepromatous leprosy, in which it is a fairly common complication. It usually occurs in patients who have received either no treatment or inadequate treatment. In contrast to ENL, fever, tenderness, and leukocytosis are absent. The lesions consist of barely palpable, hemorrhagic, sharply marginated, irregular plaques. They develop into crusted lesions and, particularly on the legs, into ulcers. There may be repeated attacks or continuous appearance of new lesions for years.

Histopathology. In the Lucio reaction, vascular changes are critical (143). Endothelial proliferation leading to luminal obliteration is observed in association with thrombosis in the medium-sized vessels of the dermis and subcutis. There is a sparse, largely mononuclear infiltrate. Dense aggregates of acid-fast bacilli are found in the walls and the endothelium of normal-appearing vessels as well as in vessels with proliferative changes (Fig. 21-47). Ischemic necrosis, brought on by the vascular occlusion, leads to hemorrhagic infarcts and results in crusted erosions or frank ulcers.

Electron Microscopy of Leprosy

Under electron microscopy, *M. leprae* can be seen to consist of an electron-dense cytoplasm lined by a trilaminal plasma membrane. Outside of this membrane lies the bacterial cell wall surrounded by a radiolucent area, the waxy coating typical of mycobacteria (81). Lepra bacilli are found in the skin, predominantly in macrophages and in Schwann cells.

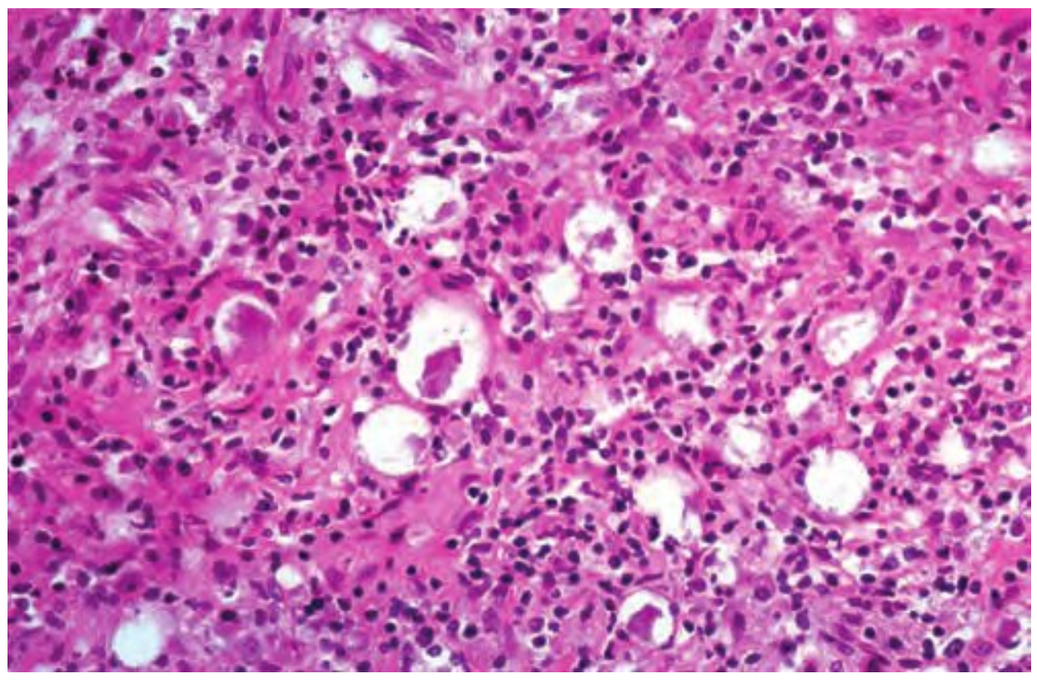


FIGURE 21-46. Leprosy: erythema nodosum leprosum (type 2 reaction). Macrophages with vacuoles and globi and a polymorphonuclear cell infiltrate (H&E stain).

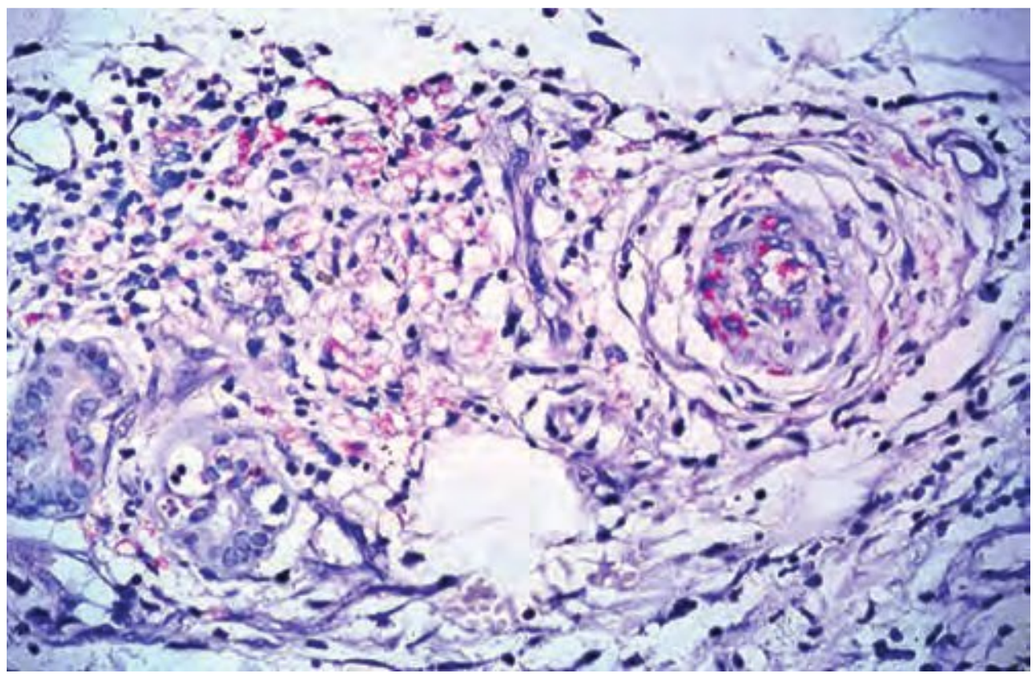


FIGURE 21-47. Leprosy, Lucio reaction. Dermal vessels showing endarteritis obliterans and abundant bacilli within endothelial cells (Wade-Fite stain).

Pathogenesis of Leprosy

With respect to immunologic reactivity, patients with lepromatous leprosy have a defect in cell-mediated immune responses to the lepra bacilli, which therefore cannot be eradicated from the body spontaneously (141,155,156). The primary defect lies in the T lymphocytes, which can be stimulated only slightly or not at all to react against the lepra bacilli and thus do not adequately activate macrophages to destroy phagocytosed bacilli. This defect is specific for *M. leprae*, because patients with lepromatous leprosy show normal immunologic responses to antigens other than lepromin in both *in vivo* and *in vitro* testing.

The specific inability of T lymphocytes obtained from patients with lepromatous leprosy to react against lepromin is shown by the fact that when these lymphocytes are incubated with lepromin, they show little or no production of macrophage migration-inhibiting factor (MIF). In contrast, the lymphocytes of patients with tuberculoid leprosy produce significant amounts of MIF on exposure to lepromin. One modern view is that in tuberculoid patients, exposure to leprosy antigens results in a predominant T helper 1 (Th-1) cytokine secretion profile, which results in macrophage activation. Conversely, in lepromatous patients, the cytokine profile (Th-2) inhibits cell-mediated immunity and promotes humoral immunity, which does not contribute to host defense (155,157). In reversal reactions, there is an increase in the lymphocyte response to lepromin during the reaction and a decrease during the postreaction phase.

Analysis of T-cell subsets in lesions has shown that in tuberculoid leprosy, with its high degree of resistance to the leprosy bacilli, the T helper lymphocytes are distributed evenly throughout the epithelioid cell aggregates, and the suppressor T lymphocytes are restricted to the peripheries of the granulomas. In lepromatous leprosy, both helper and suppressor T lymphocytes are distributed diffusely throughout the lesions (158). It is noteworthy that the distribution of helper and suppressor T cells in tuberculoid leprosy is similar to that observed in sarcoidosis.

In patients with either ENL or the Lucio reaction, deposits of IgG and the third component of complement (C3), as well as circulating immune complexes, have been found in the vessel walls of the dermal lesions. This suggests that both reactions are mediated by immune complexes (Gell and Coombes type III reaction) (146).

The lepromin skin test, or Mitsuda test, consists of the intradermal injection of a preparation of *M. leprae* derived from autoclaved infected human tissue. A positive reaction consists of the formation of a nodule measuring $\geq$5 mm in diameter after 2 to 4 weeks. On histologic examination, the nodule shows an epithelioid cell granuloma. The reaction is positive only in the high-resistance (tuberculoid and borderline tuberculoid) forms of the disease. In indeterminate leprosy, it may be positive or negative. The test reveals the inability of patients at the lepromatous end of the spectrum to react to the injection of *M. leprae* with an epithelioid cell granuloma, and its main value is therefore as a marker of specific cell-mediated immunity to this organism, which varies continuously along the immunopathologic spectrum.

HIV Infection and Leprosy

Because HIV induces a generalized immunosuppressive state, and because a wide range of intracellular infectious agents normally controlled by the T-cell/macrophage system may proliferate to cause significant disease, it was expected that leprosy might also be affected. Specifically, the disease might become more prevalent in HIV and leprosy coendemic areas, and individual patients might downgrade toward lepromatous disease as their HIV disease progresses. However, epidemiologic studies have shown no effect of HIV infection on the incidence of leprosy in properly controlled studies (159,160) nor has a change in the proportions of tuberculoid versus lepromatous patients been noted (161). At present, the only clinicopathologic difference between HIV-infected and noninfected leprosy patients that is suggested is an increased likelihood of HIV-positive patients undergoing type 1 upgrading reactions (161,162). This rather paradoxical phenomenon awaits further evaluation.

Histopathologic Differential Diagnosis

The leprosy bacillus cannot yet be grown *in vitro*. Tuberculoid (granulomatous) leprosy needs to be distinguished from the many other granulomatous dermatitides. The presence of acid-fast bacilli in nerves is conclusive proof of leprosy, as is the demonstration of an intraneural granuloma. The S-100 stain may highlight this phenomenon (163), although in practice, if the diagnosis is in doubt after investigation with ordinary stains, this immunocytochemical method is not usually diagnostic either. In leprosy, naked granulomas are found only in BB leprosy, and acid-fast bacilli will be found in the lesions. Sarcoidosis may rarely cause granulomas to form within peripheral nerves (164) but does not appear to do so in dermal nerves. The general vertical perineurovascular distribution of granulomatous inflammation and involvement of sweat glands in tuberculoid leprosy are helpful. The presence or absence of plasma cells or of intraepidermal lymphocytes is not helpful. Unlike other mycobacterial skin infections such as tuberculosis, and unlike granulomatous leishmaniasis, the epidermis in tuberculoid leprosy is usually flat and nonhyperplastic. Late secondary and tertiary cutaneous syphilis is characterized by epithelioid and giant cell granulomas in the dermis, not directly involving nerves, and the epithelium is usually hyperplastic. Intragranuloma necrosis (fibrinoid or caseating) occurs in leprosy in type 1 reactions, sometimes spontaneously; this can be confused with necrobiotic lesions such as granuloma annulare. Necrosis within a nerve that is granulomatous is diagnostic of leprosy.

Early, indeterminate leprosy overlaps with many specific and nonspecific dermatitides manifesting perineurovascular lymphocytic infiltrates. Finding bacilli in critical sites (in nerve, under the epidermis, in erector pili muscle, or in macrophages) is critical. In the absence of bacilli and the presence of a pandermal infiltrate, leprosy can only be suspected. Problems may arise from contaminant mycobacteria in staining solutions and in the water baths used for floating out sections. Such organisms are usually above the plane of the section, overlap the cell nuclei, and usually stain darker than *M. leprae*. The use of PCR for identifying paucibacillary leprosy in skin sections and tissues has not been as successful as it once was thought to be (165).

Ultimately, there is a proportion of suspect paucibacillary leprosy lesions for which the histopathologist cannot make a firm diagnosis either way, and intra- and interobserver variation may be considerable (166). Clinical diagnosis of single-lesion leprosy is also imperfect (150).

Lepromatous leprosy infiltrates can resemble xanthoma, although the cytoplasmic granularity is coarser in the latter disease. The presence of acid-fast bacilli is obviously important, and in long-treated lesions that may cause confusion, antimycobacterial immunocytochemistry is helpful. ENL may be overlooked because it is a combined chronic and acute inflammatory infiltrate, but once thought of, the presence of bacilli or antigen is diagnostic. Certain other mycobacterioses in immunosuppressed patients, such as *M. avium-intracellulare*, may produce histoid-like multibacillary lesions (119) (see Figs. 21-23 and 21-40); however, nerves are not involved in this infection.

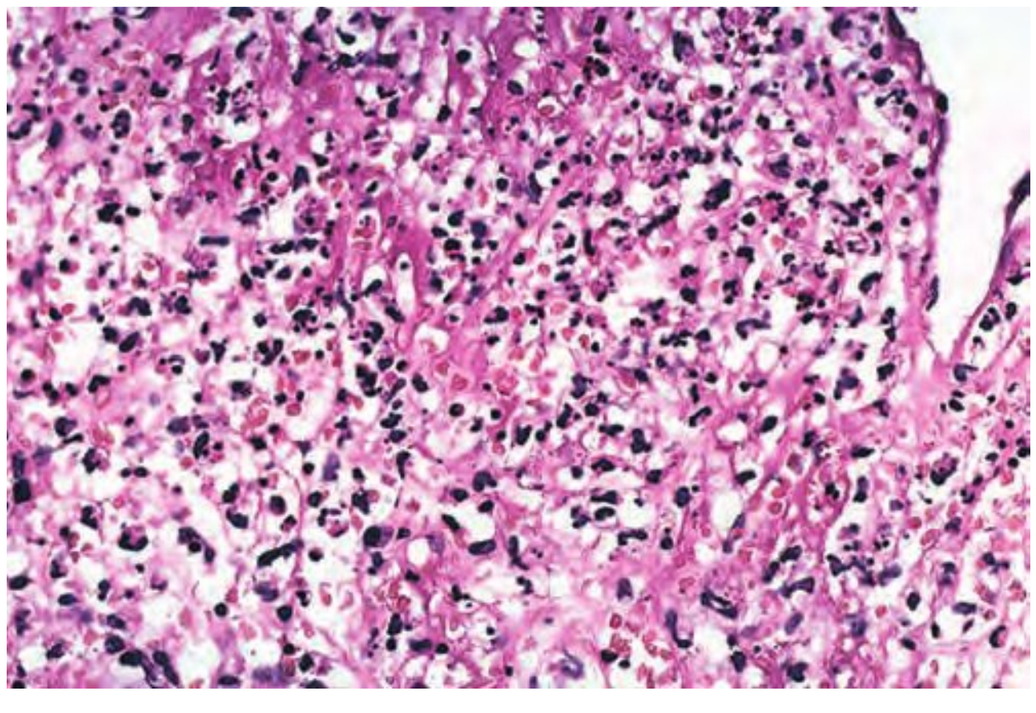


FIGURE 21-49. Anthrax. Acute inflammation and dermal edema (H&E stain).

ANTHRAX

Anthrax, caused by *Bacillus anthracis,* is enzootic in many countries (167). It occurs occasionally among workers in tanneries and wool-scouring mills through the handling of infected hides, wool, or hair imported from Asia. The lesion starts as a papule. The papule enlarges, and a hemorrhagic pustule forms (168). After the pustule has ruptured, a thick, black eschar covers the area. Marked erythema and edema surround the lesion. Characteristically, pain is slight or absent.

Histopathology. At the site of the eschar, the epidermis is destroyed and the ulcerated surface is covered with necrotic tissue. There is marked edema of the dermis. Vasculitis, hemorrhage, and variable acute and chronic inflammatory infiltrate are observed (Figs. 21-48 and 21-49).

Anthrax bacilli are present in large numbers and can be recognized in sections stained with the Gram stain. The bacillus is large, rod shaped, encapsulated, gram positive, 6 to 10 μm long, and 1 to 2 μm thick. Anthrax bacilli are found particularly in the necrotic tissue toward the surface of the ulcer but also in the dermis (Fig. 21-50). Phagocytosis of the bacilli by either neutrophils or histiocytes is absent.

INJECTION ABSCESSES

The pandemic of injection drug abuse has resulted in numerous patients presenting with dermal and subcutaneous abscesses from the use of contaminated syringes and needles. Similar abscesses have also been frequently noted in health care settings, where injection solutions may also be contaminated (169). Numerous bacterial and mycobacterial species may be found on culture, including staphylococci and streptococci. A recent epidemic in the United Kingdon involved *Clostridium perfringens* and *Clostridium novyi* infections (170). These infections may progress to necrotizing fasciitis, myosites, bacteraemia, and septic shock with fatalities.

A standard panel of Gram, silver stain (e.g., Grocott), and Ziehl-Neelsen is useful in identifying the organisms, although culture is required for specific diagnosis (Fig. 21-51). The histopathology is not usually specific. Acute inflammation, edema, and tissue necrosis are usual. In chronic lesions, much

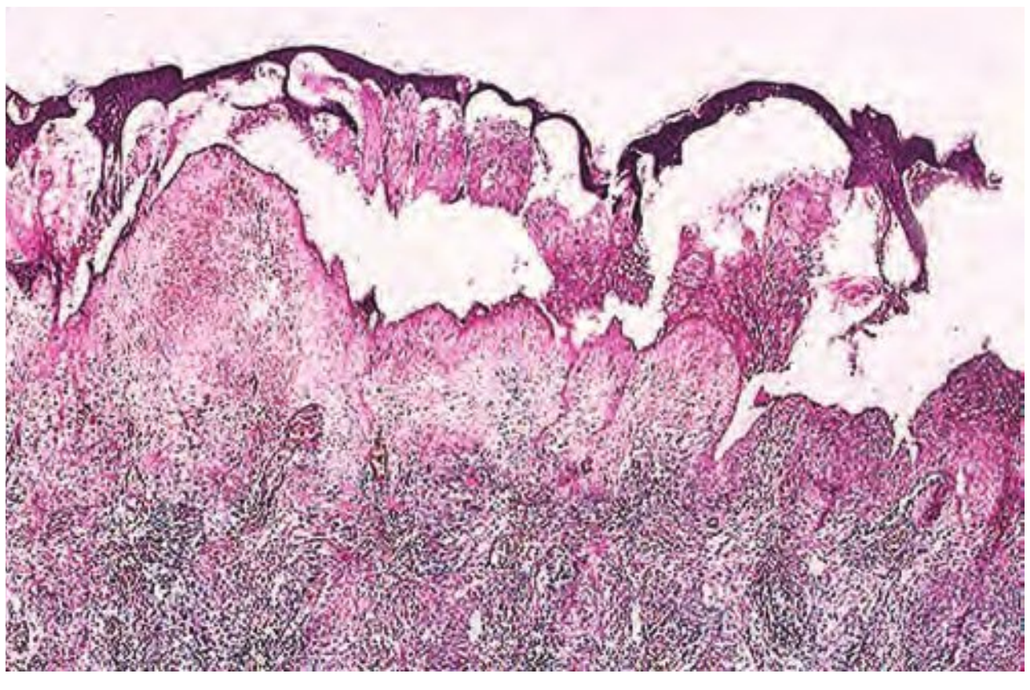


FIGURE 21-48. Anthrax. Acute lesion with epidermal necrosis and pandermal inflammation (H&E stain).

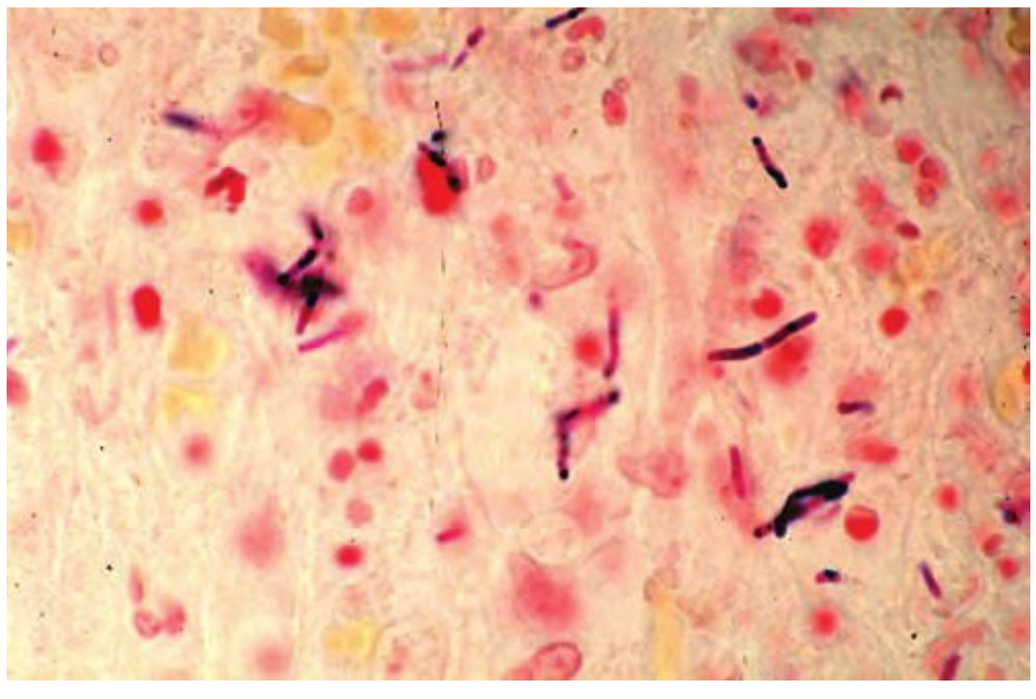


FIGURE 21-50. Anthrax. Numerous gram-positive thick bacilli within the acute inflammation (Gram stain).

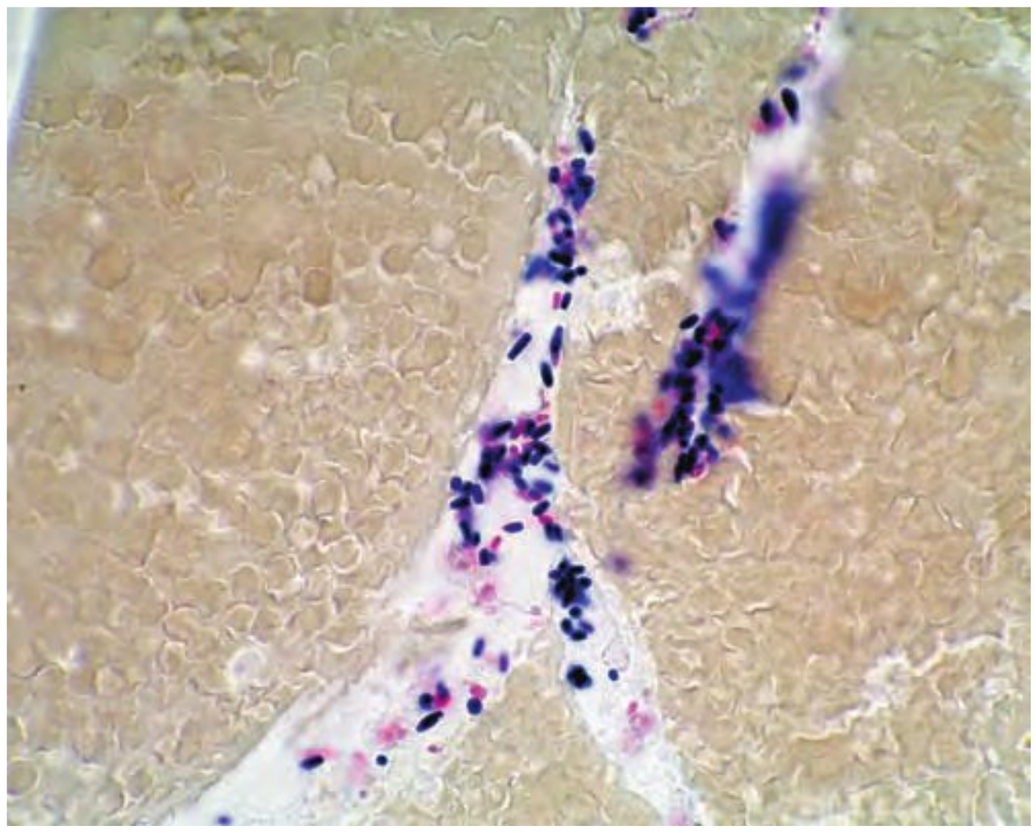


FIGURE 21-51. Clostridium perfringens injection abscess. Cluster of wide gram-positive rods, typical of Clostridium sp. (Gram stain).

granulation tissue, fibrosis, and sinuses develop. In mycobacterial injection lesions, there may also be granulomas.

TULAREMIA

Tularemia is caused by *Francisella tularensis*, a small, gram-negative, pleomorphic coccobacillus. It is usually acquired by humans through direct contact with rodents, but it may be transmitted from rodents to humans by insects, such as mosquitoes, ticks, or deer flies (171). The disease often occurs in small epidemics. There are two types: ulceroglandular (the more common type) and typhoidal. These types reflect differences in host response. In ulceroglandular tularemia, there is a vigorous inflammatory reaction, pneumonia is less common, and the patient's prognosis is good. In the typhoidal form, there are few localizing signs, pneumonia is more common, and the mortality without therapy is much higher.

In the ulceroglandular type, one or several painful ulcers occur as primary lesions at the site of infection, usually on the hands. Tender subcutaneous nodes may form along the lymph vessels that drain the primary lesion or lesions. There is considerable swelling of the regional lymph nodes, and the infection is associated with marked constitutional symptoms. Healing of the lesions takes place in 2 to 5 weeks (172,173).

Histopathology. At its base, the primary ulcer shows a nonspecific inflammatory infiltrate associated with a granulomatous reaction. In some cases, only a moderate number of epithelioid cells and a few giant cells are observed (169). In others, however, large, well-developed tuberculoid granulomas are apparent. These granulomas may show central necrosis with the presence of nuclear dust. Late lesions may show epithelioid cell tubercles that have no central necrosis and are surrounded by only a slightly inflammatory reaction, and they may thus have an appearance resembling that of sarcoidosis (174).

The tender nodes that may be found along lymph vessels show multiple granulomas deep in the dermis and extending into the subcutaneous tissue. The central zones of necrosis in the granulomas may attain a much greater size than in the primary ulcer. Similarly, the regional lymph nodes show multiple granulomas with centrally located abscess necrosis or caseous necrosis (172,175).

RICKETTSIAL INFECTIONS

Rickettsial infections are acquired by tick bites, the natural reservoir being infected animals. Rocky Mountain spotted fever is caused by *Rickettsia rickettsii*, a small, pleomorphic coccobacillus that is an obligate intracellular parasite. Contrary to its name, the disease is encountered most commonly in the southeastern United States and has been acquired even within New York City (176,177). Boutonneuse fever (Mediterranean spotted fever) is caused by *Rickettsia conorii* and is widespread in Africa as well.

In *R. rickettsii* infection, after an incubation period of 1 to 2 weeks, chills and fever develop, and a few days later, a rash appears that begins on the extremities and spreads to the trunk. The lesions at first are macular to papular but become purpuric within 2 to 3 days. There may be only petechiae, but in fatal cases widespread ecchymoses are common. Gangrene may result from small vessel occlusion (178). Because the diagnosis may not be made in the beginning and the course may be rapid, mortality exceeds 10%, despite the effectiveness of antibiotics such as tetracycline and chloramphenicol if given in time. Whenever a diagnosis of Rocky Mountain spotted fever is suspected, a search should be made for an eschar indicating the site of a tick bite. A hemorrhagic crust 8 to 10 mm in diameter surrounded by an erythematous ring may be found. In some severe systemic cases, there are no obvious skin lesions (179,180).

In boutonneuse fever, characteristic "tache noire" eschars develop. The histopathology is similar in both infections (181).

Histopathology. In the advanced lesion, there is dermal and epidermal necrosis. The small vessels of the dermis and of the subcutaneous fat exhibit a necrotizing vasculitis with a perivascular infiltrate consisting mostly of lymphocytes and macrophages (Figs. 21-52

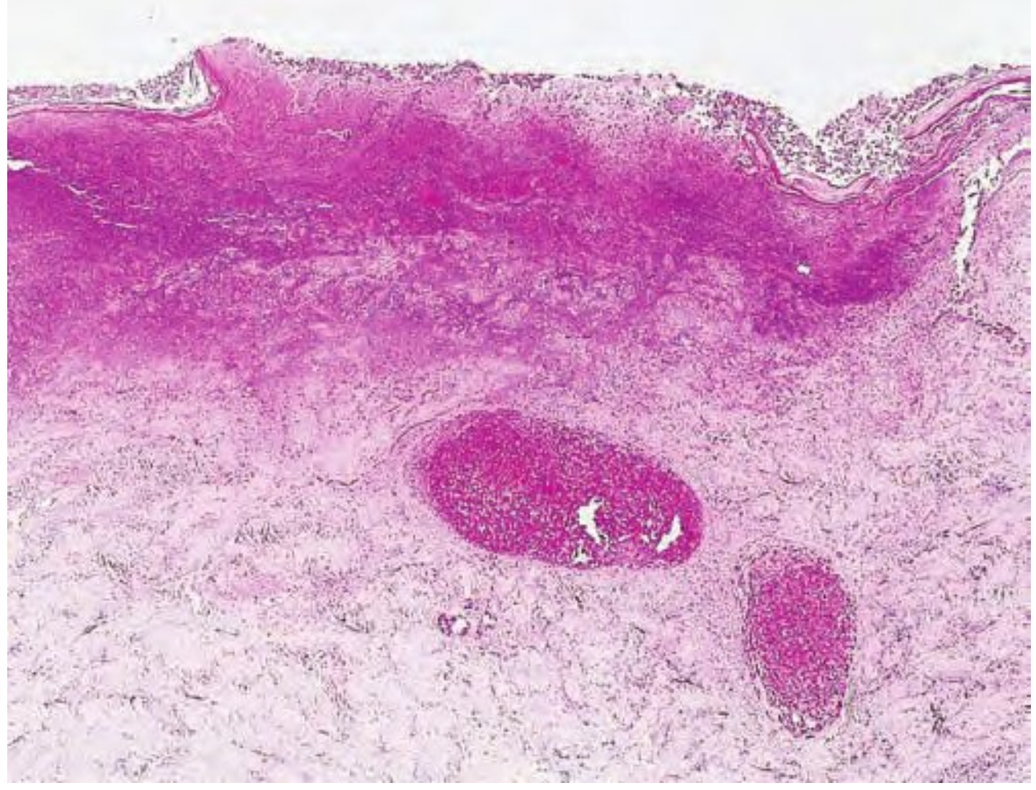


FIGURE 21-52. Rickettsia conorii infection. Typical eschar necrosis of superficial dermis and epithelium (H&E stain).

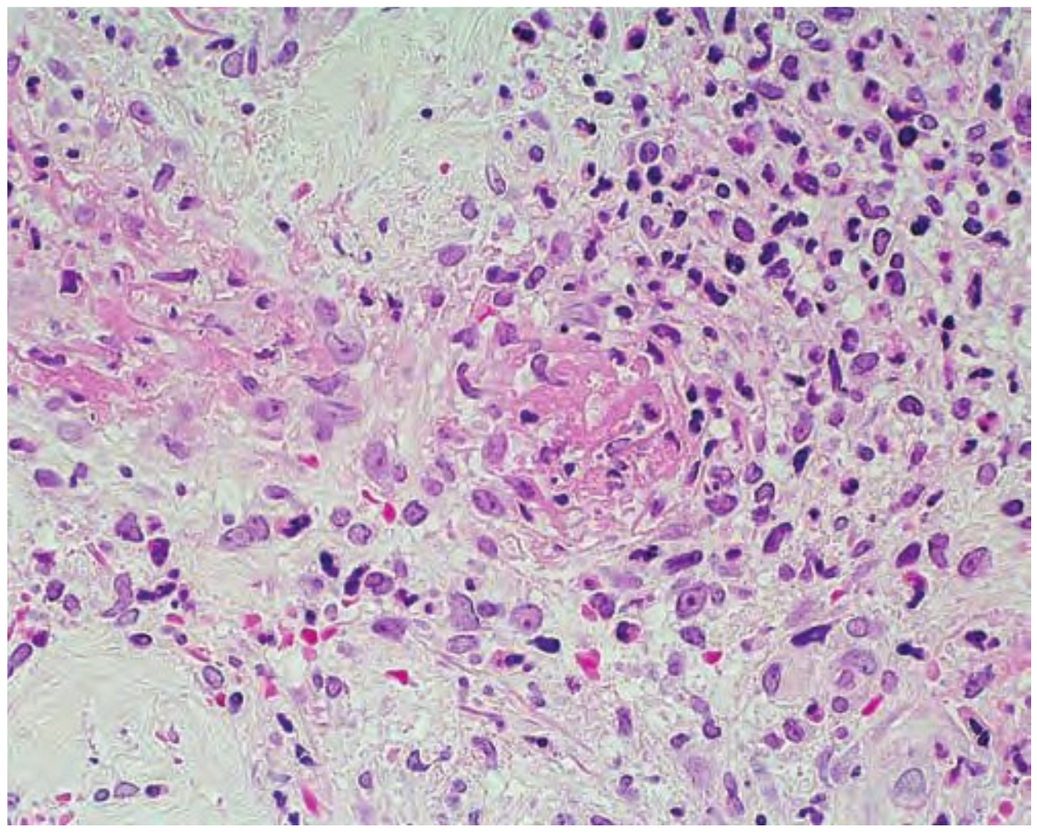


FIGURE 21-53. Rickettsia conorii infection. Dermal arteriole with arteritis and fibrin thrombosis (H&E stain).

and 21-53). There is extravasation of erythrocytes. As a result of injury to the endothelial cells, luminal thrombosis and microinfarcts occur. The causative organism, which measures 0.3 by 1.0 μm, is too small to be visible by light microscopy using ordinary stains. However, rickettsial antigen can be identified in sections of skin lesions by immunocytochemistry (180), and PCR on skin samples is specific. Coccal and bacillary forms are observed in endothelial cells in association with perivascular lymphocytic infiltration. Electron microscopic examination of the tick bite site demonstrates rickettsial organisms within the cytoplasm and the nuclei of endothelial cells. These organisms appear as electron-dense, round or oval structures surrounded by an electron-lucent halo. The entire organism is bounded by a limiting cell wall. The organisms range in size from 0.3 to 0.5 μm in greatest diameter.

CHANCROID

Chancroid, caused by *Haemophilus ducreyi*, is a sexually transmitted disease leading to one or several ulcers, chiefly in the genital region (182,183). The ulcers exhibit little if any induration and often have undermined borders. They are usually tender. Inguinal lymphadenitis, either unilateral or bilateral, is common and unless treated often results in an inguinal abscess.

Histopathology. The histologic changes observed beneath the ulcer are sufficiently distinct to permit a presumptive diagnosis of chancroid in many instances. The lesion consists of three zones overlying each other and shows characteristic vascular changes (182,183) (Fig. 21-54). The surface zone at the floor of the ulcer is rather narrow and consists of neutrophils, fibrin, erythrocytes, and necrotic tissue. The next zone is fairly wide and contains many newly formed blood vessels showing marked proliferation of their endothelial cells. As a result of the endothelial proliferation, the lumina of the vessels are often

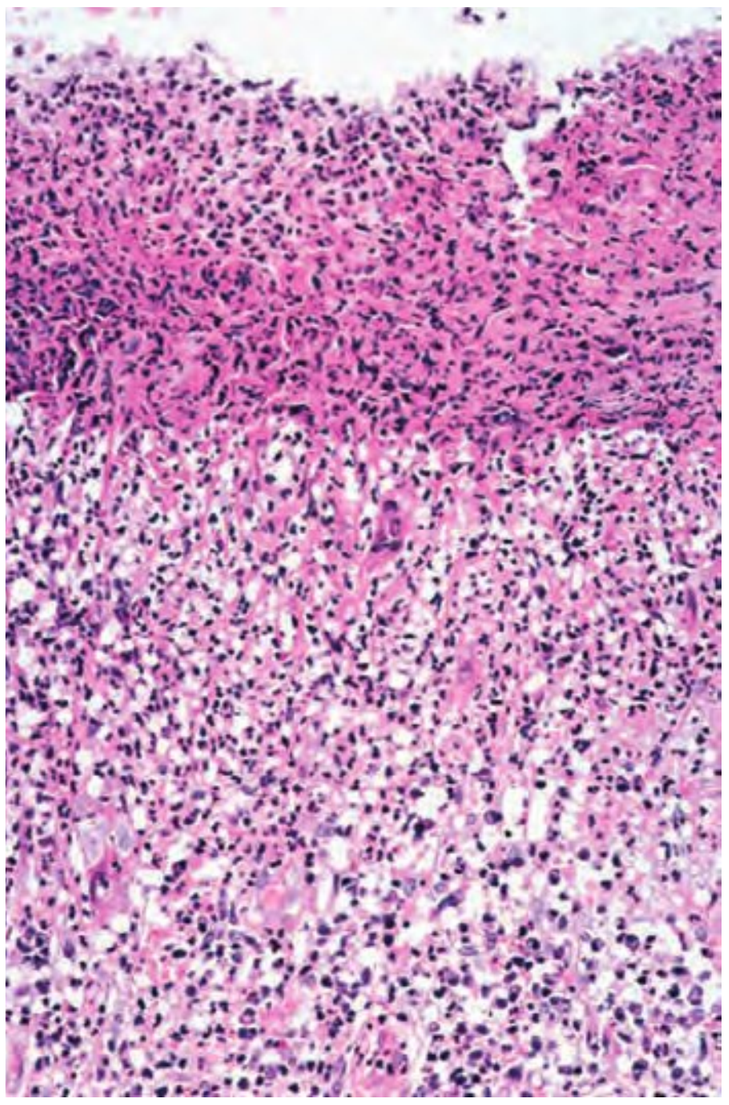


FIGURE 21-54. Chancroid. Three-zone pattern of ulcer and inflammation: superficial necrotic zone, underlying granulation tissue, and deeper fibrosis with plasma cells (H&E stain).

occluded, leading to thrombosis. In addition, there are degenerative changes in the walls of the vessels. The deep zone is composed of a dense infiltrate of plasma cells and lymphoid cells.

Demonstration of bacilli in tissue sections stained with Giemsa stain or Gram stain is occasionally possible (Fig. 21-55). The bacilli are most apt to be found between the cells of the surface zone (184). However, in smears of serous exudate obtained from the undermined edge of the ulcer, the bacilli usually can be seen on staining with the Giemsa or Gram stain. *H. ducreyi* is a fine, short, gram-negative coccobacillus, measuring about 1.5 by 0.2 μm, often arranged in parallel chains. *In situ* hybridization may also specify chancroid organisms (185). Electron

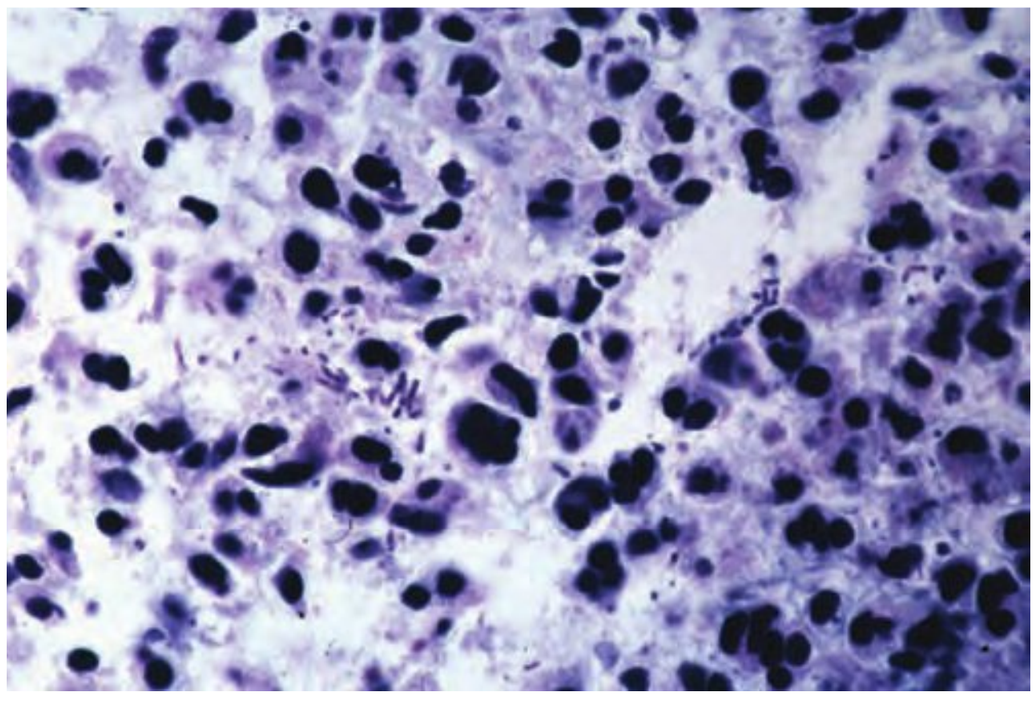


FIGURE 21-55. Chancroid. Bacilli (in the superficial zone) lying in parallel chains (Giemsa stain).

microscopy reveals that the bacilli are extracellular and thus rarely visible in phagosomes of macrophages (186).

The diagnosis of chancroid is confirmed by culture on selective blood-enriched agar (187). Chancroid may clinically resemble donovanosis by showing nontender or only slightly tender, indurated ulcers without undermined margins (188). On the other hand, particularly in the presence of several lesions, herpes simplex has to be excluded, although in herpes simplex the ulcerations usually are not as deep as those in chancroid.

GRANULOMA INGUINALE (DONOVANOSIS)

Granuloma inguinale, also called *donovanosis*, is a sexually transmitted disease caused by *Calymmatobacterium granulomatis* (189). The organism is a gram-negative short bacillus, about 2 to 3 μm long, with bipolar staining. The disease is endemic, but relatively uncommon, in the tropics (190).

Granuloma inguinale occurs in the genital or perianal region either as a single lesion or as several lesions (191). The lesions consist of ulcers filled with exuberant granulation tissue that bleeds easily (the characteristic beefy appearance). The borders of the ulcers are elevated and often have serpiginous outlines. Because the lesions spread by peripheral extension, they may attain a large size. In some instances, ulceration leads to mutilation resulting from destruction of tissue (192). In others, excessive granulation tissue causes vegetating lesions. Occasionally, squamous cell carcinoma supervenes (193). Local lymphadenopathy occurs through secondary infection of ulcerated skin.

Histopathology. At the edge of the ulcer, the epidermis exhibits acanthosis that may reach the proportions of pseudocarcinomatous hyperplasia. Present in the dermis is a dense infiltrate that is composed predominantly of histiocytes and plasma cells (Fig. 21-56). Scattered throughout this infiltrate are small abscesses composed of neutrophils. The number of lymphoid cells is conspicuously small (194).

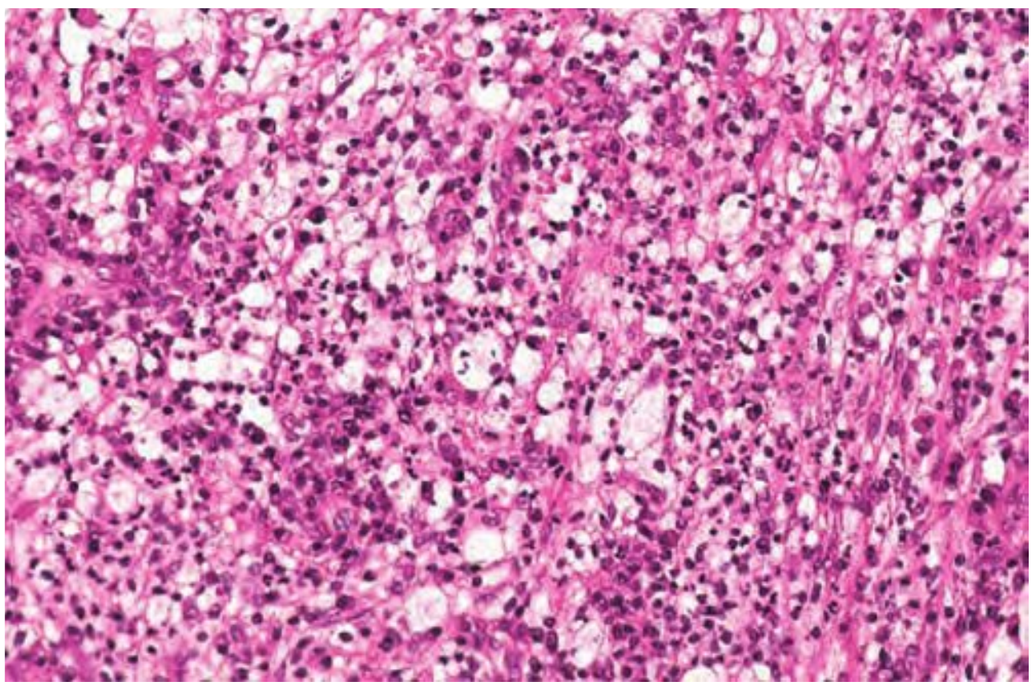


FIGURE 21-56. Donovanosis. Acute inflammation intermixed with foamy macrophages (H&E stain).

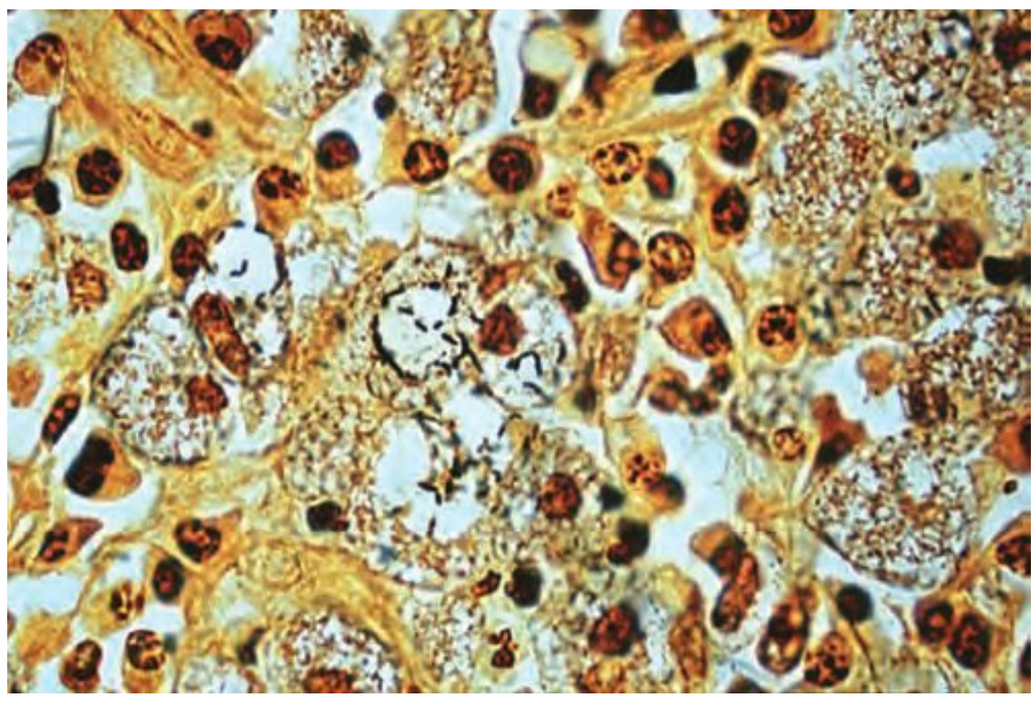


FIGURE 21-57. Donovanosis. Silver-positive bacilli within macrophages (Warthin-Starry stain).

The macrophages, which may be large, have a typical vacuolated appearance; these vacuoles contain bacilli and comprise the so-called "Donovan bodies." *C. granulomatis* does not stain with hematoxylin and eosin (H&E) stains but is well delineated by the Warthin-Starry method as short bacilli, either singly or in clumps (184,195) (Fig. 21-57). Giemsa stain shows bipolar condensations of stain. Electron microscopy reveals that the bacteria reside in phagosomes (196).

Differential Diagnosis. Overdiagnosis of carcinoma is possible because of the epithelial hyperplasia. The inflammatory pattern is similar to that observed in rhinoscleroma.

RHINOSCLEROMA

Rhinoscleroma is a chronic, infectious but only mildly contagious disease caused by *Klebsiella rhinoscleromatis*, a gram-negative bacillus. The nose, pharynx, larynx, trachea, and occasionally also the skin of the upper lip are distorted and infiltrated with hard, granulomatous masses. The disorder always begins in the nose. Although formerly endemic in Central Europe, it is now encountered mainly in Central America and Africa (197–199).

Histopathology. The cellular infiltrate is a chronic granulation tissue with abundant plasma cells and Mikulicz cells. Polymorphs may be present (but they cannot kill the bacteria). Russell bodies (plasma cells with retained globules of immunoglobulins) are frequently observed. The characteristic cell is the Mikulicz cell, a large histiocyte measuring from 10 to 100 μm in diameter (Fig. 21-58). It has a pale, vacuolated cytoplasm. Within the cytoplasm of the Mikulicz cells, one finds many bacilli (Fig. 21-59). They can be seen faintly in sections stained with H&E but are better visualized with the Giemsa stain or a Warthin-Starry silver stain (200). They are also stained red by the PAS technique. They are gram-negative rods that measure 2 to 3 μm in length and appear round or

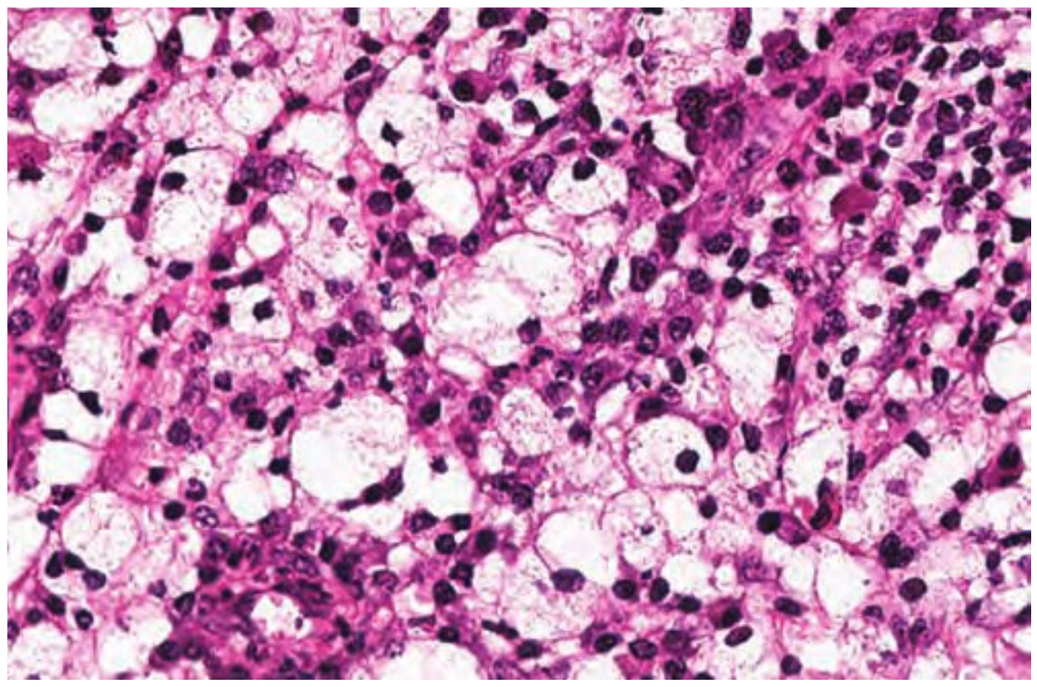


FIGURE 21-58. Rhinoscleroma. Foamy macrophages (Mikulicz cells) and plasma cells; the bacilli are faintly visible within the macrophages (H&E stain).

ovoid in cross-section. Immunocytochemistry can also be used to confirm rhinoscleroma (198,201).

In long-standing lesions, marked fibrosis is present. The mucosal epithelium overlying the cellular infiltrate often exhibits hyperplasia, which may be so pronounced as to give rise to a mistaken diagnosis of squamous cell carcinoma.

Electron microscopy reveals numerous phagosome vacuoles of varying size within the Mikulicz cells. Some vacuoles contain one or a few bacilli up to 4 μm in length. They are surrounded by a characteristic coat of finely granular, filamentous material arranged in a radial fashion. This coating material contains mucopolysaccharides and is responsible for the positive PAS reaction of the bacteria (199).

Differential Diagnosis. The histopathology of rhinoscleroma is essentially similar to that of donovanosis (granuloma inguinale). Foamy, vacuolated macrophages are also observed in many other chronic inflammatory conditions (e.g., leprosy, chronic staphyloccocal abscess, mycoses, and leishmaniasis), but special stains and associated clinicopathologic features usually enable their

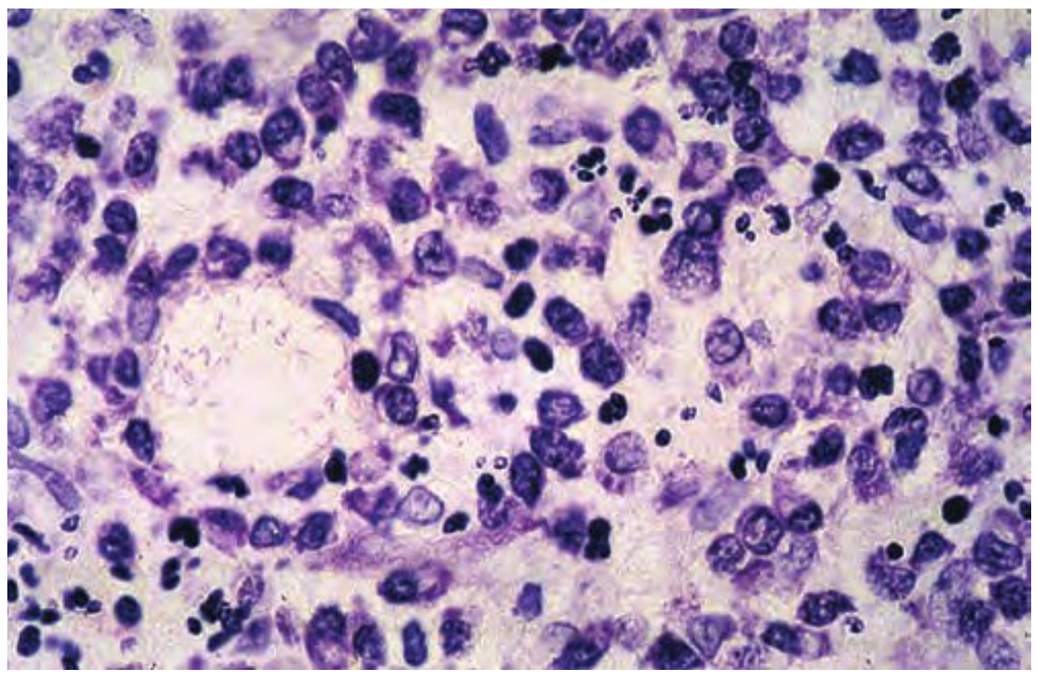


FIGURE 21-59. Rhinoscleroma. Bacilli within the macrophages (Giemsa stain).

distinction. Plasma cells and Russell bodies, similarly, correlate with chronicity in many diverse infections, such as treponematoses, amoebiasis, leishmaniasis, and tuberculosis.

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum is a sexually transmitted disease caused by *Chlamydia trachomatis*. Chlamydiae are obligate intracellular parasites with a unique biphasic life cycle (203).

The incubation period of lymphogranuloma venereum varies from 3 to 30 days but averages 7 days. The primary lesion is a small erosion or papule 5 to 8 mm in size. This lesion heals within a few days and may pass unnoticed. Within 1 to 2 weeks after the appearance of the primary lesion, enlargement of the inguinal lymph nodes begins. Inguinal lymphadenopathy occurs in most men infected with this disease but in only some women. The involved inguinal lymph nodes at first are firm but subsequently develop multiple areas of suppuration, resulting in draining sinuses. The lymphadenopathy usually subsides within 2 to 3 months. Rarely, elephantiasis of the penis and scrotum or chronic penile ulcerations arise as a late complication (203).

In women in whom the infection begins in the lower portion of the vagina, drainage is to the iliac and anorectal lymph nodes rather than to the inguinal lymph nodes, which may result in proctitis (192). Rectal stricture and perineal ulcerations are fairly common late complications in these women. Lymph stasis may lead to marked vulvar edema, referred to as *esthiomene*. Proctitis and rectal stricture also occur in homosexual men (204).

Histopathology. The changes in the initial papule are nonspecific. There is ulceration and a nonspecific granulation tissue. In the lymph nodes, stellate abscesses with surrounding epithelioid cells and macrophage giant cells represent the characteristic lesion. A similar pathology is seen in cat-scratch disease nodes. Ordinary histologic stains do not demonstrate the infecting organisms in skin or node. The diagnosis may be confirmed by culture of a skin lesion or lymph node, and serology is useful (205).

Chlamydiae undergo a developmental cycle and, as can be seen by electron microscopy, occur in two forms: elementary body and initial body (202). The elementary body is adapted to an extracellular environment and is infective for other cells. It measures about 0.3 μm in diameter and consists of a round, electron-dense inner body surrounded by an electron-lucid halo and a membrane. After entering a host cell by means of phagocytosis, it develops into a metabolically active initial body 0.5 to 1.0 μm in diameter. Multiplication takes place by division of the nucleus. This division results in two elementary bodies, which on leaving the host cell can infect other cells.

CAT-SCRATCH DISEASE

Bartonella henselae (previously *Rochalimaea henselae*) causes cat-scratch disease, and the organism is carried in the blood and oral cavities of cats (206). The skin lesion develops 2 to 4

days after a scratch or bite from a cat. It may be macular, papular, or a nodule, usually on the arm or hand. Two to 3 weeks later, a large, tender swelling of a group of lymph nodes develops in the drainage area of the scratch. The cat scratch heals in a normal fashion, but the affected lymph nodes become fluctuant as a result of suppuration. The average duration of lymph node enlargement is 2 months (207,208).

Histopathology. The primary papules at the site of the scratch show one or several acellular areas of necrobiosis in the dermis. These areas are of various shapes, including round, triangular, and stellate. Surrounding them are several layers of histiocytic and epithelioid cells, with the innermost layer exhibiting a palisading arrangement. A few giant cells may be present. The periphery of the epithelioid cell reaction is surrounded by a zone of lymphoid cells.

The reaction in the lymph nodes is similar to that observed in the skin, except that the central areas of necrosis in the epithelioid cell granulomas undergo abscess formation through the accumulation of numerous neutrophils. Macrophage giant cells are also present. As the abscesses enlarge, they become confluent.

The delicate, pleomorphic, gram-negative bacilli can be demonstrated with the Warthin-Starry silver impregnation stain peripheral to the necrosis of involved lymph nodes (209) and in the skin at the primary site of inoculation (206). Immunocytochemistry also reveals the bacilli, and serodiagnostic tests are available. For specific identification, PCR techniques and *in vitro* culture may be used (206).

Electron microscopic examination reveals that the bacteria are invariably extracellular and form small clusters. They are 0.8 to 1.5 μm long and 0.3 to 0.5 μm wide, with homogeneous bacterial walls (210).

BACILLARY ANGIOMATOSIS

Bacillary angiomatosis is a new disease, first described in 1983 (211) as a skin or disseminated infection in patients immunosuppressed by HIV infection. It is also rarely encountered in patients with other immunocompromising conditions and even in immunocompetent people (212). The agents are gram-negative bacilli: *Bartonella quintana* and *B. henselae* (213). The pathology is similar to that of the late cutaneous stage of bartonellosis, caused by *Bartonella bacilliformis* (214). As with cat-scratch disease, exposure to cats is a major risk factor for acquiring this infection (215).

The skin lesions are reddish or brown papules on any part of the body, usually in large numbers, that resemble Kaposi's sarcoma. They may also present as subcutaneous lumps without skin involvement (217,218).

Histopathology. The epidermis may be flat or hyperplastic. In the dermis, there are single or multinodular proliferations of capillaries accompanied by an inflammatory infiltrate that includes variable numbers of neutrophil polymorphs and mononuclear cells as well as edema. Leukocytoclasia is frequently observed (218). Characteristic of bacillary angiomatosis are extracellular deposits of palely hematoxyphilic granular material (Fig. 21-60). Warthin-Starry staining reveals these deposits to be dense masses of short bacilli (Fig. 21-61). The Grocott-Gomori methenamine silver method also demonstrates the argyrophilic bacilli. These bacilli may also be delineated by modified Gram stains such as the Brown-Hopps stain.

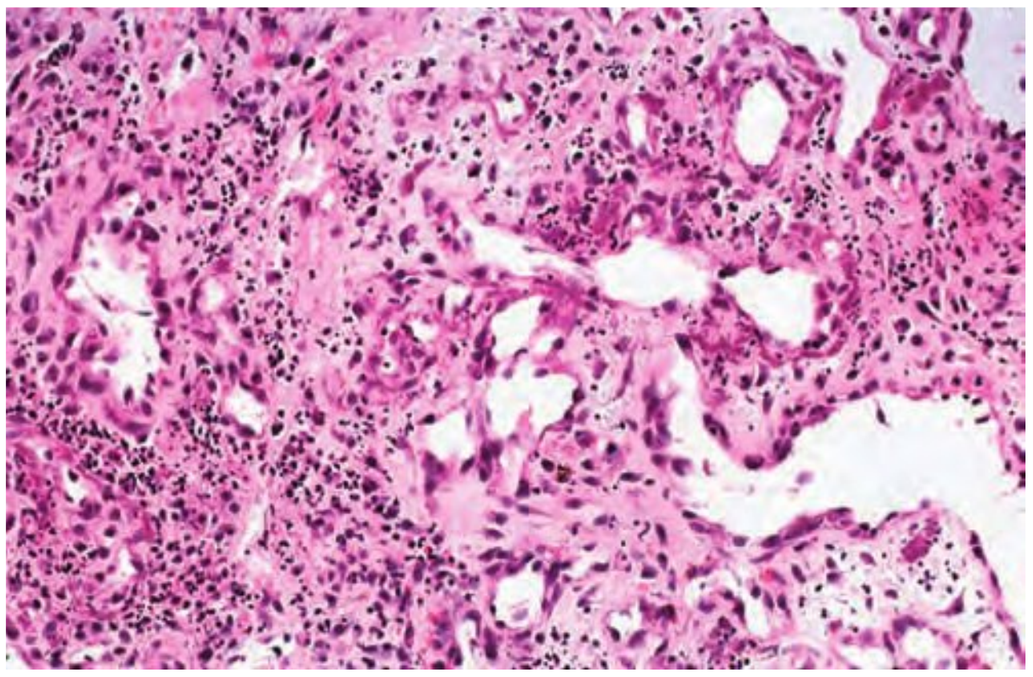


FIGURE 21-60. Bacillary angiomatosis. Dermis shows vascular proliferation, leukocytoclasia, and edema (H&E stain).

Differential Diagnosis. The major differential diagnoses are Kaposi's sarcoma, pyogenic granuloma, and epithelioid hemangioma (218). The presence of clumps of bacilli is obviously important. The capillary proliferation does not have the organized arborizing quality of that in pyogenic granuloma. Spindle cell proliferation and intracellular hyaline globules as seen in Kaposi's sarcoma are not features of bacillary angiomatosis, and Kaposi's sarcoma does not include polymorphs; however, the two conditions may be difficult to distinguish, and many pathologists have learned about bacillary angiomatosis from being informed that the lesions of "Kaposi's

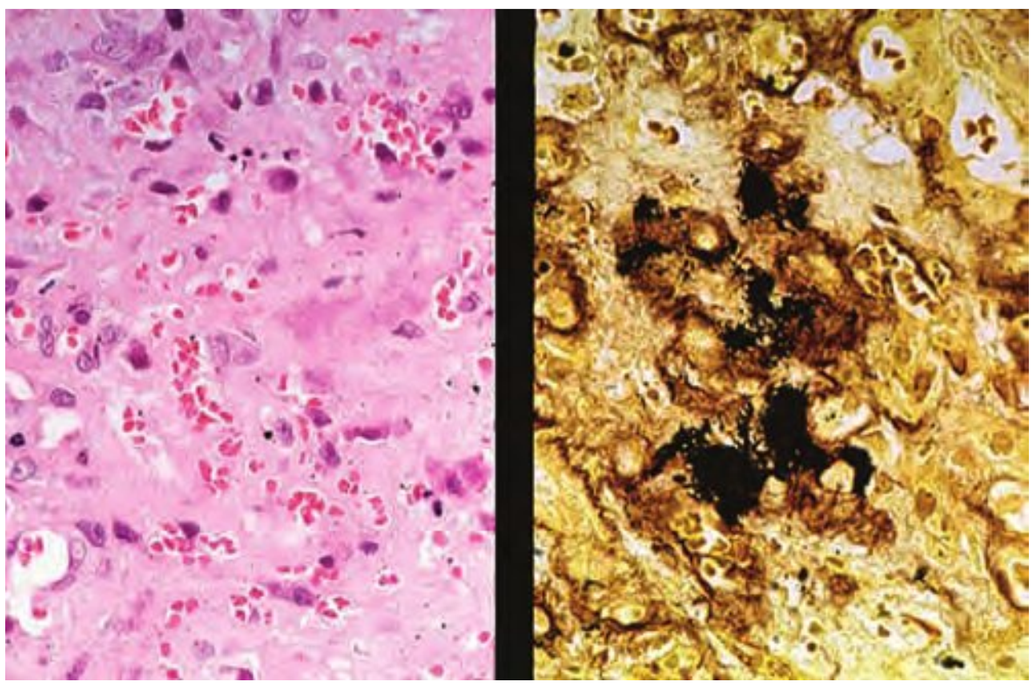


FIGURE 21-61. Bacillary angiomatosis. Left: Clumps and smudges of basophilic extracellular material—the bacteria (H&E stain). Right: Silver-positive bacilli (Warthin-Starry stain).

sarcoma" disappeared on treatment with antibiotics. Epithelioid hemangioma has plumper (histiocytoid) endothelial cell proliferation and no acute inflammation.

BOTRYOMYCOSIS

Botryomycosis, despite its name, is not a fungal infection but a chronic suppurative infection of skin (and other organs such as lungs and meninges) in which pyogenic bacteria form granules similar to those seen in mycetoma (219). Although immunosuppressed patients, including those with HIV infection, may acquire botryomycosis (220), most patients have no known immune defect. Occasionally, the lesion is associated with another dermatosis such as follicular mucinosis (221).

The skin lesions are local nodules, ulcers, or sinuses communicating with deep abscesses. They occur mainly on the extremities.

Histopathology. The dermal inflammation is predominantly that of neutrophil polymorph abscesses with surrounding granulation tissue and fibrosis (Fig. 21-62). Within the abscesses are granules (grains) shaped like a bunch of grapes, hence the name of the disease (Fig. 21-63). The grains may vary from 20 μm to 2 mm in diameter. They are composed of closely aggregated nonfilamentous bacteria with a peripheral, radial deposition of intensely eosinophilic material—a Hoeppli-Splendore (HS) reaction. The bacteria are usually *S. aureus*, but streptococci and certain gram-negative bacilli such as *Proteus*, *Pseudomonas*, and *E. coli* are sometimes found. Gram stains delineate these broad categories of infection, although sometimes the organisms in gram-positive infections are degenerate and lose their gram-positive staining reaction (Fig. 21-64). The HS reaction material comprises antibody and fibrin.

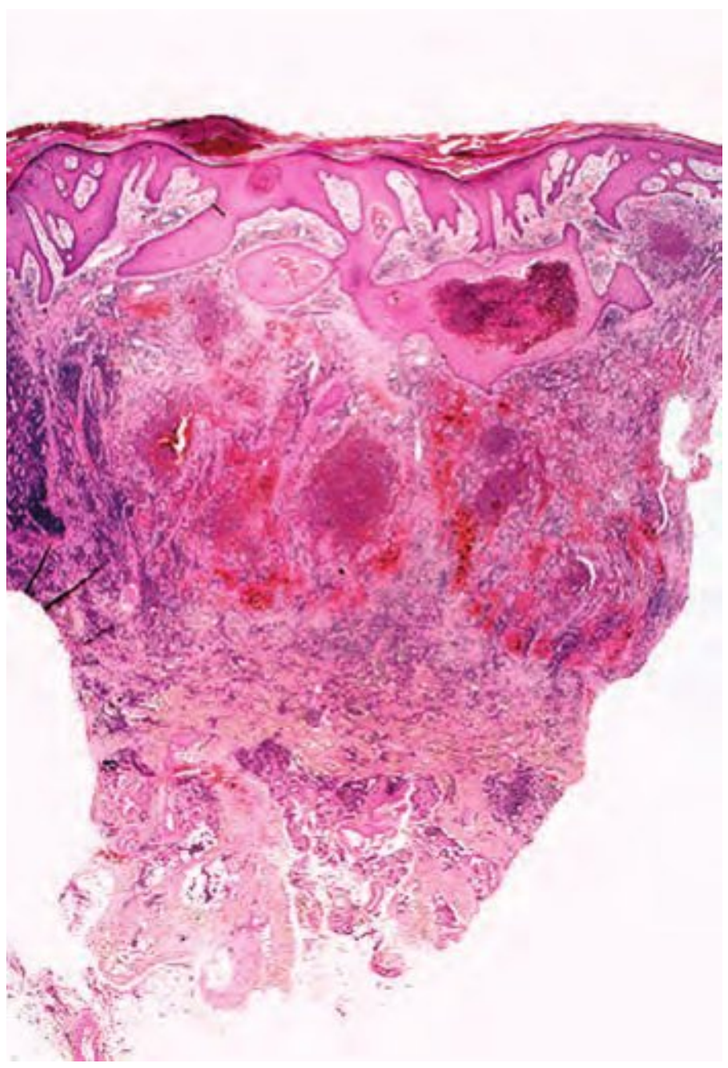


FIGURE 21-62. Botryomycosis. There are pseudoepitheliomatous hyperplasia and small abscesses in the dermis containing clumps of bacteria (H&E stain).

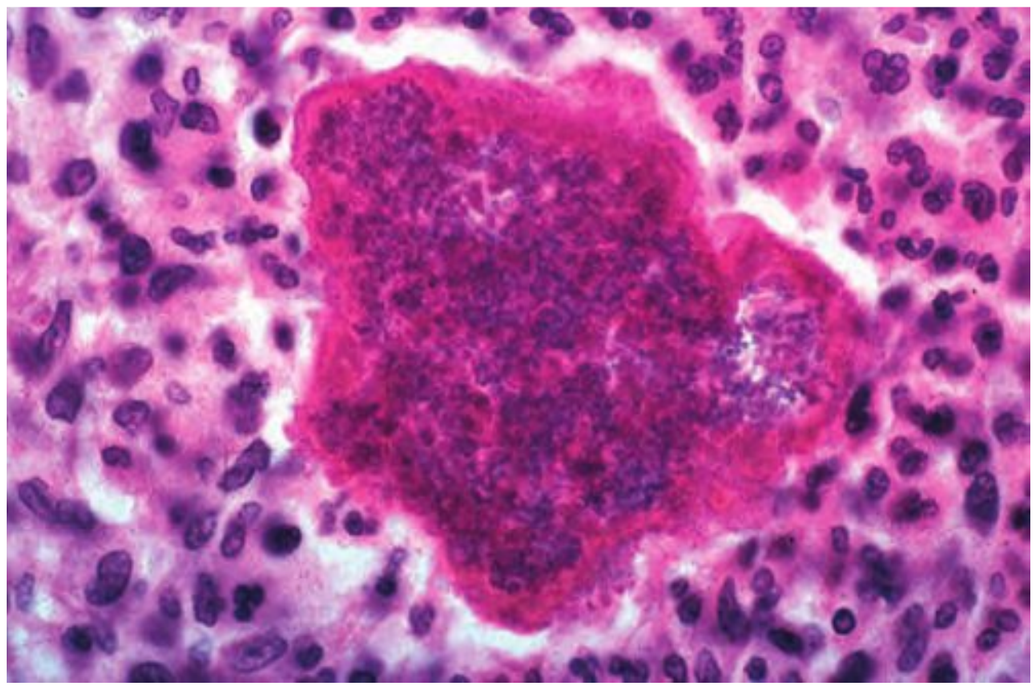


FIGURE 21-63. Botryomycosis. An abscess within which is a basophilic bacterial clump with an eosinophilic surrounding HS reaction (H&E stain, high power).

The overlying epithelium often exhibits pseudoepitheliomatous hyperplasia. Transepithelial elimination of grains may be observed (as with mycetoma) (222).

Pathogenesis. Local implantation of infection may be a factor in some cases, with persistence of a foreign body. Bacteremia is documented in many patients; however, in others, the lesions appear *de novo*. The characteristic formation of the peribacterial HS reaction probably prevents phagocytosis and intracellular killing of the bacteria, leading to chronicity.

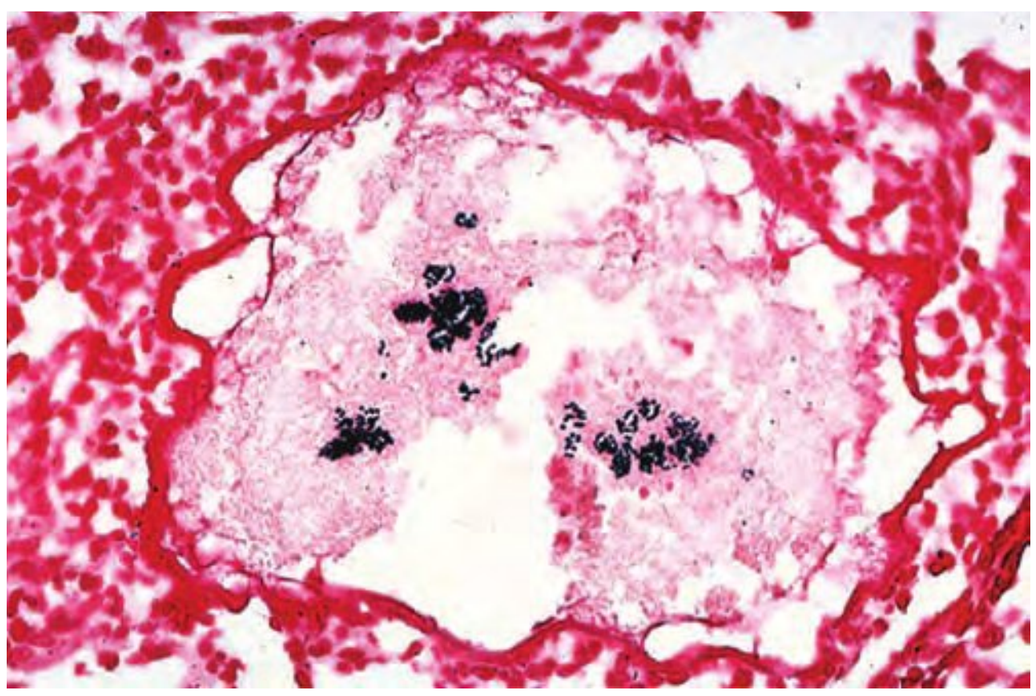


FIGURE 21-64. Botryomycosis. A staphylococcal lesion showing gram-positive cocci (the majority are degenerate and nonstaining) (Gram stain).

NOCARDIOSIS

Nocardia sp. are gram-positive, weakly acid-fast, filamentous, branching bacilli that are ubiquitous in the soil. The main species are *Nocardia asteroides*, which is global in distribution, and *Norcardia brasiliensis*, which is found mainly in the Americas (223,224).

N. asteroides is an opportunist agent, and immunocompromised patients, such as those with HIV infection (225,226) and organ transplant recipients, are liable to nocardiosis. Infection of the skin follows direct implantation from the environment, hematogenous spread from pulmonary infection, or direct spread through the chest wall from a lung lesion. The skin lesions include erythematous nodules, pustular ulcers, and sinuses. They may be single or multiple.

N. brasiliensis affects immunocompetent as well as immunosuppressed people. The primary and secondary skin lesions are similar to those of *N. asteroides*. Sporotrichoid spread up a limb, with lymphatic involvement, may occur (227). Both species may produce a chronic mycetoma-like lesion with much fibrosis and tissue destruction.

Histopathology. The bacteria induce a mixed acute abscess and granulomatous response in the skin, with fibrosis. Occasionally, the bacteria are clumped together with a surrounding HS reaction (see sections on Botryomycosis [page 573] and Mycetoma [chapter 22, chapter 23, page 614]). More often, they are more loosely dispersed and resemble *Actinomycosis* sp. H&E stains demonstrate the bacilli poorly. They are 1 μm in diameter, filamentous, branching, beaded, gram positive, Grocott silver positive, and usually weakly acid fast so that a modified Ziehl-Neelsen stain appropriate for leprosy bacilli stains them (Fig. 21-65). This latter feature assists in the distinction of *Nocardia* from *Actinomyces* and related bacilli; specific antisera with immunocytochemistry are also helpful (225), and culture is definitive. The shape of the organisms distinguishes them from mycobacteria. The Grocott silver method is the most sensitive screening stain for nocardiosis.

ACTINOMYCOSIS

Actinomyces israelii is a gram positive, branching, filamentous bacterium. It resides as a commensal organism in the oral cavity and tonsillar crypts. The main clinicopathologic manifestations are cervicofacial, thoracic, and intestinal actinomycosis (228). In the first of these, skin lesions result from extension of suppuration from the oral mucosa through to the facial skin, with sinus formation and discharge of pus and sulfur granules (see later). Thoracic and intestinal infections may produce discharging sinuses onto the skin from infection tracking outward from lung and gut (229). On rare occasions, purely cutaneous actinomycotic infection occurs, and hematogenous dissemination can produce multiple skin sinuses. An infected pilonidal sinus of the penis has been reported (230).

Histopathology. The inflammatory reaction to actinomycotic infection is typically a chronic abscess with polymorphs, surrounding granulation tissue, and fibrosis (231). The organisms are usually tangled together in a matted colony, forming a granule or grain (like botryomycosis and mycetoma). These grains, commonly termed *sulfur granules*, may be 20 μm to 4 mm in diameter. The bacilli within are 1-μm-diameter filaments that are hematoxyphilic and gram positive (Figs. 21-66 and 21-67). They stain with the Grocott silver method. Often, only the peripheral filaments stain with the Gram method, because of degeneration of the inner bacteria. The peripheral filaments often terminate in a club. A HS reaction may be found peripheral to the bacteria in the grain. The histologic differentiation from nocardiosis was discussed in the previous section.

Further detailed descriptions of these bacterial infections of the skin may be found in Connor and Chandler (232).

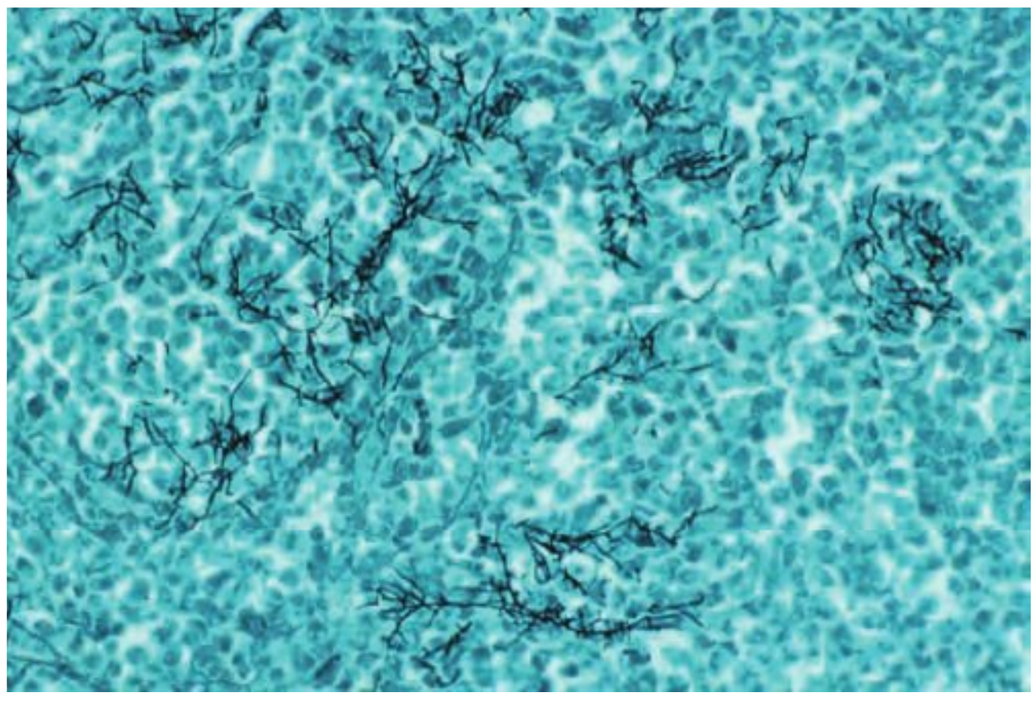


FIGURE 21-65. Nocardiosis. Fine, filamentous branching bacilli of N. asteriodes (Grocott silver stain).

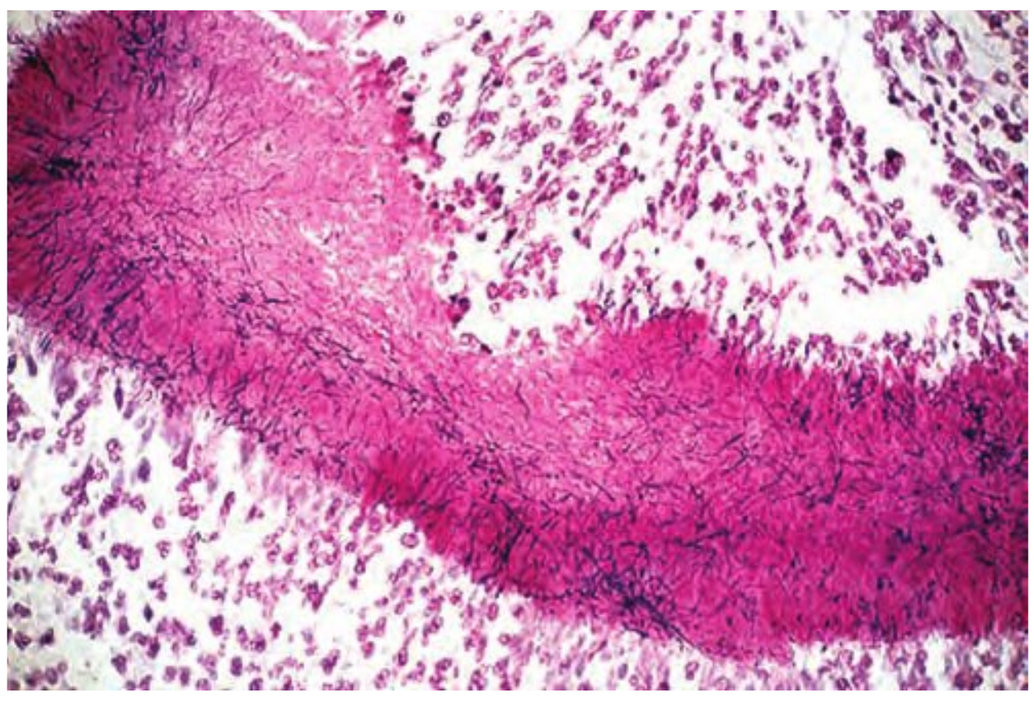


FIGURE 21-66. Actinomycosis. Part of a bacterial colony with hematoxyphilic filamentous bacteria (H&E stain).

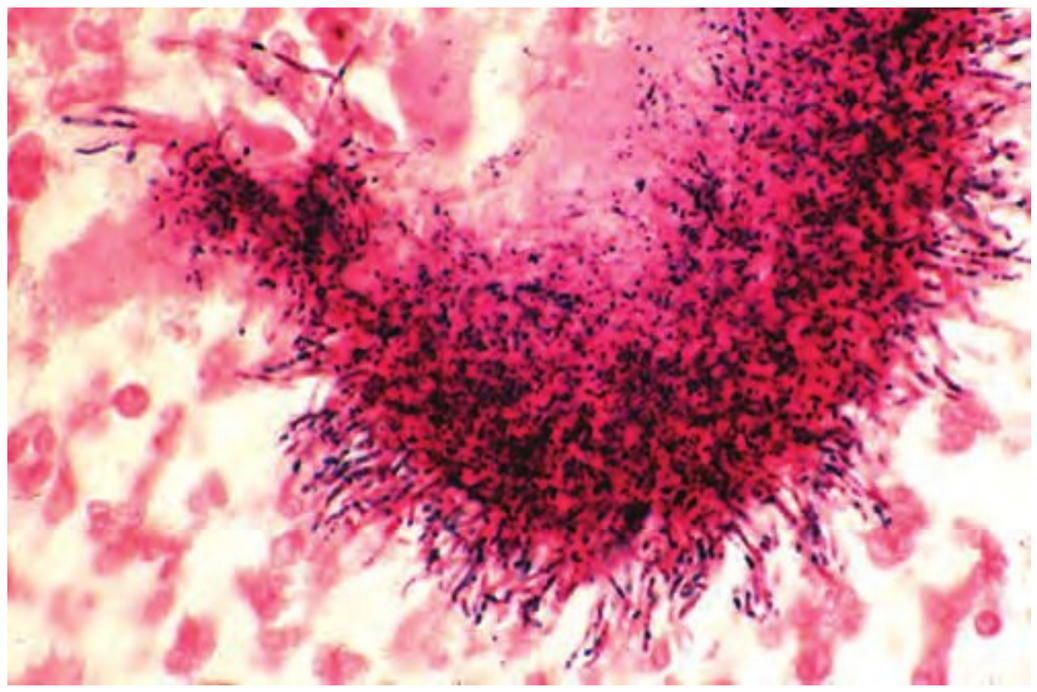


FIGURE 21-67. Actinomycosis. The edge of a grain, showing beaded gram-positive filaments (Gram stain).

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CHAPTER 22

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Treponemal Diseases

The venereal and nonvenereal treponemal diseases are caused by motile bacteria of the family Spirochetacea, which also includes the genera *Borrelia* and *Leptospira*. Accurate recognition of spirochetal infection requires correlation of a given patient's travel and medical history with a detailed knowledge of the clinical and histologic expression of each pathogen. The pathogenic treponemes resemble each other in dark-field and biopsy preparations, being coiled, silver-staining organisms 6 to 20 μm by 0.10 to 0.18 μm, and have a high degree of DNA sequence homology (1,2). A single genetic difference in the 5′ and 3′ flanking regions of the 15-kD lipoprotein gene *tpp15* was described for venereal and nonvenereal treponematoses in one study (3), evidence that suggests that these organisms evolved from a common ancestor to cause different diseases (4). Size and sequence heterogeneity is demonstrated by other treponeme genes, such as those controlling expression of the TprK antigen, a target of opsonizing antibodies that is important to host immune protection, variance in which may play a role in evasion of the host response (5). The nonvenereal treponematoses include yaws, pinta, and endemic syphilis. Recently, the role of oral treponemes in the causation of periodontitis has been explored (6–8).

VENEREAL SYPHILIS

Acquired syphilis, caused by *Treponema pallidum*, has afflicted humanity since at least the fifteenth century (9). Although it was a major cause of morbidity and mortality in the early twentieth century, public health programs and the advent of penicillin so reduced its incidence in First World countries by midcentury that many physicians became unfamiliar with its signs and symptoms (1). The incidence of acquired syphilis has since increased; in 1990, the incidence was 20 per 100,000 in the United States and 360 per 100,000 in areas of Africa, in part reflecting the epidemic of human immunodeficiency virus infection, with which acquired syphilis is linked epidemiologically and with which coinfection is common (10,11). New diagnoses of syphilis increased eightfold in the United Kingdom between 1997 and 2002 (12). In 2003, greater than 60% of all reported cases of syphilis occurred in men who had sex with men (13).

T. pallidum, of which there are three antigenically similar subspecies (14), is generally spread through contact between infectious lesions and disrupted epithelium at sites of minor trauma incurred during sexual intercourse. The transmission rate is between 10% and 60%. Early lesions reflect a delayed-hypersensitivity response to the organism, although some bacteria escape, in part due to integral outer membrane proteins that may render the treponeme invisible to the immune system (15). The result in the untreated host is persistent infectivity over the course of decades.

Primary syphilis is defined by a skin lesion, or chancre, in which organisms are identified; it typically arises 21 days after exposure at the inoculation site and is classically a painless, brown-red, indurated, round papule, nodule, or plaque 1 to 2 cm in diameter. Lesions may be multiple or ulcerative, and the regional lymph nodes may be enlarged.

Secondary syphilis results from the hematogenous dissemination of organisms, yielding widespread clinical signs accompanied by constitutional symptoms inclusive of fever, malaise, and generalized lymphadenopathy. A generalized eruption comprises brown-red macules and papules, papulosquamous lesions resembling guttate psoriasis, and, rarely, pustules (16). Lesions may be follicular based, annular, or serpiginous, particularly in recurrent attacks of secondary syphilis. Other skin signs include alopecia and condylomata lata, the latter comprising broad, raised, gray, confluent papular lesions arising in anogenital areas, pitted hyperkeratotic palmoplantar papules termed "syphilis cornee," and, in rare severe cases, ulcerating lesions that define "lues maligna." Some patients develop shallow, painless ulcers in the mucosae.

Meningovascular syphilis is usually seen in tertiary syphilis after 7 to 12 years of disease (17) but can occur in the secondary stage and be symptomatic; usually, it manifests as basilar meningitis and can be associated with cranial nerve palsies (18). Acute transverse myelitis (19), glomerulonephritis, and self-limited hepatitis are other uncommon manifestations.

Primary- and secondary-stage lesions may resolve without therapy or go unnoticed by the patient, who then passes into a latent phase. This may be subdivided into early and late stages, an arbitrary distinction that may help to guide the therapeutic approach. The Centers for Disease Control base the distinction of the early (infectious) latent stage from the late (noninfectious) latent stage on whether the duration of the infection is less or more than 1 year, respectively. The World Health Organization uses a 2-year period to make this

distinction. After a variable latent period, the patient enters the *tertiary stage*.

Tertiary syphilis comprises gummatous skin and mucosal lesions ("benign tertiary syphilis"), cardiovascular manifestations, and neurologic manifestations. The skin lesions may be solitary or multiple and can be divided into superficial nodular and deep gummatous types. The nodular type has a smooth, atrophic center with a raised, serpiginous border. The gummatous lesions present as subcutaneous swellings that ulcerate (20).

Congenital syphilis, on the rise since the mid-1980s (21), is a diagnosis rendered when organisms are identified in dark-field, immunofluorescent, or conventionally stained tissues or smears of lesional skin, placenta, or umbilical cord (22). A presumptive case is an infant born to a mother with inadequately treated syphilis at the time of delivery, or when an infant or child with a reactive treponemal test for syphilis exhibits evidence of congenital syphilis by virtue of physical or long-bone radiologic examination, a reactive cerebrospinal fluid (CSF) Venereal Disease Research Laboratory test, an elevated CSF protein or white blood cell count of unknown cause, or quantitative treponemal titers four times higher than the mother's at the time of birth (22). Clinical signs include rhinitis, chancres, or a maculopapular desquamative rash (21). Transplacental infection occurs in more than 50% of infants born to mothers with primary or secondary syphilis, roughly 40% of those born to mothers in the early latent stage, and only 10% of those born to mothers with late latent infections (22).

Histopathology of Syphilis. The two fundamental pathologic changes in syphilis are (a) swelling and proliferation of endothelial cells and (b) a perivascular infiltrate of lymphoid cells and often of plasma cells. In late secondary and tertiary syphilis, there are also granulomatous infiltrates comprising epithelioid histiocytes and giant cells. Newborns with congenital syphilis have shown at autopsy multiorgan involvement by an angioinvasive $CD68^+$ mononuclear cell infiltrate that imparts an "onion-skin" morphology to involved vessels with numerous demonstrable spirochetes (23).

Primary Syphilis

The epidermis at the periphery of the syphilitic chancre reveals changes comparable to those observed in lesions of secondary syphilis, namely, acanthosis, spongiosis, and exocytosis of lymphocytes and neutrophils. Toward the center, the epidermis becomes thinned, edematous, and permeated by inflammatory cells. In the center, the epidermis may be absent. The papillary dermis is edematous. A dense perivascular and interstitial lymphohistiocytic and plasmacellular infiltrate spans the entire thickness of the dermis (Fig. 22-1); the lymphocytes are principally of T-helper phenotype. Neutrophils are often admixed. Endarteritis obliterans characterized by endothelial swelling and mural edema is observed (Fig. 22-2).

By silver staining with the Levaditi stain or the Warthin-Starry stain and by immunofluorescent techniques, spirochetes are usually identified along the dermal–epidermal junction

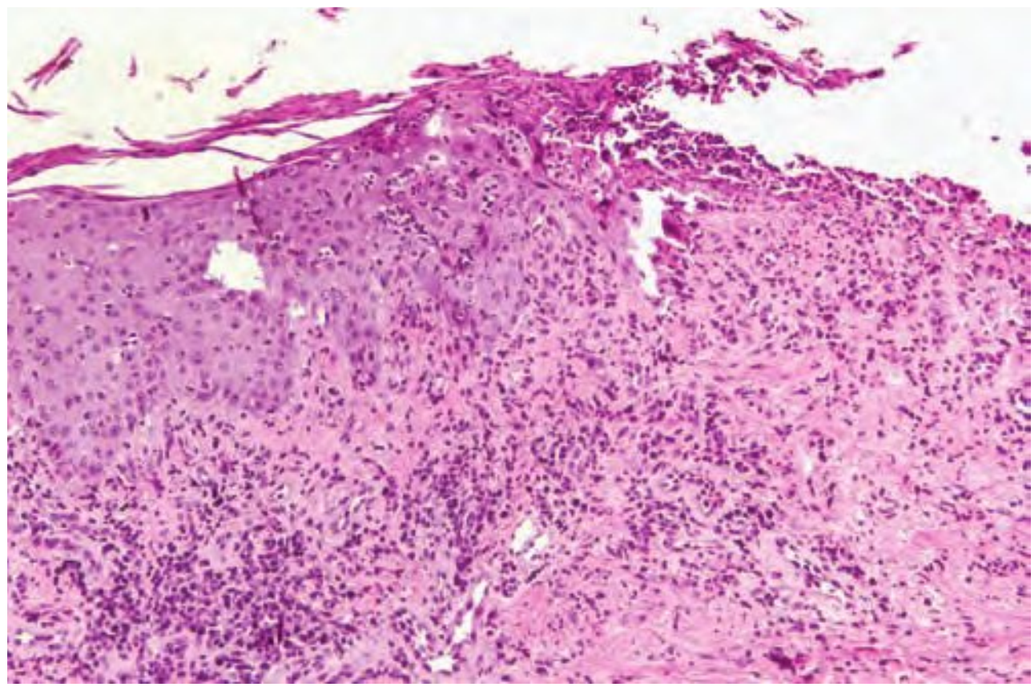


FIGURE 22-1. Primary syphilitic chancre. The epithelium is eroded, and the corium contains a dense, plasma-cell-rich infiltrate. There is neovascularization, with secondary necrotizing vasculitic changes manifested by mural fibrin deposition.

and within and around blood vessels. If seen in their full length, which is rare, spirochetes generally show 8 to 12 spiral convolutions, each measuring from 1 to 1.2 μm in length (Fig. 22-3). It should be remembered that silver also stains melanin and reticulum fibers. Differentiation may cause some difficulties but should be possible based on the fact that the melanin in the dendritic processes of melanocytes has a granular appearance, the granules being thicker and more heavily stained than *T. pallidum* (24). Reticulin fibers, although wavy, do not exhibit a spiral appearance. Correlation with serology is always prudent.

Histologic examination of enlarged regional lymph nodes in primary syphilis most commonly reveals a chronic inflammatory infiltrate containing many plasma cells with endothelial

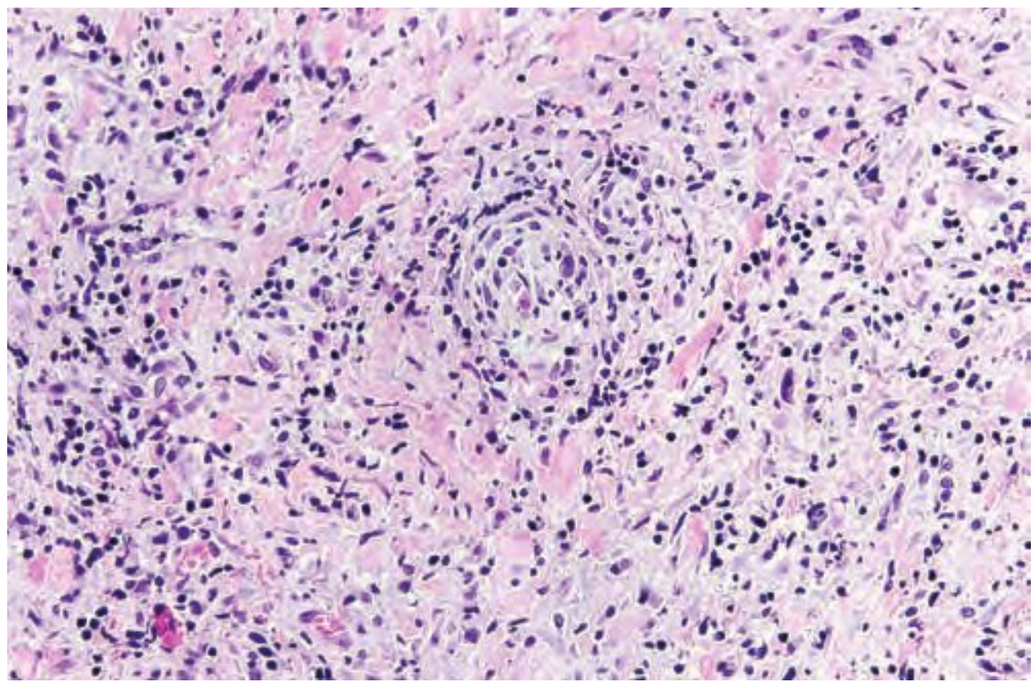


FIGURE 22-2. Primary syphilitic chancre. There is endarteritis obliterans manifested by endothelial cell swelling, endothelial hyperplasia, and expansion of vessel walls by edema and a lymphohistiocytic infiltrate with resultant lumenal attenuation. A diffuse extravascular plasma-cell-rich infiltrate is present.

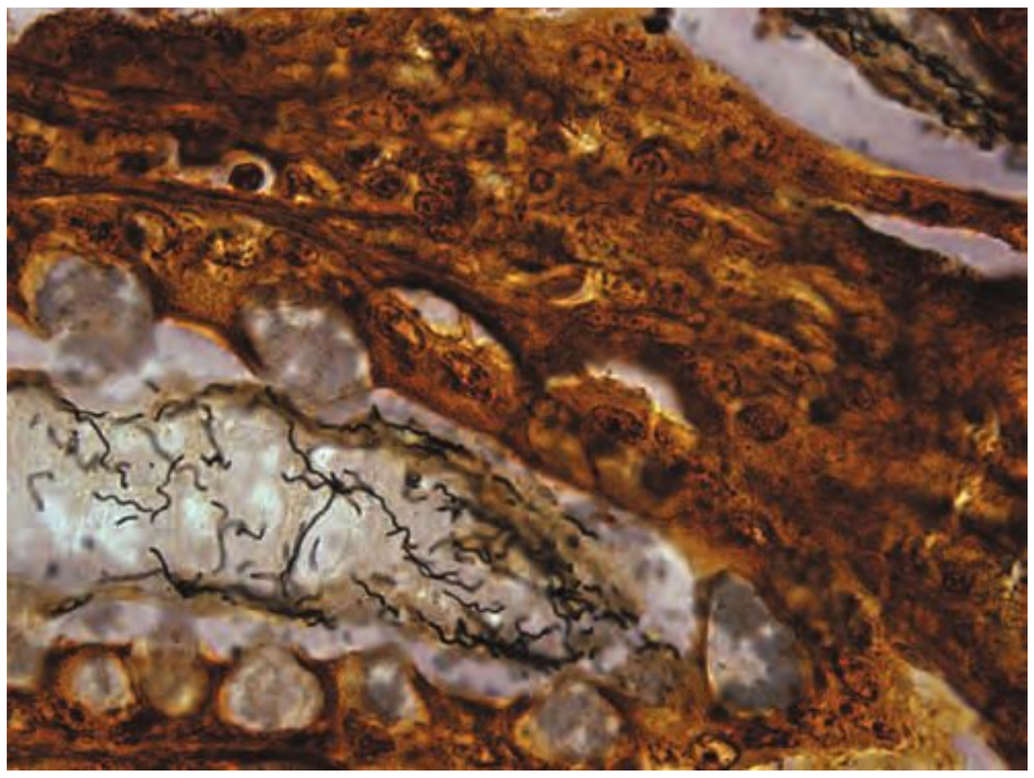


FIGURE 22-3. Treponeme morphology. A silver stain reveals numerous elongate, coiled spirochetes ranging in length from 8 to 12 μm.

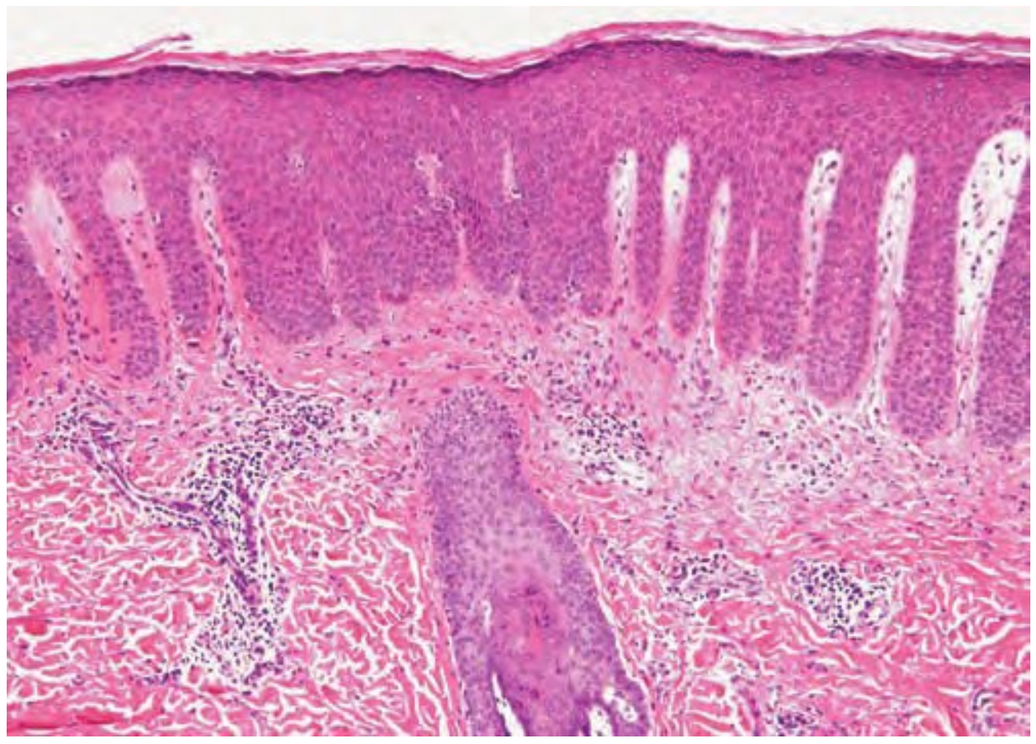


FIGURE 22-4. Secondary syphilis. There is striking psoriasiform hyperplasia of an epidermis surmounted by an orthohyperkeratotic and parakeratotic scale. There is prominent papillary dermal edema.

hyperplasia and follicular hyperplasia. Spirochetes are numerous and can nearly always be identified with the Warthin-Starry stain. In some cases, nonnecrotizing granulomas resembling those of sarcoidosis are found in the lymph nodes (25).

Histogenesis. T. pallidum can be demonstrated by histochemistry or by immunohistochemistry. The latter comprises immunofluorescent methods in frozen (26) or fresh specimens and immunoperoxidase methods employable in fixed tissues (27). By electron microscopy, the organism can be seen in both intra- and extracellular dispositions in the epidermis and dermis (28) and within keratinocyte nuclei (29), fibroblasts (29,30), nerve fibers (31), blood vessel endothelia, and the lumina of lymphatic channels (29). Phagocytic vacuoles of macrophages and neutrophils may contain organisms (32), as may the cytoplasm of plasma cells. Ultrastructurally, the organism is 8 to 16 μm in length with regular spirals, a wavelength of 0.9 μm with an amplitude of 0.2 μm, and a cytoplasmic body 0.13 μm in diameter with tapering ends, all enveloped by a 7-nm trilaminar cytoplasmic membrane (33). The organisms attach to host cells by means of acorn-shaped nosepieces. The contractile motility of the spirochete is mediated by three or four axial filaments that course the length of the cytoplasmic body (34). A paraplastic membrane surrounds these axial filaments in young organisms but is replaced by an electron-dense amorphous substance produced by the host cell as an immunologic response in older spirochetes (31).

Differential Diagnosis. Lesions of chancroid are the most difficult to differentiate clinically from a syphilitic chancre. The characteristic histopathology of chancroid is one of dense lymphohistiocytic infiltrates with a paucity of plasma cells and a granulomatous vasculitis. An epidermal reaction pattern similar to the syphilitic chancre is observed, namely, psoriasiform epidermal hyperplasia and spongiform pustulation. A Giemsa or Alcian blue stain reveals coccobacillary forms between keratinocytes and along the dermal–epidermal junction. The infiltrate is composed mainly of T-helper lymphocytes and histiocytes including Langerhans cells (35).

Secondary Syphilis

There is considerable histologic overlap among the various clinical forms of secondary syphilis, such as the macular, papular, and papulosquamous types (36,37). Nevertheless, epidermal changes are least pronounced in the macular type and most pronounced in papulosquamous lesions.

Biopsies generally reveal psoriasiform hyperplasia, often with spongiosis and basilar vacuolar alteration, often with edema of the papillary dermis (Fig. 22-4). Exocytosis of lymphocytes, spongiform pustulation, and parakeratosis also may be observed (24,36). The parakeratosis may be patchy or broad, with or without intracorneal neutrophilic abscesses. Although lesions may mimic psoriasis, attenuation of the suprapapillary plate is uncommon. Scattered necrotic keratinocytes may be observed. Ulceration is not a feature of macular, papular, or papulosquamous lesions of secondary syphilis. The dermal changes include marked papillary dermal edema and a perivascular and/or periadnexal infiltrate that may be lymphocyte predominant, lymphohistiocytic, histiocytic predominant, or frankly granulomatous and is of greatest intensity in the papillary dermis and extends as loose perivascular aggregates into the reticular dermis. Obscuration of the superficial vasculature and lichenoid morphology is observed in some cases, and a cell-poor infiltrate is seen in others. In a few cases, when the infiltrate is heavy, atypical nuclei may be present and may then suggest the possibility of mycosis fungoides (38) or non-Hodgkin's lymphoma. Neutrophils may permeate the eccrine coil to produce a neutrophilic eccrine hidradenitis or manifest as a neutrophil-imbued scale crust (Fig. 22-5) (24). Granulomatous inflammation is almost invariable in lesions of greater than 4 months' duration (37) and may be present in some cases of early syphilis (39). A plasma cell component is

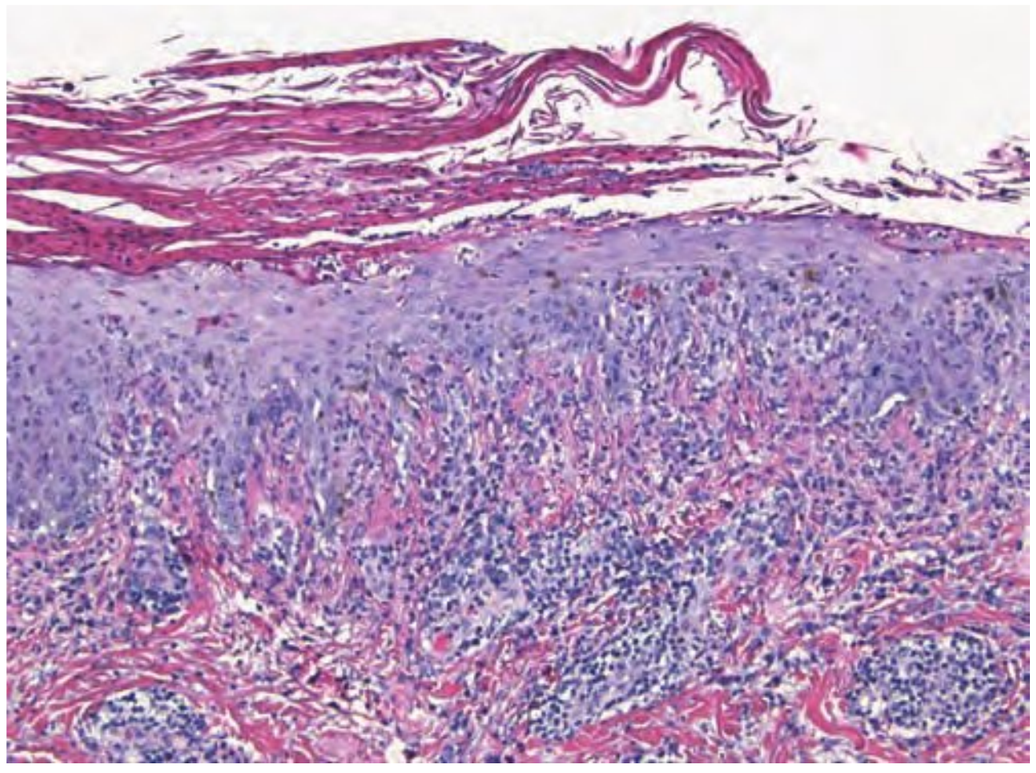


FIGURE 22-5. Secondary syphilis. There is psoriasiform epidermal hyperplasia with basilar vacuolopathy and lymphocytic interface dermatitis. The epidermis is surmounted by a parakeratotic scale rich in neutrophils. Plasma cells may be inconspicuous, as in this example.

inconspicuous or absent in 25% of the cases (Fig. 22-6) (36). Eosinophils are not usually observed. Vascular changes such as endothelial swelling and mural edema accompany the angiocentric infiltrates in half of the cases (36). Necrotizing vascular injury is distinctly unusual. A silver stain is recommended in all cases that are suspected of being secondary syphilis; it shows spirochetes in about one third of the cases of secondary syphilis, mainly within the epidermis and less commonly around the blood vessels of the superficial plexus. In some instances, the silver stain is positive even when dark-field examination of the patient's lesions is negative (24). By the immunofluorescent technique, all cases are positive. Phenotypic analysis of the infiltrate reveals a lymphoid populace composed mainly of T cells, with an equal proportion of cytotoxic and T-helper cells.

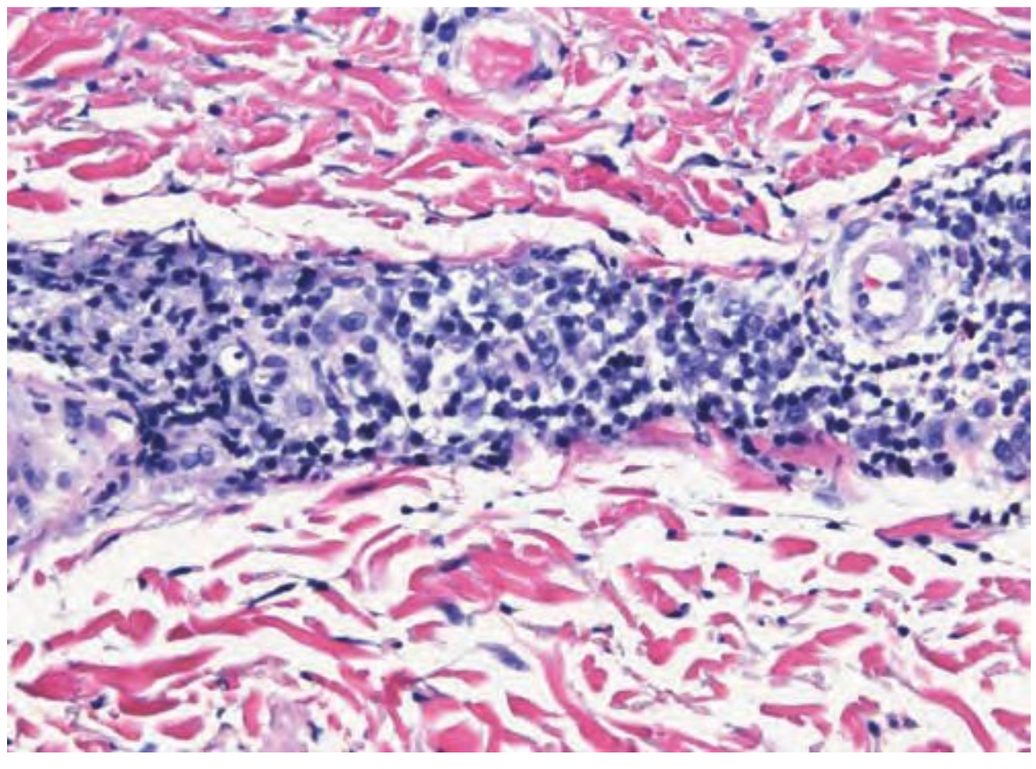


FIGURE 22-6. Secondary syphilis. A dense, lymphocytic, and often plasma-cell-rich infiltrate surrounds the cutaneous vessels of the dermis.

There are several histologic variants of secondary syphilis—namely, condylomata lata, syphilitic alopecia, pustular lesions (Fig. 22-5), syphilis cornee, and lues maligna. Lesions of condylomata lata show all of the aforementioned changes observed in macular, papular, and papulosquamous lesions, but more florid epithelial hyperplasia and intraepithelial microabscess formation are observed (24,40). A Warthin-Starry stain shows numerous treponemes (31).

Biopsies of syphilitic alopecia may demonstrate a superficial and deep perivascular and perifollicular lymphocytic and plasmacellular infiltrate that permeates the outer root sheath epithelium with a concomitant perifollicular fibrosing reaction (24). An involutional tendency characterized by increased numbers of telogen hairs is observed. A concomitant necrotizing pustular follicular reaction may also be seen (16).

An unusual variant of secondary syphilis is lues maligna (41,42), an ulcerative form characterized by severe thrombotic endarteritis obliterans involving vessels at the dermal–subcutaneous junction with resultant ischemic necrosis. A concomitant dense plasmacellular infiltrate with a variable admixture of histiocytes may be observed. Defective cell-mediated immunity may play an integral role in the pathogenesis of lues maligna, particularly in cases in which vascular alterations are minimal (43,44). Several cases of lues maligna arising in the setting of HIV disease have been described, with involvement of the oral cavity as the principal manifestation. A case of secondary syphilis resembling bullous pemphigoid by both light microscopy and immunofluorescent studies has been described (45).

Syphilis cornee/keratoderma punctatum associated with secondary syphilis manifests an epidermal invagination containing a horny plug composed of laminated layers of parakeratotic cells with loss of the granular cell layer and thinning of the stratum spinosum (46). A moderately dense perivascular plasmacellular infiltrate with concomitant capillary wall thickening involves the cutaneous vasculature.

In the rare pustular lesions of secondary syphilis, a necrotizing pustular follicular reaction accompanied by noncaseating granulomata and a perivascular lymphoplasmacellular infiltrate typically characterizes the histopathology (16). A pustular psoriasiform process with an absent granular cell layer and a strikingly thickened cornified layer laced with neutrophils may be seen (Fig. 22-5); if the clinical correlate is rugose or elephantine skin thickening, the designation *rupial syphilis* may be applied (16).

In addition to small, sarcoidal granulomata in papular lesions of early secondary syphilis, late secondary syphilis may show extensive lymphoplasmacellular and histiocytic infiltrates resembling nodular tertiary syphilis (47). Conversely, lesions of early tertiary syphilis may lack granulomata (48).

Although often nonspecific, the hepatitis of secondary syphilis may produce a granulomatous or cholestatic morphology on liver biopsy; hepatic necrosis and spirochetes may also be

observed (49). The nephrosis or glomerulonephritis of secondary syphilis shows proliferative changes in the glomeruli (50).

Histogenesis. The renal changes in secondary syphilis relate to immune complexes containing treponemal antigen. Not only has direct immunofluorescence shown granular deposits of immunoglobulin and complement along the glomerular basement membrane (50,51), but indirect immunofluorescence antibody studies using rabbit treponemal antibody and sheep antirabbit globulin conjugate have demonstrated treponemal antigen in the glomerular deposits (50).

Differential Diagnosis. The differential diagnosis of lesions of secondary syphilis includes other causes of lichenoid dermatitis, including lichen planus, a lichenoid hypersensitivity reaction, pityriasis lichenoides and connective tissue disease, sarcoidosis, psoriasis, and psoriasiform drug eruptions (24). Prominent spongiosis, suprabasilar dyskeratosis, a mid and deep perivascular component, and the presence of plasma cells are not histologic features of lichen planus or psoriasis. Although a middermal perivascular infiltrate, keratinocyte necrosis, and prominent lymphocytic exocytosis are present in pityriasis lichenoides, the infiltrate is purely mononuclear in nature, and neither spongiform pustulation nor plasmacellular infiltration is observed (52). Although lichenoid hypersensitivity reactions and psoriasiform drug reactions may also demonstrate a perivascular infiltrate of plasma cells, tissue eosinophilia is typically observed as well.

Tertiary Syphilis

Tertiary syphilis is categorized into nodular tertiary syphilis confined to the skin; benign gummatous syphilis principally affecting skin, bone, and liver; cardiovascular syphilis; syphilitic hepatic cirrhosis; and neurosyphilis. In the first variant, the granulomas are small and may be absent in rare cases (48). The granulomatous process is limited to the dermis, with scattered islands of epithelioid cells admixed with a few multinucleated giant cells, lymphocytes, and plasma cells. As a rule, necrosis is not conspicuous. The vessels may show endothelial swelling (44).

In benign gummatous syphilis, the main pathology, irrespective of the organ involved, is one of granulomatous inflammation with central zones of acellular necrosis. In cutaneous lesions, the blood vessels throughout the dermis and subcutaneous fat exhibit endarteritis obliterans along with angiocentric plasmacellular infiltrates of variable density. The skin lesions involve the subcutaneous fat and the dermis (53).

In cardiovascular syphilis, elastic tissue fragmentation and reduplication with neovascularization and fibrosis of main arteries occurs. Neurosyphilis includes an asymptomatic form—meningovascular syphilis—and parenchymatous syphilis, which is divided into generalized paresis of the insane and tabes dorsalis (54). In meningovascular syphilis, an inflammatory endarteritis involves the leptomeningeal vessels. In generalized paresis of the insane, gliosis with ventricular dilation is observed; spirochetes are identified in the cortex in 50% of the cases. In tabes dorsalis there is demyelinization of the posterior columns of the spinal cord, atrophy of the posterior spinal roots, and lymphoplasmacellular leptomeningitis (17,54).

NONVENEREAL TREPONEMATOSES

Yaws (Frambesia Tropica)

Yaws is caused by *T. pallidum*, subspecies *pertenue,* which is indistinguishable microscopically from *T. pallidum* subspecies *pallidum* but has been shown to be distinctive by virtue of the substitution of a single nucleotide coding for a 19-kD polypeptide demonstrable by Southern blot analysis (55). Other molecular methodologies confirm distinctive DNA sequences (2,4). Yaws is spread by casual contact between primary or secondary lesions and abraded skin and is most prevalent in warm, moist, tropical climates; 95% of the studied population in one province of Ecuador proved seropositive in one series (56). It is estimated that 2.5 million people globally are affected by this disease (57). Children are particularly afflicted (58). Sites of involvement include buttocks, legs, and feet. Unlike syphilis, yaws does not manifest transplacental spread to neonates (4).

Primary Yaws

The initial primary stage lesion, or "mother yaw," begins as an erythematous papule roughly 21 days postinoculation, which enlarges peripherally to form a 1- to 5-cm nodule surrounded by satellite pustules covered by an amber crust. A red, crusted appearance prompted German physicians to give the appellation "frambesia" to the disease. Lesions may heal as pitted, hypopigmented scars. Fever, arthralgia, and lymphadenopathy may coexist.

Secondary Yaws

Similar constitutional symptoms weeks to months later may herald progression to the secondary stage, characterized by involvement of any or all of skin, bones, joints, and cerebrospinal fluid. *Skin lesions* resemble the "mother yaw" but tend to be smaller and more numerous, hence the designation "daughter yaws." Periorificial lesions may mimic venereal syphilis. A circinate appearance ("tinea yaws") may be observed, as may a morbilliform eruption and/or condylomatous vegetations involving the axillae and groins. Macular, hyperkeratotic, and papillomatous lesions may be present on palmoplantar surfaces and may cause the patient to walk with a painful, crablike gait ("crab yaws"). Papillomatous nail-fold lesions may give rise to "pianic onychia." Relapsing cutaneous disease occurs up to 5 years later, tending to involve periorificial and periaxillary sites. A lifelong noninfectious latent state may then eventuate. *Bone lesions* consist of painful, sometimes palpable periosteal thickening of arms and legs, occasionally accompanied by soft tissue swellings around the involved small bones of the hands and feet.

Tertiary Yaws

Roughly 10% of cases progress to *tertiary yaws*, the skin manifestations of which comprise subcutaneous abscesses, ulcers that may coalesce to form serpiginous tracts, keloids, keratoderma, and palmoplantar hyperkeratosis. The bone and joint lesions of this stage include osteomyelitis, hypertrophic or gummatous periostitis, and chronic tibial osteitis, which may lead to "saber shin" deformities. Bilateral hypertrophy of the nasal processes of the maxilla produces the rare but characteristic "goundou," which obstructs the nasal passages and, if not treated with early antibiotic therapy, may require surgery. Another otorhinolaryngologic complication is "gangosa," characterized by nasal septal or palatal perforation. Although neurologic and ophthalmologic involvement is not a universally accepted phenomenon, reports of macular atrophy and culture-positive aqueous humor suggest that yaws may exhibit neuroophthalmologic manifestations similar to those of venereal syphilis. A less virulent form of the disease, observed in lower-prevalence areas, is termed "attenuated yaws," the cutaneous manifestations of which comprise greasy gray lesions in the skin folds.

Histopathology. *Primary lesions* show acanthosis, papillomatosis, spongiosis, and neutrophilic exocytosis with intraepidermal microabscess formation. A heavy, diffuse, dermal infiltrate of plasma cells, lymphocytes, histiocytes, and granulocytes is observed; unlike the case in syphilis, blood vessels manifest little or no endothelial proliferation (Figs. 22.7and 22.8) (59,60). *Secondary lesions* show the same histologic appearance, resembling condylomata lata in their epidermal changes but differing by virtue of the dermal infiltrate being in a diffuse, as opposed to a perivascular, disposition. The ulcerative lesions of *tertiary yaws* greatly resemble those observed in late syphilis in histologic appearance (60). The spirochetes can be demonstrated in primary and secondary lesions by dark-field examination. Silver stains demonstrate numerous organisms between keratinocytes. Unlike *T. pallidum*, which is found in both epidermis and dermis, *T. pertenue* is almost entirely epidermotropic (60).

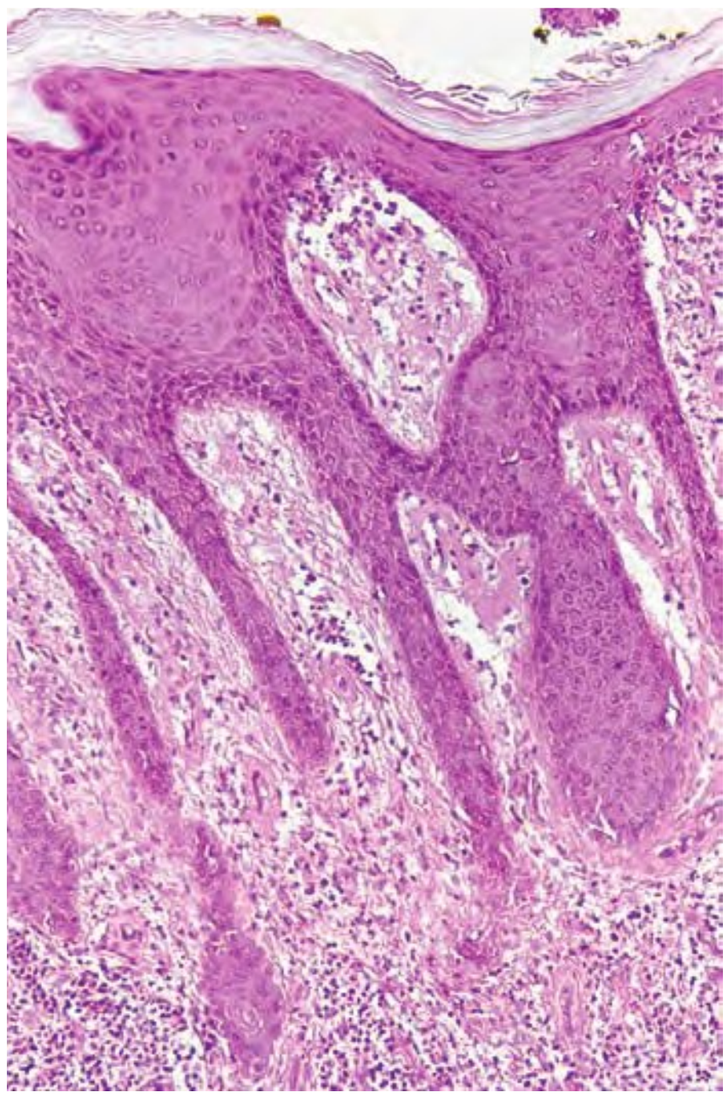


FIGURE 22-7. Yaws, the primary lesion. The biopsy shows a psoriasiform hyperplasia of the epidermis, accompanied by slight spongiosis and an intense lymphohistiocytic and plasmacellular infiltrate in the subjacent corium.

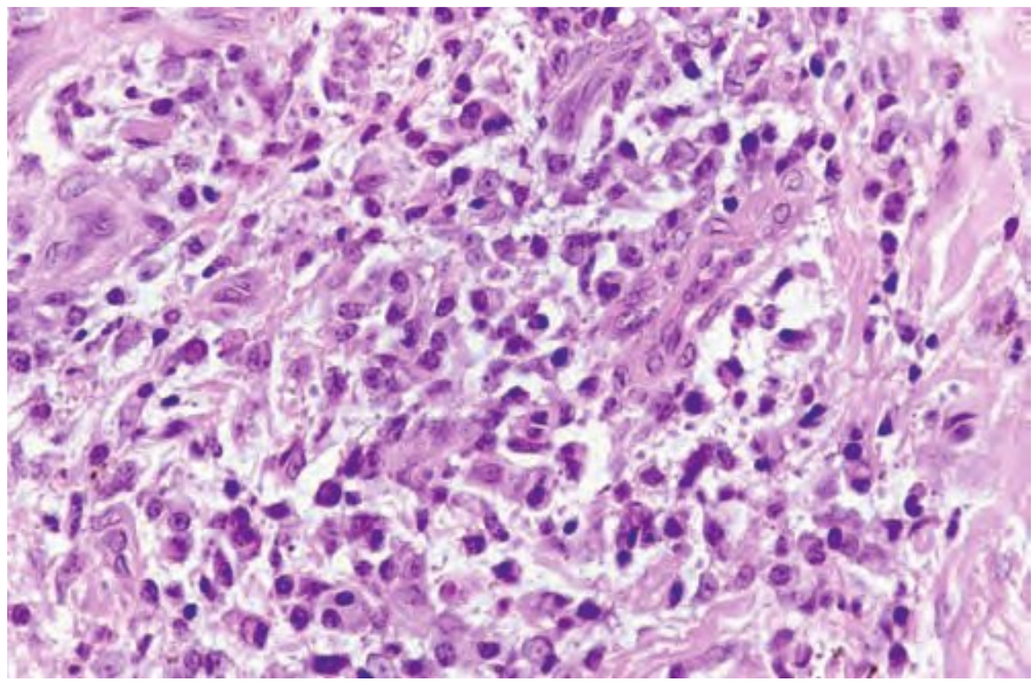


FIGURE 22-8. Yaws, the primary lesion. The biopsy shows an intense angiocentric lymphohistiocytic and plasmacellular infiltrate without the characteristic endarteritis obliterans vascular alterations observed in syphilis.

Differential Diagnosis. The distinction between yaws and syphilis is based on clinical features; although the location of the organism in a skin biopsy may be helpful, no histologic feature or laboratory test absolutely distinguishes the two diseases (61).

Pinta

Unique among the treponematoses, pinta, caused by *T. carateum*, demonstrates only skin manifestations (62). The disorder is endemic to Central America and restricted to the Western hemisphere. It affects no age group preferentially and is the mildest of the treponematoses, with hypopigmentation being the only significant sequela. The incidence of pinta is declining precipitously for unknown reasons. Transmission appears to be from lesion to skin, classically between family members; the ritualistic whipping of diseased adults and unaffected youths is the putative mode of transmission in one aboriginal tribe in the Amazon basin (62).

The *primary lesion* is characterized by an erythematous papule surrounded by a halo and occurs 1 to 8 weeks postinoculation. By direct extension or through fusion of satellite lesions, the primary site may grow to a diameter of 12 cm,

forming an ill-defined erythematous plaque on the legs or other exposed sites. In infants, the primary lesion classically occurs at the sites where the baby was held most closely to the affected mother. The *secondary lesions*, or "pintids," manifest months after inoculation as small, erythematous, scaly papules that coalesce to form psoriasiform plaques. Both primary and secondary lesions are highly infectious. In the tertiary stage, hypopigmented macules are present over bony prominences such as wrists, ankles, and elbows. Symmetric areas of achromia alternating with areas of normal or hyperpigmented skin may result in a mottled appearance. Atrophy and/or hyperkeratosis may be present. An attenuated variant is not described.

Histopathology. *Primary* and *secondary* lesions show a similar morphology—namely, acanthosis with spongiosis and a sparse dermal infiltrate of lymphocytes, plasma cells, and neutrophils disposed about dilated blood vessels (63). Endothelial swelling in the dermal vasculature is inconspicuous (64). Lichenoid inflammation may be present, accompanied by hyperkeratosis, hypergranulosis, basal layer vacuolopathy, and pigmentary incontinence. Increased numbers of Langerhans cells are present in the epidermis (65). Lesions of the *tertiary stage* are hyperpigmented, characterized by a large number of melanophages within the dermis, or depigmented, manifesting complete absence of epidermal melanin. Both lesions show epidermal atrophy and perivascular lymphocytic infiltrates. Organisms are present in all but late, longstanding lesions.

Histogenesis. Electron microscopy reveals absent melanocytes in depigmented lesions of tertiary or late pinta (65).

Endemic Syphilis (Bejel)

Unlike yaws, endemic syphilis, caused by *T. pallidum* subspecies *endemicum*, is largely confined to the arid climates of the Arabian peninsula and the southern border of the Sahara desert (62), whose seminomadic populations term the disease "bejel." Children 2 to 15 years of age constitute the principal reservoir. Infection occurs by skin-to-skin contact or by means of fomites such as communal pipes or drinking vessels.

Primary stage skin lesions are rare and are characterized by erythematous papules or ulcers of the oropharyngeal mucosa or the skin of the nipple of an uninfected mother nursing an infected infant.

More commonly, the initial manifestation is the presence of *secondary-stage* lesions, characteristically multiple, shallow, rather painless ulcers involving lips, buccal mucosa, tongue, fauces, or tonsils. Such lesions may be accompanied by hoarseness due to treponemal laryngitis and/or regional lymphadenopathy. Condylomata lata involving the axillae and anogenital regions are also observed. Rarely, the secondary stage manifests as erythematous, crusted papules, macules, or an annular papulosquamous eruption, which may be accompanied by generalized lymphadenopathy or periostitis.

The *tertiary stage* comprises gummatous lesions of nasopharynx, larynx, skin, and bone, which may progress to ulcers that heal as depigmented, sometimes geographic scars with peripheral hyperpigmentation. Bone and joint involvement may manifest as tibial periostitis, which mimics that of yaws, or as mutilating lesions involving the nasal septum and palate. Ophthalmologic involvement comprises uveitis, chorioretinitis, choroiditis, and optic atrophy; *T. pallidum* has been cultured from intraocular fluid.

Histopathology. Although the pathology of early lesions of endemic syphilis is not well characterized, late lesions are said to show parakeratosis, acanthosis, spongiosis, pigmentary incontinence, and a dermal lymphohistiocytic and plasma cell infiltrate.

Lyme Disease

Background

First described in patients from Lyme, Connecticut, in 1975 (66), Lyme disease is a systemic spirochetosis caused by *Borrelia burgdorferi* and transmitted by the soft ticks of the species *Ornithodorus* (67). Although the disease in the index cases manifested as inflammatory arthritis and central nervous system and cardiac symptoms (68) preceded by cutaneous erythema, manifestations may be protean and perplexing to the clinician. Lyme disease is the most common vector-borne disease in the United States, with roughly 20,000 new cases in 2005 (69). Males are predominantly affected, with a bimodal age peak: children aged 5 to 14 years and adults aged 60 to 65 years; most cases occur between June and August (69). Recurrences after appropriate antimicrobial therapy have been reported, and it appears that most represent second tick bite inoculations as opposed to relapses (70).

Although the tick *Ixodes dammini* is the prototypic vector (67,71), other species of ticks from the genus *Ixodes* can also be infected—namely, *I. ricinus* (72), *I. pacificus,* and *I. scapularis* (73–75). Lyme disease has been reported in 43 states, Europe, elsewhere in North America, Africa, and Asia (73). Infection by multiple different bacterial species transmitted by the same infected tick may occur. Coinfection of ticks and of humans by *Ehrlichia chaffeensis*, the etiologic agent of human granulocytic ehrlichosis, and by *B. burgdorferi* is demonstrable in areas where the two diseases are endemic (76–80). Babesiosis is anther tick-borne infection that can be coexpressed with Lyme disease (78,81). Although it seems counterintuitive, one model suggests that certain animals, such as the lizard *Eumeces fasciatus* (the five-lined skink), can act as a dilutional host, whereby reservoir incompetence can act to reduce vector infection prevalence and the associated risk of human infection (82).

There are three phases of Lyme disease. In stage I disease, hematogenous dissemination from lesions of erythema chronicum migrans to other organs may occur, the effects of which are usually self- limited (83) and include orchitis, splenomegaly, lymphadenopathy, and mild pneumonitis. The two main systems involved in stage II are neural and cardiac (83). The triad of meningitis, cranial neuritis, and radiculoneuritis is characteristic for neural involvement (84); Lyme cerebritis may also occur, and alteration of mental status may be the only initial clinical manifestation (85). Cardiac involvement manifests

mainly as tachycardia and heart blocks, the basis of which is epi- and transmyocarditis. A biopsy of myocardium may show interstitial lymphoplasmacellular infiltrates, with a bandlike endocardial disposition said to be characteristic. A nonneutrophilic myocardial vasculitis has been described. Chronic disease at organ sites where spirochetes persist, most commonly the skin and nervous system in Europe and the musculoskeletal system in North America, constitutes stage III. Lyme arthritis and synovitis are characterized by a migratory oligoarthritis usually involving the knee joint, with the shoulder, wrist, temporomandibular, and ankle joints involved in some cases. Rarely reported is involvement of other sites such as metatarsal heads with edema and soft tissue swelling (86).

Erythema Chronicum Migrans

First described by Arvid Afzelius in 1909 (73), erythema chronicum migrans is the distinctive, albeit not pathognomonic, cutaneous manifestation of stage I Lyme disease in both Europe and the United States and represents the site of primary tick inoculation. Erythema chronicum migrans appears to occur in only roughly half of cases of Lyme disease (69); in the absence of a rash, the diagnosis depends on the demonstration of an antibody response to *B. burgdorferi* in an appropriate clinical setting (87). Unfortunately, patients who are immunosuppressed, such as those with underlying lymphoproliferative diseases, may never mount a detectable antibody response (88). Patients are often unaware of the often painless tick bite (89). The lesion starts as an area of scaly erythema or a distinct red papule within 3 to 30 days after the tick bite, before spreading centrifugally with central clearing after a few weeks, occasionally reaching a diameter of 25 cm (90). The clinical presentation may be atypical by virtue of purpuric, vesicular, or linear lesions. Average lesional duration is 10 weeks in the European variant and 4 weeks in the American variant; in some cases, lesions persist for as long as 12 months. Females are affected more frequently in the European variant than in the American variant. The lesions may be solitary or multiple, the latter reflecting hematogenous dissemination of the spirochete, which may be accompanied by fever, fatigue, headaches, cough, and arthralgias (67).

Histopathology. An intense superficial and deep angiocentric, neurotropic, and eccrinotropic infiltrate predominated by lymphocytes with a variable admixture of plasma cells and eosinophils is the principal histopathology (Fig. 22-9). Plasma cells have been identified most frequently in the peripheries of lesions of erythema chronicum migrans, whereas eosinophils are identified in the centers of the lesions (91). Not infrequently, these florid dermal alterations are accompanied by eczematous epithelial alterations, and some cases exhibit edema of blood vessels with transmural migration of lymphocytes, histiocytes and plasma cells (Fig. 22-9), granulomatous neuritis or vasculitis with luminal thrombosis (personal observation), and interstitial infiltration of the reticular dermis with a concomitant incipient sclerosing reaction. A Warthin-Starry stain may be positive; one study demonstrated spirochetes by this technique in 41% of the cases, with approximately one to two spirochetes, measuring 10 to 25 μm by 0.2 to 0.3 μm, per section (91). Spirochetes have been identified primarily from the advancing border of the lesion. Most patients have elevated immunoglobulin M antibody titers (89).

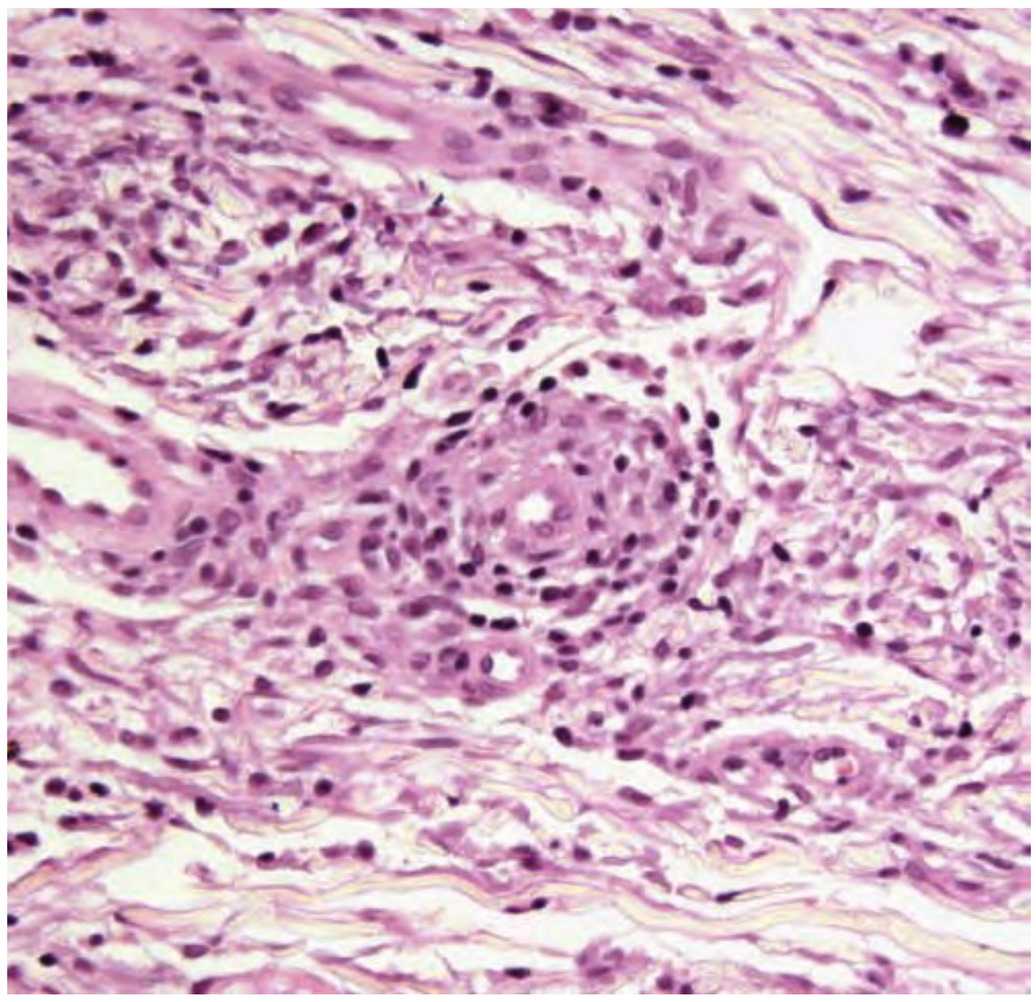


FIGURE 22-9. Erythema chronicum migrans. The central nidus at the inoculation site demonstrates a necrotizing granulomatous vasculitis, whereas the periphery is predominated by an angiocentric lymphohistiocytic vasculopathy, shown here.

Differential Diagnosis. The differential diagnosis includes other causes of delayed hypersensitivity in which potential antigenic stimuli include other forms of arthropod assaults, drugs, and contactants. A similar distribution of the dermal infiltrate is observed in connective tissue disease; however, the presence of tissue eosinophilia along with concomitant eczematous changes is not a feature of the latter. Differentiation from erythema annulare centrifugum may be impossible.

Dermal Atrophying and Sclerosing Lesions as Manifestations of Lyme Disease: Acrodermatitis Chronica Atrophicans

First described in 1883 in Germany and subsequently named by Herxheimer in 1902 (92), acrodermatitis chronica atrophicans usually begins as a diffuse or localized erythema on one extremity with the underlying dermis having a doughy consistency. After several months, the lesions become atrophic. The skin is frequently so thin that vessels and subcutaneous tissue can be easily visualized (93). Appendageal structures disappear, resulting in hair loss and decreased sweat and sebum production. The lesions are located mainly on the upper and lower extremities, frequently around joints, and spare the palms, soles, face, and trunk (93). Sclerosis may predominate in late-stage lesions and take several distinct forms: pseudosclerodermatous plaques over

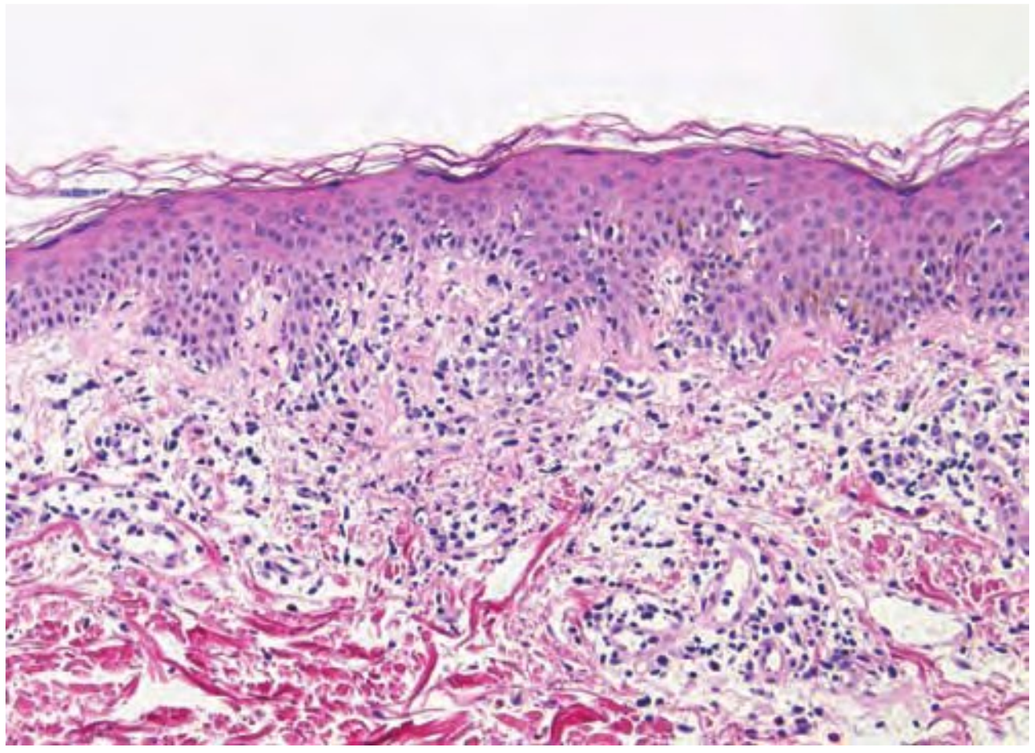


FIGURE 22-10. Acrodermatitis chronica atrophicans. The epidermis shows basket-weave orthokeratosis with a sparse interface dermatitis with lymphocyte tagging along the dermal–epidermal junction. The papillary dermis is edematous, and the reticular dermal collagen fibers exhibit an orientation parallel to the epidermis. A concomitant interstitial lymphohistiocytic infiltrate is found in intimate apposition to the attenuated collagen fibers. This is an incipient or evolving lesion; atrophy follows with loss of the retiform pattern.

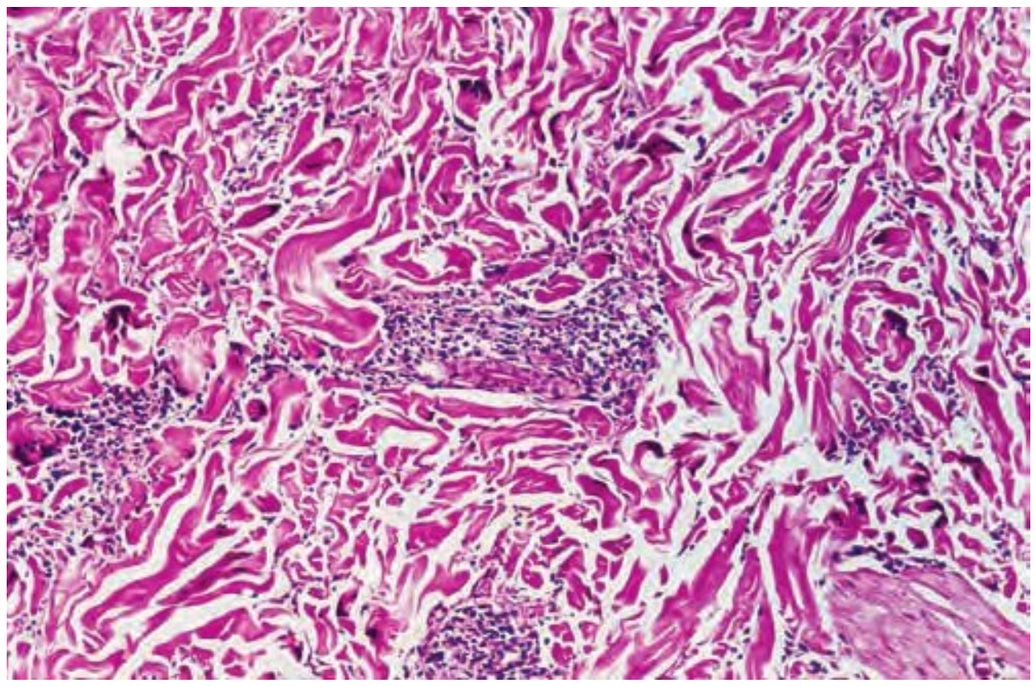


FIGURE 22-11. Borrelia burgdorferi–associated morphea. The dermis exhibits a sclerodermoid tissue reaction characterized by widened hypereosinophilic collagen fibers with loss of the normal fibrillar architecture and an interstitial lymphohistiocytic infiltrate in close apposition to the altered collagen fibers. Special stains reveal spirochetal forms amid the inflammatory infiltrate.

the dorsa of the feet; dense, fibrotic linear bands over ulnar and tibial areas; or localized fibromas overlying joint surfaces (92). Antibodies against *B. burgdorferi* are present in 100% of cases. Patients frequently have an elevated erythrocyte sedimentation rate and hypergammaglobulinemia. Either at the peripheries of lesions or distant from them, anetoderma, lymphocytoma, and morphea have also been described (93).

Histopathology. Within a few months to a year, the epidermis appears atrophic with loss of the rete ridges. There is granular layer diminution, and the epidermis is surmounted by a hyperkeratotic scale. In one study, a sparse interface dermatitis characterized by lymphocyte tagging along the dermal–epidermal junction, as well as basal layer cytolysis, was seen in 41% of cases (Fig. 22-10) (94), resulting in variable postinflammatory pigmentary alterations ranging from leukoderma to hyperpigmentation (92). The papillary dermis appears edematous, with a grenz zone of collagen fibers oriented parallel to the epidermis (95) ranging from a few strands to a wide zone (96), with subsequent eosinophilic homogenization (95). A bandlike lymphocytic infiltrate is found in the mid and upper dermis and in some cases may produce a lichenoid morphology, obscuring the dermal–epidermal junction. Occasionally it extends throughout the cutis and subcutis (94,95). The infiltrate is predominantly in an angiocentric, eccrinotropic, and folliculotropic disposition and comprises mainly lymphocytes and histiocytes (95). Eosinophils, neutrophils, and plasma cells form a minor cell populace (95). The vessels amid the superficial infiltrate appear destroyed (94). Within the infiltrate, there is piecemeal fragmentation of collagen, and elastic tissue is lacking. Beneath the infiltrate, disorganization and destruction of the collagen, along with hyperplasia, fragmentation, and basophilia of the elastic fibers (95), are observed. An end-stage lesion exhibits a characteristic constellation of epidermal atrophy, large dilated dermal vessels, and an attenuated dermis composed of damaged and degenerated collagen and elastic fibers with lipoid phanerosis (95). The collagen may appear homogenized and hypereosinophilic (Fig. 22-11) (95). There is ultimately marked atrophy of adnexae with periadnexal fibrosis.

Histogenesis. Acrodermatitis chronica atrophicans is mainly a stage III (late) cutaneous manifestation of the European variant of Lyme disease; the major vector is *I. racinus* (92), and hence the distribution of the lesion is worldwide, with middle Europe being the epicenter (92). Most North American cases occur in European immigrants; *I. ricinus* is not an inhabitant of North America (92). Immunophenotyping reveals that most of the lymphocytes are of T cell phenotype and that the elastic fibers express HLA-DR (94), suggesting a role for cell-mediated immunity in lesional development.

Other Atrophying and Sclerosing Disorders Associated with Lyme Disease

Atrophoderma of Pasini and Pierini, facial hemiatrophy of Perry-Romberg, lichen sclerosus et atrophicus, eosinophilic fasciitis, and morphea (Fig. 22-11) are among the atrophying and sclerosing disorders of connective tissue that have been associated with *B. burgdorferi* infection based on the positive serology for *B. burgdorferi* in patients with these conditions, the isolation of spirochetal organisms in cultures of the respective skin lesions, and/or their identification in histologic sections (73,74,96,97). In addition, acrodermatitis chronica atrophicans and morphea may coexist in the same patient.

A possible etiologic basis of the sclerosis in all five entities—either as the inciting event (in morphea and eosinophilic fasciitis) or as an end-stage phenomenon (in atrophoderma, facial hemiatrophy, and lichen sclerosus)—may relate to increased production of interleukin-1 mediated by the *B. burgdorferi* spirochete, resulting in enhanced fibroblast production (95). Only progressive facial hemiatrophy will be considered further; all of the conditions are covered elsewhere in this book (see Chapter 10).

Facial hemiatrophy is an apposite term for an atrophying condition of the skin, subcutaneous fat, muscle, and bone involving either one division of the trigeminal nerve or half of the face. Occasionally the entire ipsilateral side of the body may be affected, or the atrophy may first manifest on the trunk or extremities.

Histopathology. A sclerodermoid tissue reaction mimicking morphea is observed, including the presence of adnexal atrophy and subcutaneous fibrosis. The muscles are atrophic, with loss of striations, edema, and vacuolation. Ocular and neurologic complications including iritis, keratitis, optic nerve atrophy, trigeminal neuralgia, and facial palsy may occur (73).

Borrelial Lymphocytoma Cutis

Lymphocytoma cutis is a benign cutaneous lymphoid hyperplasia first described by Spiegler before the end of the nineteenth century and subsequently named lymphocytoma cutis in 1921 by Kaufmann-Wolff. Various triggering factors have been isolated, such as drugs, contactants, and infections, suggesting that an excessive immune response to antigen may be its etiologic basis. The *B. burgdorferi* spirochete transmitted by *I. ricinus* has been implicated among the infectious agents. Evidence supportive of a spirochetal etiology of some cases of lymphocytoma cutis includes the identification of spirochete-like structures in mercury- and silver-stained sections of skin biopsies from patients with lymphocytoma cutis in whom increased serum titers of antibodies against *Borrelia* spirochetes are observed (98). The term *borrelioma* has been coined to describe such lesions. Lymphocytoma cutis in association with *B. burgdorferi* infection has the same clinical appearance as lesions arising in other settings—namely, as isolated or multiple violaceous, firm nodules and infiltrative plaques (73). Sites of predilection for the solitary lesions are the earlobes, nipples, and areolae mammae. Lesions of lymphocytoma cutis may occur at sites of erythema chronicum migrans or in patients with stage II Lyme disease. Jessner's lymphocytic infiltrate of skin is considered by some authors to be a form of lymphocytoma cutis and was reported in one patient whose biopsy showed spirochetes (73).

Histopathology. Skin biopsies show superficial and deep angiocentric, neurotropic, and eccrinotropic lymphocytic infiltrates, often accompanied by plasma cells and eosinophils, the former at the periphery and the latter in the center of lesions (91). The dermal alterations may be accompanied by epidermal spongiosis, and some cases show edema of blood vessels, transmural migration of lymphocytes and plasma cells, granulomatous vasculitis with luminal thrombosis, lymphohistiocytic neuritis, and interstitial reticular dermal infiltrates with a sclerosing reaction. Germinal centers may be observed. A florid inflammatory cell infiltrate with granulomatous vasculitis and neuritis is seen at the tick bite punctum, whereas a biopsy taken within 1 cm of the edge shows a pauci-inflammatory process with only sparse mononuclear cells, no eosinophils or plasma cells, and a vasculopathy comprising endothelial swelling and hyperplasia and mural edema accompanied by mucinosis (99). Biopsies taken between the center and edge show superficial and deep perivascular lymphocytic, plasmacellular, and eosinophilic infiltrates with variable eczematous alterations. Although spirochetes have been identified in the lesional border in only 40% of cases (91), most patients manifest elevated immunoglobulin M antibody titers (74), and we therefore rely heavily on serology to make the diagnosis. Others hold that the diagnosis at this stage is largely a clinical one due to the incidence of false-positive and false-negative results (100); the sensitivity and specificity of confirmatory molecular tests are not optimal, and culture is insensitive (101). The background high seropositivity rates in healthy patients in endemic and nonendemic areas have prompted a two-tiered approach through which seropositive patients undergo a subsequent and more specific Western blot analysis (102,103). Meta-analysis of molecular methods shows that assays of skin and synovial fluid have the highest sensitivities and specificities; plasma and cerebrospinal fluid assays are less accurate (101). Quantitative polymerase chain reaction of erythema chronicum migrans lesions shows positivity in up to 80% of cases, with the mean number of spirochetes in a 2-mm biopsy specimen ranging from 10 to 11,000; larger numbers of spirochetes correlate with smaller lesions and shorter duration of skin symptomatology (104). Molecular tests for Lyme disease are reserved as complementary or confirmatory tools for cases in which the index of suspicion is high (101).

Differential Diagnosis. The clinical differential diagnosis encompasses other forms of annular erythema (105). Other causes of lymphocytoma cutis should be considered, such as drug therapy (106) or other infections (e.g., herpetic or mycobacterial). A well-differentiated lymphocytic lymphoma and chronic lymphocytic leukemia should be excluded because both may mimic the diffuse type of lymphocytoma cutis. When eosinophils and plasma cells are present and when there are germinal centers, the distinction from malignant lymphoma (apart from marginal zone lymphoma) is less challenging.

Other arthropod assaults, drug hypersensitivity, contact reactions, and connective tissue diseases such as lupus erythematosus, scleroderma, morphea, Sjögren's syndrome, mixed connective tissue disease, and relapsing polychondritis can mimic Lyme disease. Tissue eosinophilia and epidermal changes help to discriminate Lyme disease from connective tissue disease, but differentiation from erythema annulare centrifugum is more problematic. Tissue necrosis at the primary inoculation site of Lyme disease can mimic a brown recluse spider bite (107).

Histogenesis. Most ticks become infected with *B. burgdorferi* by feeding on small animals, in particular the white-footed

mouse. *B. burgdorferi* is a long, narrow spirochete with flagella (108). It has at least 30 different proteins, including two major outer-surface proteins—Osp A and Osp B, which elicit antibody responses late in the course of the disease (108). It has been suggested that phagocytosis of the spirochete by macrophages leads to two different mechanisms of degradation: a phagolysosomal process, which may lead to major histocompatibility class (MHC) class II–restricted antigen processing, and cytosolic degradation, which leads to MHC class I–restricted antigen presentation. This disparity may in part explain the variable immunologic aspects of Lyme disease (109).

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CHAPTER 23

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B. Jack Longley

Fungal Diseases

Fungi are eukaryotic protists that are distinguished from plants by their lack of chlorophyll (1). The Greek word *mycoses* means "fungus" and was first penned by R. Virchow in 1856 to describe infections by this group of organisms. In the past, bacterial infections, lymphoma, and other disorders have also been termed *mycoses* despite a lack of relation to fungi. Actinomycosis, botryomycosis, and erythrasma are examples of bacterial diseases that have historically been discussed with fungal diseases. These entities are covered in Chapter 21. Protothecosis is a cutaneous infection by algae of the genus *Prototheca* and will continue to be included in this chapter because there is no separate chapter for infections by algae.

Defining terminology in fungal diseases aids comprehension and diagnostic consistency (Table 23-1). *Hyphae* are elongated filamentous forms of fungi that usually form an intertwining mass called a *mycelium*. Septate hyphae give rise to arthrospores by asexual reproduction. Frequently, rounded, boxlike, or short cylindrical arthrospores can be identified. *Yeasts* are single-celled, usually rounded fungi that reproduce by budding (blastospore formation). Yeast cells and their progeny may adhere to one another and form chains or *pseudohyphae* that may also form mycelia; thus, they may be difficult to distinguish from true hyphae by light microscopy. *Dematiaceous fungi* are fungi that bear melanin-like pigment in their walls. *Tinea* is a clinical term that describes superficial fungal infections of the skin; it is usually modified with an anatomic or other term to describe the location or color of the infection. The *dermatophytes* are fungi that were originally classified by Sabouraud (2) and redefined by Emmons (3), including the three genera *Microsporum*, *Trichophyton*, and *Epidermophyton*. Therefore, *dermatophytosis* is not an appropriate histologic diagnostic term unless a definite assignment of an organism to one of these three genera of dermatophytes can be made. *Dermatomycosis* refers to any fungal infection of the skin and may be caused by dermatophytes, yeast, or other fungi, including those that do not usually cause cutaneous disease.

The primary cutaneous fungal pathogens can be separated into two groups: those that tend to cause superficial infections and those that cause deep infections. A third group of cutaneous fungal pathogens are those that usually cause systemic disease and only secondarily involve the skin. The basic pattern of cutaneous infection is relatively uniform within each of these three groups. The degree of inflammatory response to these three categories of fungal infection, however, varies based on a number of factors, particularly host immune status. For example, infections with organisms causing superficial dermatomycoses, such as the dermatophytes, *Candida* sp., *Malassezia* (*Pityrosporum*) *furfur*, and *Cladosporium* (*Exophiala* or *Phaeoannellomyces*) *werneckii*, are generally characterized by hyphae or pseudohyphae and sometimes yeast cells in the keratin layer of the epidermis and in follicles. The variable intensity of the tissue reaction in the epidermis and follicular epithelium ranges from almost no response to a very mild focal spongiosis to a more exuberant or chronic spongiotic-psoriasiform pattern. Superficial fungal infections may provoke a superficial lymphocytic or a mixed dermal inflammatory infiltrate. Organisms causing superficial dermatomycosis are not found in the dermis except in the case of follicular rupture.

Deep cutaneous fungal infections typically show a mixed dermal inflammatory cell infiltrate that is often associated with pseudoepitheliomatous hyperplasia and occasionally with dermal fibrosis. Primary cutaneous aspergillosis, chromomycosis, phaeohyphomycosis, eumycetoma, rhinosporidiosis, and lobomycosis are examples of fungi that infect the deeper cutaneous tissues.

Incidental cutaneous infections by fungi that usually primarily involve other organs, such as blastomycosis or coccidioidomycosis, typically show a pattern similar to that seen with the deep primary cutaneous fungi: a mixed dermal infiltrate with multinucleated giant cells associated with pseudoepitheliomatous hyperplasia. However, a few organisms such as *Histoplasma* and *Lobo̧a loboi* are more likely to be associated with epidermal thinning than with hyperplasia. Other systemic fungal infections show characteristic tissue reaction patterns. For example, disseminated candidiasis has prominent microabscess formation, cryptococcosis has a gelatinous or granulomatous reaction pattern, and zygomycosis and aspergillosis have a tendency for vascular invasion and infarction.

Multiple special stains highlight certain fungal elements. These techniques can be helpful especially when the overall histologic pattern is suspicious for a fungal infection but fungi are not apparent on hematoxylin and eosin (H&E)-stained sections. The periodic acid-Schiff (PAS) reaction stains fungi red and can be used with diastase (PAS-D), which clears the tissue of glycogen granules that may be mistaken for fungal spores. Fungi stain positively with PAS-D because their walls contain cellulose

TABLE 23-1 Terminology of Fungi

Term	Definition	Example
Dermatophyte	Imperfect fungi	Trichophyton, Microsporum, Epidermophyton
Dermatomycosis	Any fungal infection of the skin caused by dermatophytes, yeast, or fungi, including those that do not usually cause disease. Dermatomycoses may be superficial or deep.	
Mold	Filamentous structural morphology of fungus	Dermatophytes, chromomycosis
Arthrospores	Asexual fungal spore formed by hyphal segmentation	Dermatophytes
Hyphae	Elongated filamentous forms of fungi	Dermatophytes
Mycelium	Intertwining mass of hyphae	
Yeast	Round to oval fungal forms that reproduce by budding or blastogenesis	Candida, Cryptococcus, Malassezia
Blastoconidia	Daughter cells of parent yeast	
Pseudohyphae	Chains of yeastlike cells that resemble hyphae	Candida sp.
Dematiaceous fungi	Mold or yeast with melanin pigment in their walls	Phaeohyphomycosis, chromomycosis
Sporangia	Spherule containing endospores	Coccidioides imitis
Sporangioblasts	Another term for endospores	Rhinosporidium seeberi
Grains	Dense accumulations (microcolonies) of fungi or bacteria	Eumycetoma
Tinea	Clinical term to describe superficial fungal infections of the skin	Facei, cruris, pedis, manus
Dimorphic	Fungus that grows in more than one form (mold, yeast, sclerotic body, sulfur grains, spherules with endospores, etc.)	Histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidiomycosis

and chitin, both of which are rich in neutral polysaccharides and diastase resistant. Gomori methenamine silver (GMS) nitrate stains fungi black and is also useful. Giemsa, Gram, silver, Fontana-Masson, mucicarmine, Alcian blue, India ink and acid-fast stains also highlight various fungal elements in other primary or secondary cutaneous fungal infections.

DERMATOPHYTOSIS

Dermatophytes are a group of molds that invade and consume keratin by generating proteases (4). They originally came from soil where they lived on keratinaceous debris but ultimately were picked up by animals and humans to become the pathogens known today (5,6).

Three genera of imperfect fungi comprise the dermatophytes: *Epidermophyton*, *Microsporum*, and *Trichophyton*. More than 40 species exist, although many are not pathogenic to humans. Dermatophytes may be grouped according to their natural habitat as anthropophilic, zoophilic, and geophilic, with primary reservoirs of infection in humans, animals, and soil, respectively (5). Fungi in all three categories may cause human infections. In immunocompetent hosts, the dermatophytes cause only superficial infections of the epidermis, hair, and nails. *Epidermophyton* sp., as the name suggests, infect mainly the epidermis, although occasionally the nails are involved. *Microsporum* sp. infect the epidermis and hair, while *Trichophyton* sp. may infect the epidermis, hair, and nails.

Clinically, fungal infections of seven anatomical regions are commonly recognized: tinea capitis (including tinea favosa or favus of the scalp), tinea faciei, tinea barbae, tinea corporis (including tinea imbricata), tinea cruris, tinea of the hands and feet, and tinea unguium (Table 23-2).

Tinea capitis is dermatophytosis of the skin and hair of the scalp. Clinically, scale crust and hairs that are broken off either at the level of the scalp or slightly above it are often seen. In the United States, *Tricophyton tonsurans* is the most common pathogen of this anatomic site where only broken-off hairs (black-dot ringworm) are seen in some patients and a marked inflammatory reaction in others. *Tricophyton schoenleinii* causes *favus*, but favus may also rarely be caused by other *Trichophyton*. *Microsporum audouinii*, *Microsporum canis*, and much less commonly other *Microsporum* sp. may also cause tinea capitis. *M. canis* is zoophilic and therefore tends to cause a more inflammatory

TABLE 23-2 Common Causal Dermatophytes by Anatomic Regions

Clinical diagnosis	Causal organisms
Tinea capitis	T. tonsurans (black dot), T. violaceum (black dot), T. schoenlenii (favus), M. canis
Tinea faciei	T. verrucosum, T. mentagrophytes, T. rubrum
Tinea corporis	T. rubrum, T. mentagrophytes, E. floccosum, T. concentricum
Tinea manus	T. rubrum
Tinea pedis	T. rubrum, T. mentagrophytes, E. floccosum
Tinea unguium	T. rubrum, T. mentagrophytes (vesicobullous), E. floccosum

response than *M. audouinii*, which is anthropophilic; both show a band of bright green fluorescence in the hair under a Wood light. A severe inflammatory boggy plaque, called *kerion Celsi*, may result from infection with zoophilic dermatophytes such as *M. canis*. *Trichophyton* sp. other than *T. schoenleinii*, which shows subtle pale green fluorescence along the length of the hair, do not fluoresce in a Wood light.

Favus is a severe tinea capitis usually caused by *T. schoenleinii*, although a similar clinical picture may occasionally be seen with other fungi. Favus affects mainly the scalp, where it produces inflammation with formation of perifollicular hyperkeratotic crusts called *scutula*. Destruction of the hair occurs relatively late in the infection. The lesions may heal with scarring and permanent alopecia.

Tinea faciei is a fungal infection of the glabrous skin of the face characterized by a persistent eruption of red macules, papules, and patches, the latter of which may show an arcuate border. It is caused usually by *Tricophyton rubrum* and occasionally by *Tricophyton mentagrophytes* or *T. tonsurans* (7).

Tinea barbae is a fungal infection limited to the coarse hair-bearing beard and mustache areas of men. Tinea barbae may be caused by *T. mentagrophytes* but usually is due to *Trichophyton verrucosum* (*faviforme*), an infection also often referred to as *cattle ringworm* because it is usually contracted from cattle. Both *T. mentagrophytes* and *T. verrucosum* are zoophilic and typically cause a kerion-like, boggy, nodular inflammatory infiltration (8).

Tinea corporis is a dermatophytosis of glabrous skin most commonly caused by *T. rubrum* followed by *M. canis* and *T. mentagrophytes*. In cases caused by *T. rubrum*, large erythematous patches with central clearing and an arcuate or polycyclic scaly border are seen. In infections with *M. canis*, tinea corporis is more inflammatory, and annular lesions with raised papulovesicular borders and central clearing are common. *T. mentagrophytes* typically produces a few annular lesions with little or no central clearing. *T. verrucosum* may occasionally cause tinea corporis appearing as grouped follicular pustules referred to as *agminate folliculitis* (8). The term *Majocchi's granuloma* describes a nodular granulomatous perifolliculitis caused by rupture of an infected follicle, typically of the lower extremity. Majocchi's granuloma is often associated with tinea pedis or onychomycosis and therefore is commonly caused by *T. rubrum*.

Tinea cruris, usually caused by *T. rubrum* and occasionally by *T. mentagrophytes* or *Epidermophyton floccosum*, shows sharply demarcated erythematous patches or thin plaques in the groin. The infection may spread to the perineal and/or perianal regions as well as the scrotum.

Tinea of the feet and hands (tinea pedis et manus) is the most common form of dermatophyte infection and is usually caused by *T. rubrum*, *E. floccosum*, or *T. mentagrophytes*. Tinea pedis may present clinically as interdigital maceration, plantar (i.e., "moccasin" scale), or vesiculobullous lesions. *T. rubrum* is anthropophilic and causes relatively noninflammatory scaling on the plantar feet. Infections with *T. mentagrophytes* tend to cause inflammatory, vesicobullous tinea pedis.

Tinea unguium specifically refers to a dermatophyte infection of the nail whereas onychomycosis is a nail infection due to any fungi including dermatophytes, *Candida*, or a nondermatophyte (9). Up to 90% of mycotic toenail infections and 50% of fingernail infections are caused by dermatophytes, but yeasts (especially *Candida albicans*) and nondermatophyte molds are also implicated (10). Criteria for diagnosing nondermatophyte onychomycosis have been offered as (a) the presence of hyphae in the infected subungual debris, (b) the persistent failure to culture recognized dermatophytes, and (c) positive cultures of a nondermatophyte (11).

The four clinical types of onychomycosis include distal and lateral subungual onychomycosis (DLSO), superficial white onychomycosis (SWO), proximal subungual onychomycosis (PSO), and *Candida* infections of the nail. In general, hyperkatosis and onycholysis are common clinical presentations of onychomycosis. DLSO is the most common form found in all patients, including those with HIV, and is caused by dermatophytes, usually *T. rubrum* (12). SWO is caused primarily by *T. mentagrophytes* and is more commonly seen in HIV. PSO is typically caused by *T. rubrum* and is rare in the general population but can be a presenting sign of HIV. PSO in AIDS is often caused by *T. mentagrophytes* (13). *Candida* nail infections present as paronychia, hyperkeratosis, or onycholysis. Nondermatophytes implicated in onychomycosis include *Candida* sp., *Scytalidium* (*Hendersonula*), and *Aspergillus* (most commonly *Aspergillus niger*). Fungi thought to be contaminants in nail cultures in all but the immunosuppressed include *Cladosporium*, *Alternaria*, *Fusarium*, *Acremonium*, and *Scopulariopsis* (14). There is considerable controversy about the clinical significance of nondermatophyte fungi in nail cultures when a dermatophyte is also identified on culture.

Histopathology. In *tinea capitis* and *tinea barbae*, infection of follicles usually starts with colonization of the stratum corneum of the perifollicular epidermis (Fig. 23-1). Hyphae extend down the follicle and invade the hair, penetrating the cuticle first in the subcuticular portion of the cortex, just under the hair surface, and then more deeply in the hair cortex, extending to the upper limit of the zone of keratinization. Rounded and boxlike arthrospores may be found mainly

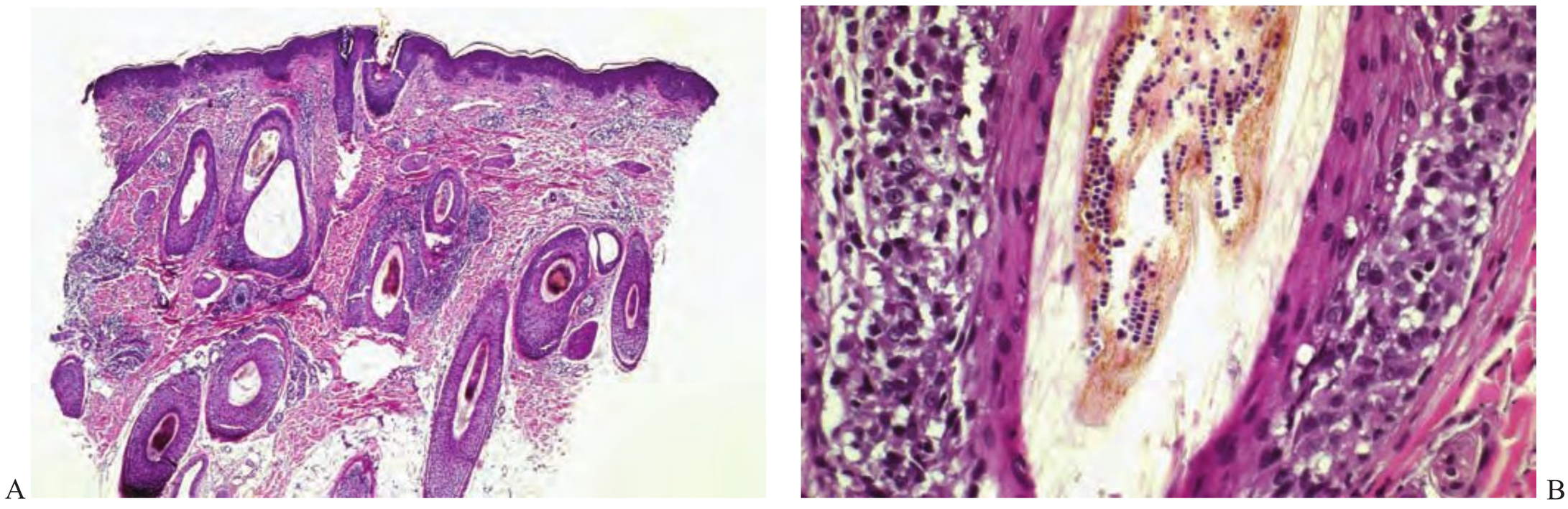


FIGURE 23-1. Tinea capitis. A: H&E stain shows arthrospores and hyphal elements in most follicles. A lymphohistiocytic, perifollicular infiltrate is present. B: H&E stain shows arthrospores in endothrix infection.

within the hair shaft in *endothrix* infections or penetrating the surface of the hair shaft and forming a sheath around it in *ectothrix* infections. *Endothrix* infections are caused by *T. tonsurans* or *Trichophyton violaceum*. Except for *T. schoenleinii*, which causes favus, dermatophytes infecting hair shafts cause *ectothrix* infections. Although hyphae invade the shafts in both types of infections, they may not be evident in a hair plucked from an endothrix infection because the more superficial hyphae rapidly break up into arthrospores and destroy the keratin of the hair shaft. When plucked, the weakened shaft typically breaks at a relatively superficial point so that only the arthrospores are seen. The dermis, which rarely contains fungi, shows a perifollicular mononuclear cell infiltrate of varying intensity. In addition to a chronic inflammatory infiltrate, multinucleated giant cells may be present in the vicinity of disrupted or degenerated hair follicles. In kerion Celsi, there is a pronounced inflammatory tissue reaction to the fungi with follicular pustule formation and interfollicular neutrophilic infiltration as well as a marked chronic inflammatory infiltrate surrounding the hair follicles. In cases with a severe inflammatory reaction, fungi may be difficult to identify either by microscopic examination or by culture but may be demonstrated by using fluorescein-labeled *T. mentagrophytes* antiserum that cross-reacts with antigens of all dermatophyte species.

In *tinea of the glabrous skin*, which includes tinea faciei, tinea corporis, tinea cruris, and tinea of the feet and hands, fungi occur only in the horny layers of the epidermis and do not invade hairs and hair follicles. Two exceptions to this are *T. rubrum* and *T. verrucosum*, both of which may invade hairs and hair follicles, causing a subsequent perifolliculitis.

The number of fungi seen in the horny layer varies greatly but may be so small that they may be challenging to find even when treated with the PAS reaction or stained with GMS. Occasionally, they are present in sufficient numbers that even in sections stained with H&E, they can be recognized as faintly basophilic, refractile structures (Fig. 23-2). Their identification in H&E-stained sections may be aided by lowering the microscope condenser, which enhances the refractility of the

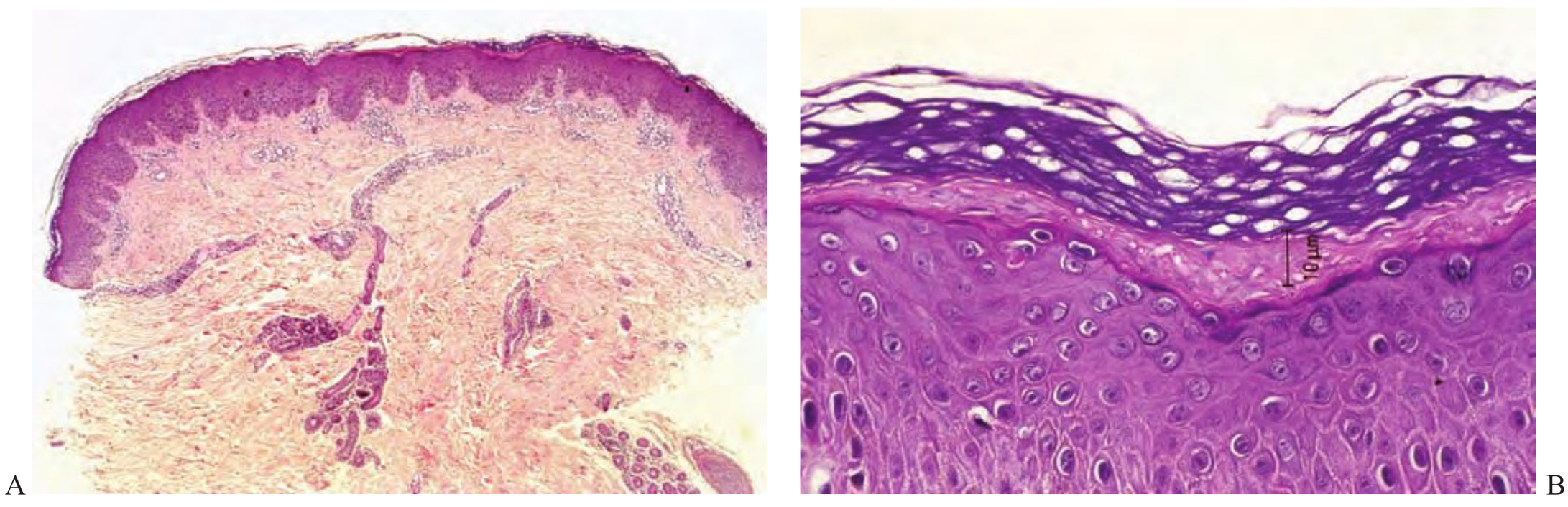


FIGURE 23-2. Tinea corporis. A: H&E stain shows a superficial perivascular, predominantly lymphoid infiltrate with mild psoriasiform epidermal hyperplasia and compact hyperkeratosis. B: Cross-sections of refractile hyphae are visible as clear spaces in parakeratotic stratum corneum (H&E stain).

fungal elements. In infections with *Microsporum* or *Trichophyton*, only hyphae are seen, and in infections with *E. floccosum*, chains of spores are present. If fungi are present in the horny layer, they usually are "sandwiched" between two zones of cornified cells, the upper being orthokeratotic and the lower consisting partially of parakeratotic cells. This "sandwich sign" should prompt the performance of a stain for fungi for verification. The presence of neutrophils in the stratum corneum is another valuable diagnostic clue (15). In the absence of demonstrable fungi, the histologic picture of fungal infections of the glabrous skin is not diagnostic. Depending on the degree of reaction of the skin to the presence of fungi, the histologic features of an acute, subacute, or chronic spongiotic dermatitis can be seen (see Chapter 9).

On staining with the PAS reaction or GMS, nodular perifolliculitis, or Majocchi's granuloma, caused by *T. rubrum* shows numerous hyphae and spores within hairs and hair follicles and in the inflammatory infiltrate of the dermis. Fungal elements may also reach the dermis through a break in the follicular wall. Although the spores present within hairs or hair follicles measure about 2 μm in diameter, those located in the dermis, especially within multinucleated giant cells, may be larger measuring up to 6 μm (16). The dermal process shows an inflammatory infiltrate of lymphoid cells, macrophages, epitheloid cells, and multinucleated giant cells as well as central necrosis and occasionally suppuration.

The agminate folliculitis caused by *T. verrucosum* (*faviforme*) shows hyphae and spores within hairs and hair follicles in PAS-stained sections (10). However, the dermis around the hair follicles contains no fungi. Depending on the severity and stage of the inflammatory reaction, either an acute or a chronic inflammatory infiltrate is predominant around the hair follicles in the dermis. In well-established lesions, the inflammatory infiltrate contains many plasma cells, microabscesses, and small aggregates of foreign body giant cells (8).

In *tinea unguium*, nail plate biopsy is potentially the method of choice for diagnosis. Although microscopic examination of potassium hydroxide mounts or cultures of nail fragments often establish a diagnosis of onychomycosis, false-negative results may occur if the infection is in the nail bed or situated in the lower portion of the nail plate. Nail clippings or nail biopsy taken by punch technique or scalpel under local anesthesia will often reveal the fungi on PAS-D–stained sections (17). By far, *T. rubrum* is the most common causal fungus; occasionally, *T. mentagrophytes* is present.

Three histologic patterns are common in nail plate biopsies of onychomycosis (18). In superficial infections, mycelial elements, best visualized with PAS or GMS, are seen in the outer layer of the nail plate. Routine histologic examination of nail plate with PAS staining is a simple, rapid, and sensitive test for fungal elements (19). The second histologic pattern is seen in clinical onycholysis when PAS stained sections of nail plate reveal slender, uniform mycelial elements invading the undersurface of the nail plate (Fig. 23-3). In this pattern, there may also be an inflammatory infiltrate of lymphocytes and neutrophils as well as serum and keratotic debris on the undersurface of the nail plate. Biopsies of nail bed or nail fold epithelium may reveal psoriasiform hyperplasia, spongiosis, and hyperkeratosis, making the identification of fungal elements critical to the correct diagnosis. The third common histologic pattern is seen in *Candida* infections, where hyphal forms are seen on the undersurface of the nail plate; this will be discussed in a later section (see page 599). Other less typical morphologic patterns of onychomycosis may signal an infection with unusual fungi or partial treatment with antimycotics.

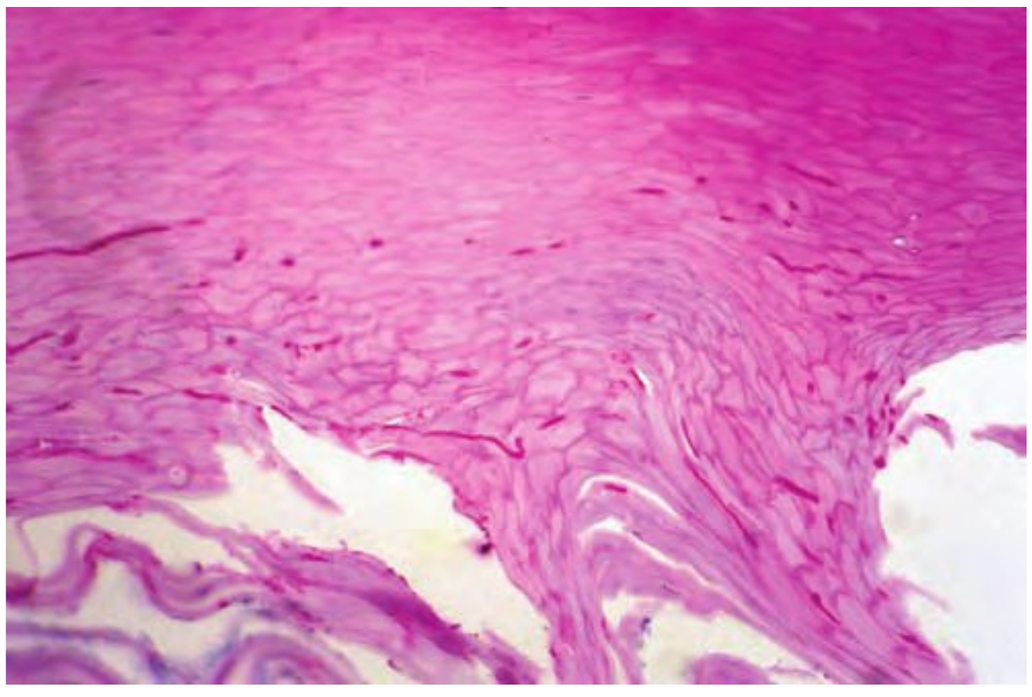


FIGURE 23-3. Tinea unguium. Slender, uniform mycelial elements can be seen within this parakeratotic nail plate (PAS-D stain).

Polymerase chain reaction (PCR) amplification of DNA from nail plate biopsies has been studied for the diagnosis of onychomycosis but is not routinely used (20). PCR is very senstitive and could be used to identify individual species of fungus, but ubiquitous contaminant fungi may cause false-positive results, meaning that fungal cultures or histologic confirmation of true hyphal or yeast forms might still be needed.

Pathogenesis. Debate exists regarding factors that predispose individuals to onychomycosis. Trauma is thought to facilitate the entry of fungus into the nail. Epidemiologic data suggests that the incidence increases with age, but other factors such as humidity, local trauma, and common living/bathing sites have been variably significant predictors (21).

In *favus*, mainly hyphae and only a few spores of *T. schoenleinii* are present in the stratum corneum of the epidermis around and within hairs. The scutula (see page 593) consist of compact keratin as well as parakeratotic cells, exudate, and inflammatory cells intermingled with segmented hyphae and spores that are well preserved at the periphery but appear degenerated and granular in the center of the scutula (22). In active areas, the dermis shows a pronounced inflammatory infiltrate containing multinucleated giant cells and many plasma cells in association with degenerating hair follicles. In old areas, there is fibrosis and an absence of pilosebaceous structures.

DISEASES CAUSED BY MALASSEZIA FURFUR

Malassezia is a genus of lipophilic yeast that causes two dermatoses: pityriasis versicolor and *Malassezia* (*Pityrosporum*) folliculitis (23). The frequently used term *tinea versicolor* is not accurate, because *Malassezia* are not dermatophytes. In pityriasis versicolor, multiple round to oval pink to light brown patches with fine white scale are seen primarily on the trunk and upper extremities. Gentle scraping of the patches will induce the scale that can be examined for spores and short hyphae. *Malassezia (Pityrosporum)* folliculitis is a pruritic eruption of 2- to 4-mm acneiform follicular papules and pustules on the trunk and arms of otherwise healthy hosts (24). Potassium hydroxide (KOH) examination of the lesions will reveal only yeast forms.

In addition to these two diseases, *Malassezia* has been found in lesions of seborrheic dermatitis, atopic dermatitis, neonatal cephalic pustulosis, and confluent and reticulated papillomatosis of Gougerot and Carteaud (25,26). Seborrheic dermatitis, for example, has been reported to respond to antifungal therapy and has been associated with heavy colonization by *M. furfur.* However, these observations and their interpretation are controversial, and it has not been definitively established that *M. furfur* contributes to the pathogenesis of seborrheic dermatitis (27,28).

Histopathology. In contrast to other fungal infections of the glabrous skin, the horny layer in lesions of *pityriasis* (*tinea*) *versicolor* contains abundant fungi, which can often be visualized in sections stained with H&E as faintly basophilic structures. *Malassezia* (*Pityrosporum*) is present as a combination of both hyphae and spores (Fig. 23-4), the light microscopic appearance of which is often referred to as *spaghetti and meatballs.* The inflammatory response in pityriasis versicolor is usually minimal, although there may occasionally be slight hyperkeratosis (29), slight spongiosis, or a minimal superficial perivascular lymphocytic infiltrate.

Histogenesis. The names *M. furfur, Pityrosporum orbiculare,* and *Pityrosporum ovale* are often used interchangeably probably because these are identical in culture (30). *In vivo, M. furfur* becomes dimorphous by forming numerous true septate hyphae in addition to spores. The organism then becomes pathogenic (23).

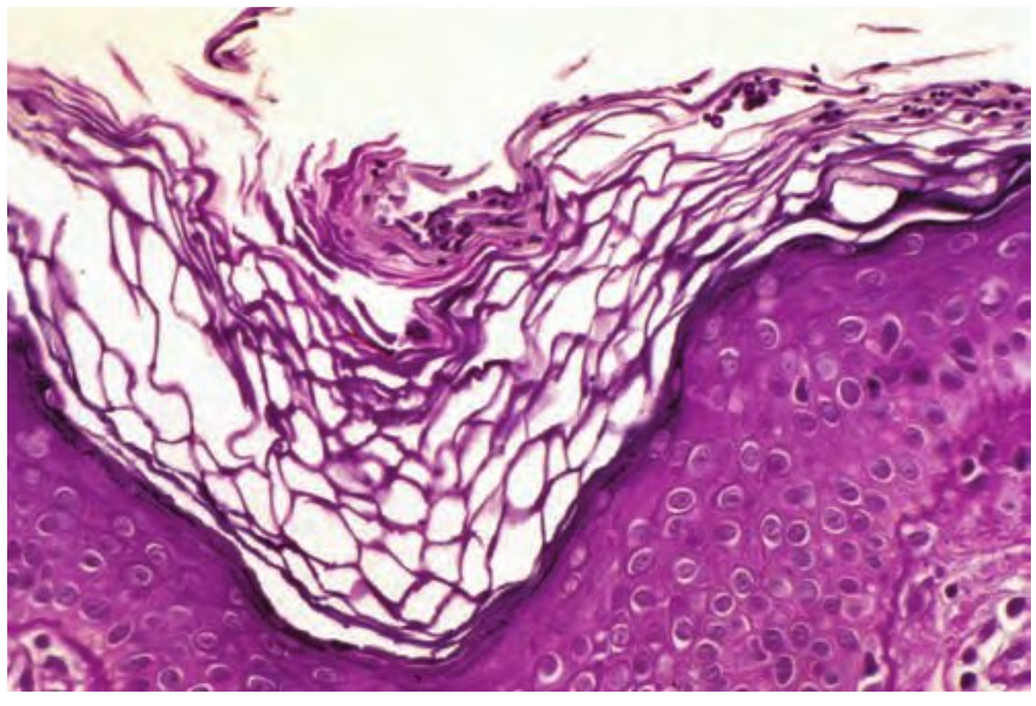
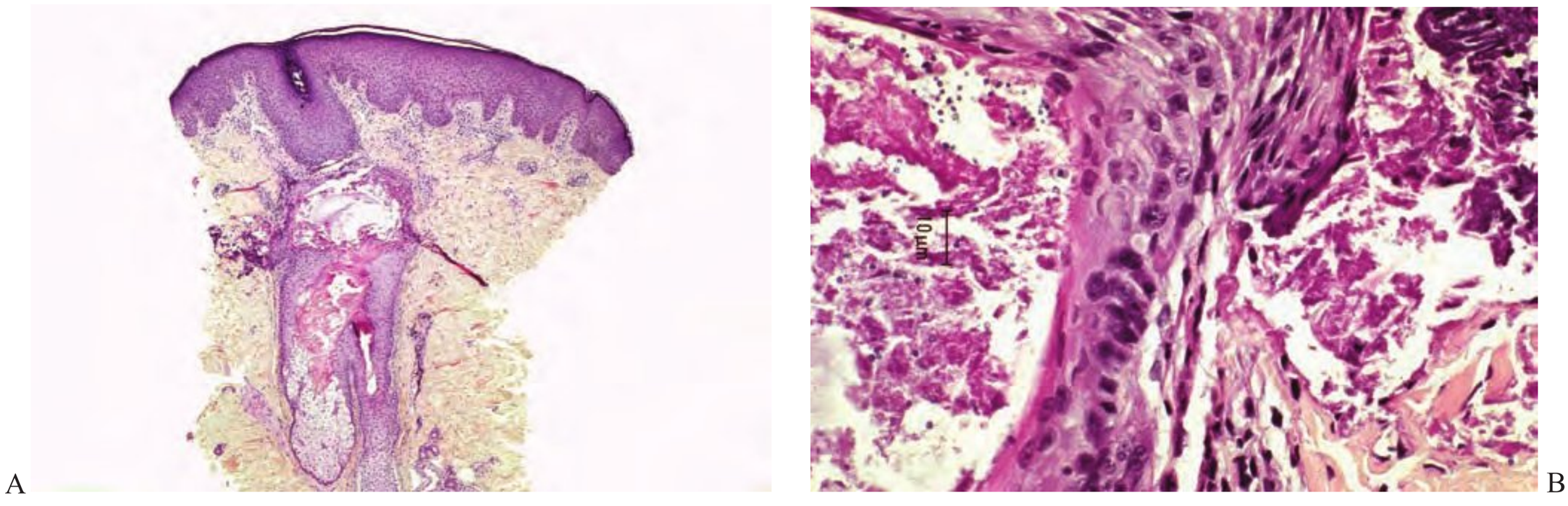


FIGURE 23-4. Pityriasis (tinea) versicolor. A slightly hyperkeratotic stratum corneum contains numerous hyphae and spores (H&E stain).

Several theories exist to explain the characteristic pigmentary alterations in pityriasis versicolor, although none have been convincingly proven. Hypopigmentation may be caused by filtering of ultraviolet light by the organism, a block in melanosome transfer to keratinocytes, or the inhibition of melanin synthesis by azelaic acid or lipoxygenase produced by *Malassezia* (31). Hyperpigmentation is thought by some to be secondary to inflammation, hyperkeratosis, or greater numbers of organisms in the skin.

Malassezia (Pityrosporum) Folliculitis

The involved pilosebaceous follicles show hyperkeratosis with dilatation resulting from plugging of the infundibulum with keratinous material. Inflammatory cells are present both within and around the follicular infundibulum. In some instances, the follicular epithelium is disrupted with development of a peri-infundibular abscess (32) (Fig. 23-5). PAS-stained sections show PAS-positive, diastase-resistant, spheric



A B

FIGURE 23-5. Malassezia (Pityrosporum) folliculitis. A: A plugged and ruptured follicle contains numerous round yeast forms (H&E stain). B: H&E stain shows round and budding yeast forms in follicle and surrounding dermis.

to oval, singly budding yeast organisms that are 2 to 4 μm in diameter. They are located predominantly within the infundibulum and at the dilated orifice of the follicular lumen but are occasionally observed also in the perifollicular dermis.

Histogenesis. It has been assumed that *Malassezia* organisms cause hyperkeratosis in the follicular ostium, thereby preventing the normal flow of sebum and causing the follicular, acne-like lesions.

CANDIDIASIS

C. albicans is a dimorphous fungus growing in both yeast and filamentous forms on the skin. It exists in a commensal relationship with man. The spectrum of infection may be divided into four groups: acute mucocutaneous candidiasis, chronic mucocutaneous candidiasis (CMC), disseminated candidiasis, and *Candida* onychomycosis.

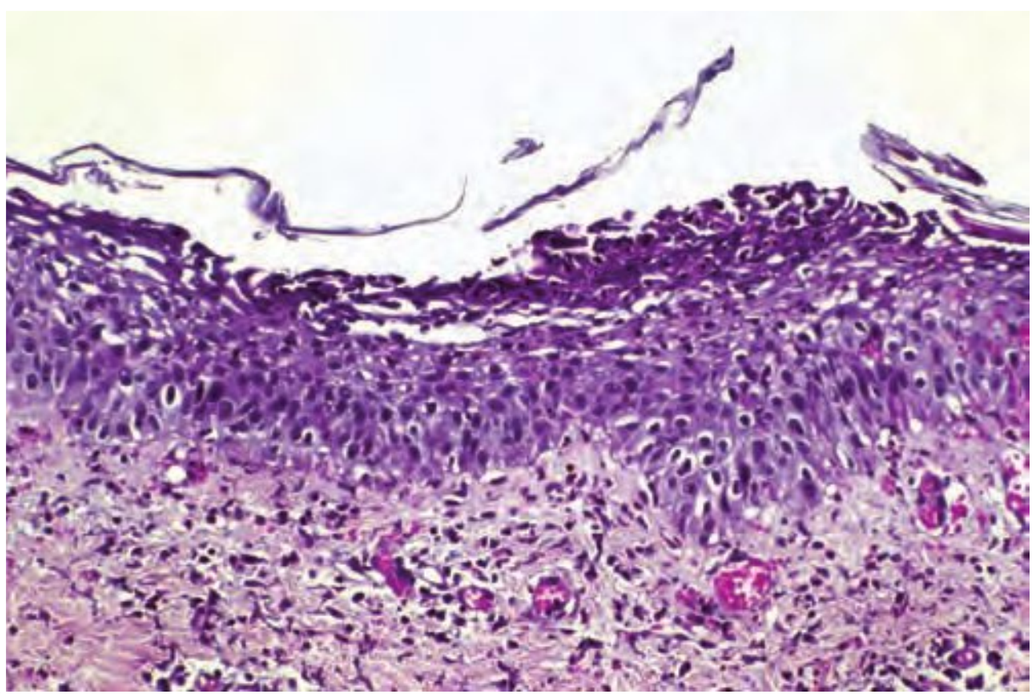
Acute Mucocutaneous Candidiasis

Acute mucocutaneous candidiasis is the benign, self-limited form of candidiasis and is caused by environmental changes that are local, as in hot, humid conditions, or that are systemic, as in antibiotic or corticosteroid therapy. Clinical variants of acute mucocutaneous candidiasis include erosio interdigitalis blastomycetica, *Candida* vaginitis, paronychia, *Candida* intertrigo, and thrush. Intertriginous lesions show erythematous, often-eroded patches and thin plaques often with peripheral erythematous macules and papules, the so-called satellite lesions. *Candida* infection of the mucous membranes is noted as erythematous patches or white plaques that reveal a glistening, erythematous undersurface when scraped.

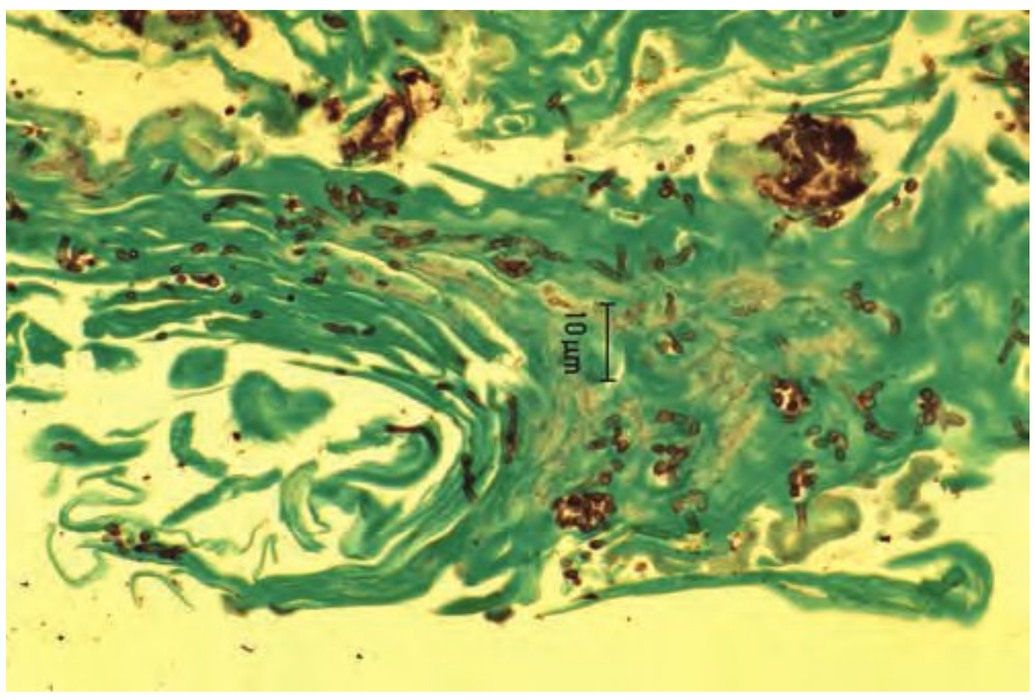
Candida infection is associated with specific host and environmental factors. *Candida* is the most common pathogen in patients who have had a solid organ transplant, and candidiasis tends to occur within the first 6 months after transplant. Age (infancy, old age), antibiotic use, malignancy, chemotherapy, endocrinopathies (diabetes, Cushing's syndrome), and disorders of immunity including HIV/AIDS are risk factors for *Candida* infection (33,34). More effective treatment of AIDS has led to a decline in the incidence of clinically apparent candidiasis in these patients.

Congenital cutaneous candidiasis is a result of ascending intrauterine infection from vaginal candidiasis. There are widely scattered macules, papulovesicles, and pustules at birth or in a few days thereafter. *Neonatal candidiasis*, on the other hand, manifests as oral candidiasis or diaper dermatitis after the first week of life and is acquired during passage through the birth canal (35).

Histopathology. Cutaneous and mucous membrane *Candida* infection show similar features. If the primary lesion is a vesicle or pustule, it is usually subcorneal as in impetigo (Fig. 23-6A, B).



A



B



C

FIGURE 23-6. Candidiasis. A: H&E stain shows a subcorneal pustule with an underlying mixed dermal infiltrate. B: GMS stain shows pseudohyphae and ovoid yeast in hyperkeratotic stratum corneum. C: Erythematous to violaceous papulonodules of disseminated candidiasis in a patient with leukemia.

TABLE 23-3 Histological Appearance of Tissue and Fungi in Superficial Dermatomycoses

Disease	Histologic appearance	Fungal size and morphology
Dermatophytosis	Minimal to spongiotic-psoriasiform, pustular, or folliculitis pattern with mixed dermal infiltrate	Refractile, 1–2 μm septate hyaline hyphae in stratum corneum, occasional chains of spores.
Pityriasis (tinea) versicolor	Slight hyperkeratosis	2–8 μm round spores, 2–3 μm thick, short sometimes curved hyphae
Mallassezia (Pityrosporum) folliculitis	Plugged, sometimes ruptured follicle with follicular and perifollicular mixed infilterate	2–8 μm round spores within follical, rarely in perfollicular tissue. Usually no hyphae.
Candidiasis	Spongiotic or subcorneal pustular dermatitis with mixed dermal infiltrate. Erosions may be present.	3–6 μm round to oval, sometimes budding spores, 2–4 μm thick pseudohyphae

In some instances, the pustules have a spongiform appearance, similar to the spongiform pustules of Kogoj seen in pustular psoriasis (see Chapter 7).

The fungal organisms are present, usually in small amounts only, in the stratum corneum. They are predominantly pseudohyphae and ovoid spores, with some of the latter in the budding stage. These septate pseudohyphae show branching at a 90-degree angle and measure from 2 to 4 μm in diameter. The pseudohyphae tend to be constricted at their septa and to have septa at their branch points (36). The ovoid spores vary from 3 to 6 μm in size (Table 23-3).

Pathogenesis. By electron microscopy, the majority of the mycelia and spores are situated inside the cells of the stratum corneum, many of which are parakeratotic (37).

Chronic Mucocutaneous Candidiasis

CMC is a heterogeneous group of conditions in which patients have chronic and recurrent candidal infections of the skin, nails, and mucous membranes. CMC may be inherited as an autosomal dominant or recessive condition. It may also be due to endocrinopathies or immunodeficiency. By definition, systemic involvment does not occur in CMC (38). The individual lesions of CMC are similar clinically and histologically to those seen in acute mucocutaneous candidiasis and must be distinguished by their clinical course (38). The exception is seen in CMC beginning in childhood when a rare clinical variant called *Candida granuloma* may develop. Candida granuloma presents clinically as numerous hyperkeratotic, crusted plaques on the face and scalp but occasionally elsewhere (39).

Currently, the most common type of CMC is probably seen in patients with AIDS who often have recurrent candidal infections of the mouth and perianal area. Oral candidiasis may occur as an early sign of immunosuppression, before other symptoms have appeared (40), and if persistent may be an indication of esophageal candidiasis (41). In addition, *Candida* organisms are frequently observed on the surface of lesions of oral hairy leukoplakia, which is a viral leukoplakia caused by Epstein-Barr virus, perhaps in combination with human papillomavirus (see Chapter 25).

Histopathology. The histologic findings are identical with those of acute mucocutaneous candidiasis, except in cases of candidal granuloma. *Candidal granuloma* shows pronounced epidermal papillomatosis and hyperkeratosis and a dense infiltrate in the dermis composed of lymphoid cells, neutrophils, plasma cells, and multinucleated giant cells. The infiltrate may extend into the subcutis. *C. albicans* usually is present only in the stratum corneum (39). In some instances, however, fungal elements are found also within hairs, viable epidermis, and dermis.

Disseminated Candidiasis

Candida is the fourth leading cause of hospital-acquired bloodstream infection in the United States, but cutaneous involvement is only seen in 13% of cases (42). It primarily affects those with impaired host-defense mechanisms, particularly those with hematologic malignancies. *C. albicans* accounts for just over half of the cases of *Candida* fungemia, and *Candida glabrata* ranks number two, with incidence of the latter increasing directly with age (42,43). Cutaneous lesions of disseminated candidiasis are erythematous or violaceous papulonodules with central clearing that measure 0.5 to 1.0 cm in diameter (Fig. 23-6C). They are distributed singly or, more commonly, grouped on the trunk and proximal extremities. The triad of fever, rash, and diffuse muscle tenderness in an immunocomprised host is presumptive for disseminated candidiasis. However, the clinical diagnosis may be delayed, as patients often present with nonspecific symptoms and current methods for diagnosing candidemia rely on blood cultures that require several days. In addition, the speciation of *Candida* by culture is problematic given that all yeast cultures that form germ tubes and chlamydospores are by generalization designated *C. albicans* in many labs (44). Thus, a skin biopsy may be critical to the early diagnosis of disseminated candidiasis. Because the diffuse muscle tenderness is caused by infiltration of muscle tissue by yeast organisms, biopsy of a tender muscle may also aid in establishing the diagnosis of disseminated candidiasis (45).

Histopathology. Histologic examination reveals one or several aggregates of hyphae and spores focally within the dermis, often at sites of vascular damage and generally visible only in sections stained with the PAS reaction or GMS. Some of the spores,

which are 3 to 6 μm in diameter, show budding. The aggregates of hyphae and spores may lie in an area of leukocytoclastic vasculitis (46), within a microabscess (44), or in an area of only mild inflammation. The aggregates of *Candida* often are small, and step sections through the biopsy specimen may be necessary to find them. The epidermis is usually unaffected.

Candida Onychomycosis

Candida onychomycosis is a form of nail infection characterized by separation of the nail plate from the nail bed. Paronychia and loss of the proximal nail fold are not uncommon in *Candida* infections of the nail unit.

Histopathology. *Candida* commonly causes onycholysis but distinguishes itself histologically from the dermatophytes by its lack of nail plate invasion (18). Yeast forms may be seen along the undersurface of the nail plate. *Candida* may mimic the psoriasiform changes and inflammatory response of onychomycosis caused by dermatophytes. *Candida* sp. occur as ovoid yeasts that measure 3 to 6 μm in diameter and as pseudohyphae that measure 2 to 4 μm in diameter. These pseudohyphae may appear thick and bulbous, and have an irregular caliber compared with the smooth, thin, and regular hyphae of dermatophytes.

ASPERGILLOSIS

Aspergillus sp. are ubiquitous in the environment. Humans are constantly exposed to and frequently colonized by these organisms, although they rarely cause disease. Severe, invasive aspergillosis typically involves the lungs and is usually seen only in immunocompromised hosts, particularly those with neutropenia, hematologic malignancy, or a history of chronic corticosteroid or antibiotic therapy (47). *Aspergillus fumigatus* is the most common cause of both colonization and invasive aspergillosis, followed in frequency by *Aspergillus flavus* and *A. niger* (48). Cutaneous aspergillosis may occur as a primary infection or may be secondary to disseminated aspergillosis (Table 23-4). The lesions of primary cutaneous aspergillosis are usually found at an intravenous infusion site: either at the actual access site (49) or where the unit has been secured with a colonized board or tape (50). There may be one or more macules, papules, plaques, or hemorrhagic bullae that may rapidly progress into necrotic ulcers with a heavy black surface eschar (Fig. 23-7A). In immunocompromised patients, dissemination may follow and is often fatal if untreated with amphotericin B, itraconazole, or newer antifungals such as caspofungin (47).

Primary cutaneous infection has been seen in patients with AIDS, but dissemination is not typical in these patients unless they have one or more of the previously mentioned risk factors mentioned in the previous paragraph (51). Umbilicated papules clinically resembling lesions of molluscum contagiosium, and representing "dermatophyte-like" involvement of follicles, have been described in AIDS-related cases (50). In addition, *Aspergillus* may colonize burn or surgical wounds and subsequently invade viable tissue; in these cases, the prognosis is generally good.

Secondary cutaneous aspergillosis, usually associated with invasive lung disease, shows multiple scattered lesions as a result of embolic hematogenous spread and has a poor prognosis (47,52).

Histopathology. Unlike the case with most deep cutaneous fungal infections, pseudoepitheliomatous epidermal hyperplasia is not characteristic of cutaneous aspergillosis. In the more serious primary forms and in the secondary disseminated form, numerous *Aspergillus* hyphae are seen in the dermis (Fig. 23-7B, C). Hyphae may be seen in H&E-stained sections, but PAS or silver methenamine staining may be required. The hyphae, which measure 2 to 4 μm in diameter (47), are often arranged in a radiate fashion, are septate, and show branching at an acute angle. Spores are absent. Hyphae may be seen invading blood vessels (47) and may be seen around areas of ischemic necrosis with very little inflammation in some instances. In other cases, there may be an acute inflammatory reaction with polymorphonuclear leukocytes in addition to lymphocytes and histiocytes.

In patients with primary cutaneous or subcutaneous aspergillosis who are otherwise in good health, the number of hyphae present is relatively small, and there may be a well-developed granulomatous reaction.

ZYGOMYCOSIS (MUCORMYCOSIS, PHYCOMYCOSIS)

Zygomycosis describes infections by ubiquitous molds of two orders: Mucorales and Entomophthorales. The term *mucormycoses* describes infection with *Rhizopus* or *Mucor*, the two medically significant genera of the order Mucorales (53). Infections with these organisms are aggressive and often occur in ketotic diabetics, but infections may also be seen in other settings such as burns, iatrogenic immunosuppression, chronic renal failure, hematopoietic malignancy, and AIDS (54). Entomophthoraceae may cause chronic cutaneous and subcutaneous infections in otherwise healthy hosts.

Cutaneous zygomycosis occurs by implantation of fungi or by hematogenous dissemination. Three main forms exist: rhinocerebral, primary cutaneous, and chronic subcutaneous zygomycosis.

Rhinocerebral zygomycosis is a fulminant infection of the paranasal sinuses that quickly spreads to contiguous structures such as the skin, nose, orbit, and brain (53). Clinical findings include nasal discharge, swelling, mucocutaneous ulceration, and eschar formation.

Primary cutaneous zygomycosis may occur following burns or major trauma or following minor trauma in immunosuppressed patients or those with diabetes (53). It has also been reported after the use of infected tape (55,56). Individual lesions occur early as pustules or blisters that soon ulcerate and form eschars. Depending on the host status, the ulcers either heal or lead to fatal systemic spread. These molds may cause acute, rapidly developing, often lethal infections of immunocompromised

TABLE 23-4 Histologic Appearance of Tissue and Fungi in Deep and Secondary Dermatomycoses

Disease	Histologic appearance	Fungal size and morphology
Aspergillosis	Primary infection: granulomatous infiltrate. Immunocompromised host (primary and secondary infection): angioinvasion, ischemic necrosis, and hemorrhage.	2–4 μm septate hyphae with dichotomous branching at 45-degree angle.
Zygomycosis (mucormycosis, phycomycosis)	Angioinvasion with thrombosis and infarction, necrosis, and variable, mild, neutrophilic infiltrate.	7–30 μm hyphae with branching at irregular angles and intervals. Variably thin, often collapsed or twisted walls.
Subcutaneous phaeohyphomycosis (phaeohyphomycotic cyst)	Deep, coalescing, suppurative granulomatous foci surrounded by fibrous capsule.	Loosely arranged, septate, occasionally branching pigmented hyphae varying from 2 to 25 μm in diameter.
Alternariosis	Pseudocarcinomatous epithelial hyperplasia with intraepidermal microabscesses and suppurative granulomatous dermal infiltrate.	5–7 μm septate hyphae with variable branching and brown pigmentation. 3–10 μm round to oval spores, often with double contours.
North American blastomycosis	Pseudocarcinomatous epithelial hyperplasia with intraepidermal microabscesses. Suppurative granulomatous dermal infiltrate with giant cells.	8–15 μm thick-walled spores with single broad-based buds.
Paracoccidioidomycosis	Like North American blastomycosis.	6–20 μm spores with narrow-necked, single or multiple buds. "Mariner's wheels" up to 60 μm in diameter.
Lobomycosis	Atrophic epidermis with dermal macrophage and giant cell infiltrate. Unstained organisms give sievelike appearance to dermis.	9–10 μm "lemon-shaped" spores with single budding, often in chains.
Chromoblastomycosis	Like North American blastomycosis.	6–12 μm thick-walled, dark brown spores, often in clusters. Some cells possess cross walls.
Coccidioidomycosis	Primary inoculation: mixed dermal infiltrate with granulocytes, lymphocytes, and occasional histiocytic giant cells. Systemic: like North American blastomycosis, but granulomas may be more tuberculoid in nature.	10–80 μm thick-walled spores with granular cytoplasm. The larger spores contain endospores.
Cryptococcosis	"Gelatinous reaction" with many spores; "granulomatous reaction" with fewer spores.	4–12 μm spore with wide capsule in "gelatinous reaction;" 2–4 μm spore in "granulomatous reaction."
Histoplasmosis		
var. capsulatum	Suppurative granulomatous infiltrate in ulcerative skin lesions, neutrophils and eosinophils in oral lesions. Histiocytes contain variable numbers of organisms.	2–4 μm round, narrow-necked budding spores with clear halo (pseudocapsule) in the cytoplasm of large histiocytes.
var. duboisii (African)	Granulomatous dermal infiltrate with focal suppuration.	8–5 μm ovoid spores in macrophages and free in tissue.
Sporotrichosis	Cutaneous lesions: epidermal hyperplasia with intraepidermal abscesses, suppurative granulomatous dermal infiltrate, occasional asteroid bodies. Subcutaneous nodules: central zone of neutrophils surrounded by zones of epithelioid macrophages and round cells.	4–6 μm round to ovel spores.
Eumycetoma	Abscess in granulation tissue, fibrosis, and sinus tracts.	0.5–2.0 mm sulfur granules composed of 4–5 μm thick septate hyphae.
Rhinosporidiosis	Hyperplastic epithelium with papillomatosis, deep invagination with pseudocysts, and "Swiss cheese" corium.	7–12 μm spores, sporangia up to 300 μm.

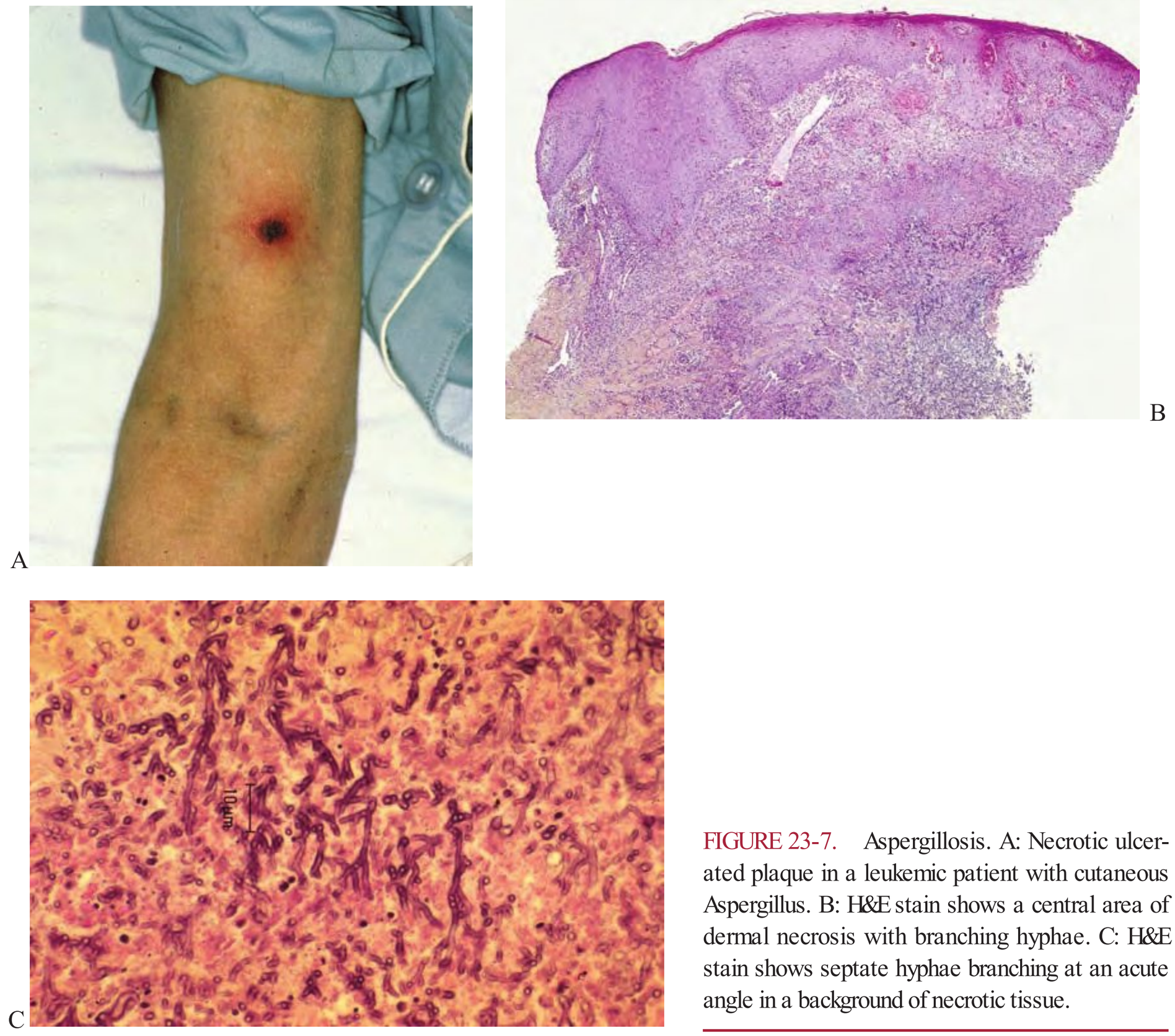


FIGURE 23-7. Aspergillosis. A: Necrotic ulcerated plaque in a leukemic patient with cutaneous Aspergillus. B: H&E stain shows a central area of dermal necrosis with branching hyphae. C: H&E stain shows septate hyphae branching at an acute angle in a background of necrotic tissue.

patients. Cutaneous lesions may also be seen as a result of embolization and infarction in patients with systemic zygomycosis. The lesions may begin as erythematous macules that blister and ulcerate or may occur as an indurated nodule (57).

Chronic subcutaneous zygomycosis occurs in tropical and subtropical areas in otherwise healthy people. Lesions most commonly occur on the face and are slowly enlarging, painless, firm swellings in the dermis (53).

Histopathology. The histologic changes in zygomycosis are primarily dermal. The hallmark of zygomycosis is vascular invasion by very large, long, nonseptate hyphae with thrombosis and infarction (53,57) (Fig. 23-8A). Hyphae branch at 90-degree angles and may also be found in the surrounding tissue (58). The hyphae are thin walled, so they may be twisted or collapsed and often appear ring shaped or oval in cross- or tangential sections (53) (Fig. 23-8B). They are often easily located even in routinely stained sections because of their very large size, up to 30 μm in diameter, although they may be visualized even better in PAS- or GMS-stained sections. Spores are rarely seen.

SUBCUTANEOUS PHAEOHYPHOMYCOSIS

Phaeohyphomycosis is a subcutaneous or systemic infection caused by dematiaceous, mycelia-forming fungi (59). This is a histopathologic definition of a disease process that can be caused by many different organisms and can have multiple different clinical presentations. *Bipolaris*, *Phialophora*, *Alternaria*, and *Exophiala* are fungi responsible for phaeohyphomycosis (60,61). Phaeohyphomycosis has been labeled a "chromic mycosis" in the past but is distinct from chromomycosis, which is characterized by pigmented spores without hyphal forms. Although eumycetoma caused by dematiaceous fungi

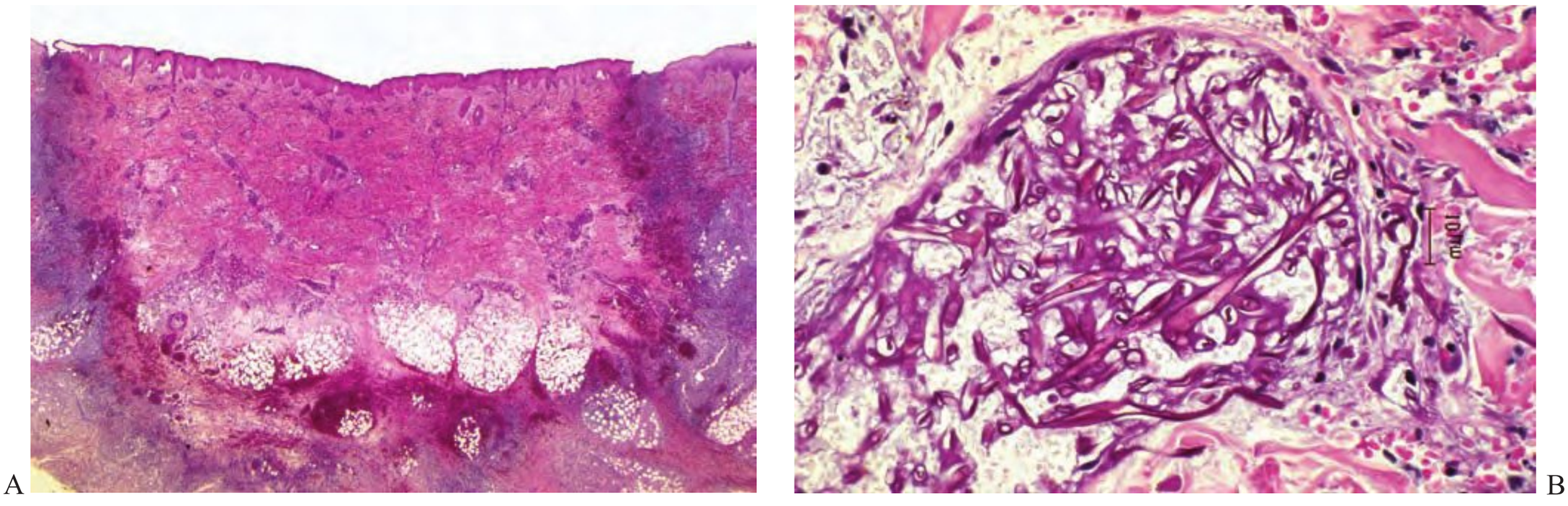


FIGURE 23-8. Zygomycosis (mucormycosis). A: H&E stain shows infarction of dermis, epidermis, and subcutaneous fat with lymphohistiocytic and neutrophilic infiltrate as well as angioinvasion by broad nonseptate hyphae. B: H&E stain shows irregularly branching, twisted, and collapsed hyphae.

could be included under this definition, that has not generally been the case, probably since eumycetoma is such a distinctive clinical entity (62).

Phaeohyphomycetes often infect people who are not overtly immunosuppressed. However, immunosuppression does increase the risk of infection with less commonly pathogenic phaeohyphomycetes such as *Alternaria infectoria* and increases the risk for disseminated disease (63,64).

Subcutaneous phaeohyphomycosis typically presents as a solitary abscess or nodule on the extremity of an adult male. A history of trauma or a splinter can sometimes be elicited. The other major clinical forms of phaeohyphomycosis are infection of the paranasal sinuses and central nervous system.

Histopathology. Lesions of subcutaneous phaeohyphomycosis start as small, often stellate foci of suppurative granulomatous inflammation. The area of inflammation gradually enlarges and usually forms a single large cavity with a surrounding fibrous capsule, the so-called phaeohyphomycotic cyst (65) (Fig. 23-9A). The central space is filled with pus formed of polymorphonuclear leukocytes and fibrin. There is a surrounding granulomatous reaction composed of histiocytes, including epithelioid cells and multinucleated giant cells; lymphocytes; and plasma cells. Diligent search may identify an associated splinter in the tissue or liquid pus. The organisms are found within the cavity and at its edge, often within histiocytes (Fig. 23-9B). The hyphae often have irregularly placed branches and show constrictions around their septae that may

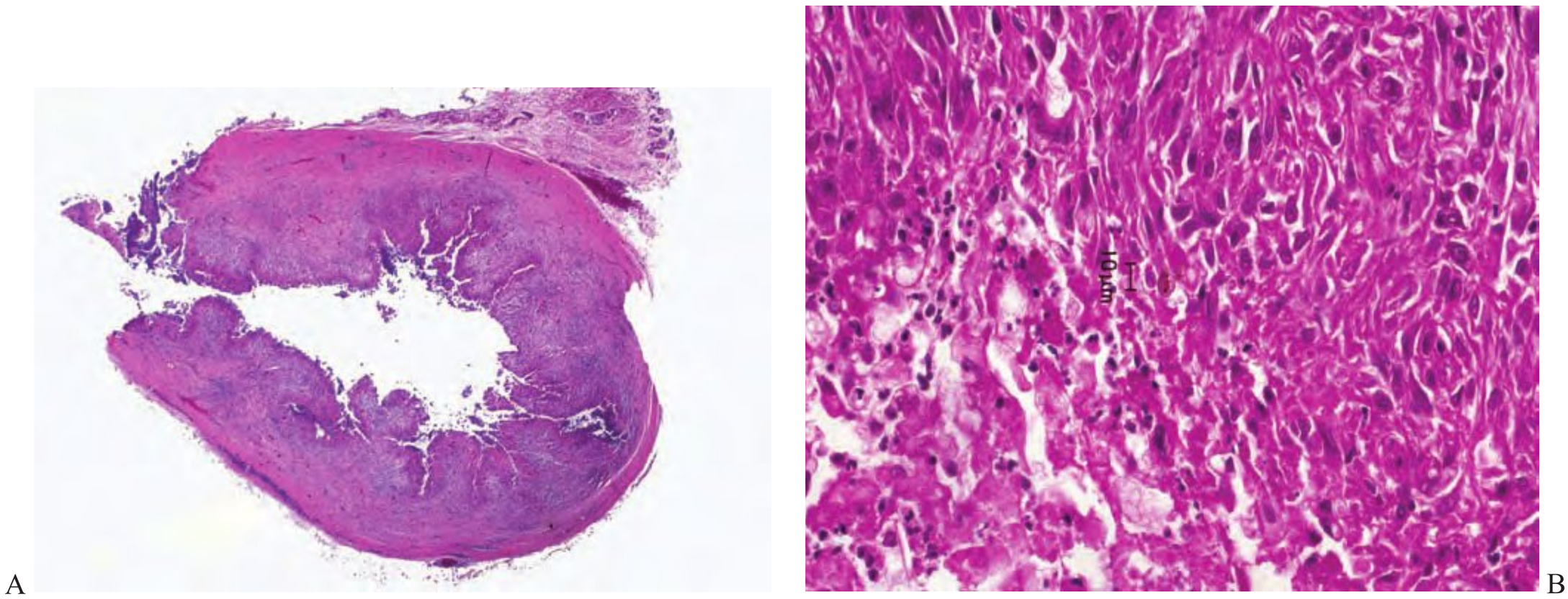


FIGURE 23-9. Phaeohyphomycosis. A: H&E stain shows a pseudocyst with a large central cavity and a fibrous capsule. B: H&E stain shows pigmented hyphal forms at edge of cavity.

cause them to resemble pseudohyphae or yeast forms, but true yeast forms are rare. Mycelia, if present, are more loosely arranged than the compact masses of hyphae seen in eumycetoma. Pigment is not always obvious and may be highlighted using the Fontana-Masson stain (60).

Pathogenesis. The subcutaneous cystic type of phaeohyphomycosis is usually caused by *Phialophora gougerotii* (formerly called *Sporotrichum gougerotii*) *(*66). Less commonly, it is due to *Exophiala (Fonsecaea, Wangiella) dermatitidis* (67). Melanin is directly involved in the virulence of phaeohyphomycetes. Melanin is able to scavenge free radicals used by phagocytic cells to kill fungi, and melanin may also bind the hydrolytic enzymes used by phagocytic cells to lyse fungal cell membranes. Strains of these fungi that lack pigment demonstrate reduced virulence in mouse models (68,69). Nondematiaceous strains have decreased resistance to fungicidal effects of the phagolysosome (70). These factors may also help to explain the virulence of phaeohyphomycetes in immunocompetent patients.

Differential Diagnosis. The organisms of phaeohyphomycosis can be distinguished from *Aspergillus* sp. because the latter have hyphae with relatively uniform diameter and regular dichotomous branching (71). Furthermore, disseminated aspergillosis is associated with vascular invasion, ischemic necrosis, and relatively less inflammation.

CUTANEOUS ALTERNARIOSIS

Because the hyphae of *Alternaria* sp. are pigmented, alternariosis may also be considered a phaeohyphomycosis. *Alternaria* sp. commonly colonize human skin (72) but are generally nonpathogenic for humans. Cutaneous alternariosis may occur following trauma (73); by colonization of a preexisting lesion (74); or rarely by hematologic spread, most commonly from pulmonary infection caused by inhalation of the organism. Patients with cutaneous alternariosis are often debilitated, immunocompromised, or receiving immunosuppressive therapy (71,75). Despite the increasing prevalence of HIV infection, however, the disease is rare in patients with AIDS (76). Morphologically, the lesions of cutaneous alternariosis are so variable as to be nonspecific and include crusted ulcers, verrucous or granulomatous and multilocular lesions (74), and subcutaneous nodules (73).

Histopathology. Although fungi are found mainly in the deeper layers of the dermis and in the subcutaneous region in the hematogenous and the traumatogenic forms, they are localized predominantly in the epidermis in cases in which *Alternaria* colonizes preexisting lesions (74). The dermis shows a suppurative granulomatous reaction associated with variable pseudoepitheliomatous epidermal hyperplasia and ulceration. Organisms may be present both as broad, branching, brown septate hyphae, 5 to 7 μm thick (62) (Fig. 23-10), and as large, round to oval, often doubly contoured spores measuring 3 to 10 μm in diameter (74). The spores may be seen both lying free in the tissue (72) and within macrophages and giant cells (77). There may be intraepidermal microabscesses with hyphae in the stratum corneum and stratum spinosum (72). The hyphae and spores stain deeply with PAS or silver methenamine.

NORTH AMERICAN BLASTOMYCOSIS

North American blastomycosis, caused by *Blastomyces dermatitidis*, occurs in three forms: primary cutaneous inoculation blastomycosis, pulmonary blastomycosis, and systemic blastomycosis (78).

Primary cutaneous inoculation blastomycosis is very rare and occurs almost exclusively as a laboratory or autopsy room infection. It starts at the site of injury on a hand or wrist as an indurated, ulcerated, chancriform solitary lesion. Lymphangitis

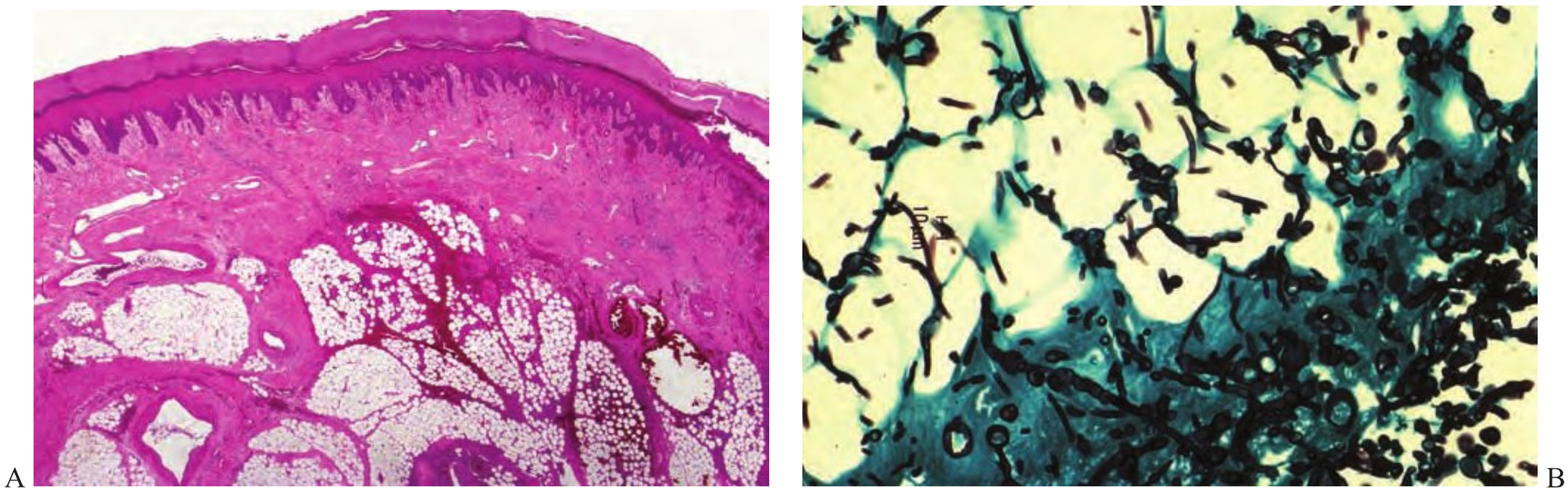


FIGURE 23-10. Alternariosis. A: H&E stain shows a mixed inflammatory infiltrate in the deep dermis and subcutaneous fat. B: GMS stain shows broad, branching hyphae.

and lymphadenitis may develop in the affected arm. Small nodules may be present along the involved lymph vessel. Spontaneous healing takes place within a few weeks or months (79).

Pulmonary blastomycosis, the usual route of acquisition of the infection, may be asymptomatic or may produce mild to moderately severe, acute pulmonary signs, such as fever, chest pain, cough, and hemoptysis. The pulmonary lesions either resolve or progress to chronic pulmonary blastomycosis with cavity formation. In rare instances, acute pulmonary blastomycosis is accompanied by erythema nodosum (80). Occasionally, however, cutaneous lesions are the only clinical manifestation after pulmonary infection. This phenomenon of a benign systemic disease presenting with cutaneous lesions may also be seen rarely after infection with coccidioidomycosis, cryptococcosis, histoplasmosis, and sporotrichosis. In the benign systemic form of blastomycosis with only cutaneous lesions, the lesions usually are on the face and are of the verrucous type (81).

In systemic blastomycosis, the lungs are the primary site of infection. Granulomatous and suppurative lesions may occur in many different organs, but aside from the lungs, they are most commonly found in the skin, followed by the bones, male genital system, oral and nasal mucosa, and central nervous system. Untreated systemic blastomycosis has a mortality rate in excess of 80% (82). Antimycotic therapy can reduce mortality to 10% in otherwise uncomplicated cases, but systemic blastomycosis has a particularly aggressive course in immunosuppressed patients and carries at least a 30% mortality rate even with treatment (83,84).

Cutaneous lesions are very common in systemic blastomycosis, occurring in about 70% of patients. They may be solitary or numerous. They occur in two types, either as verrucous lesions, the more common type, or ulcerative lesions. Verrucous lesions show central healing with scarring and a slowly advancing, raised, verrucous border that is beset by a large number of pustules or small, crusted abscesses. Ulcerative lesions begin as pustules and rapidly develop into ulcers with a granulating base. In addition, subcutaneous abscesses may occur; they usually develop as an extension of bone lesions. Lesions of the oral or nasal mucosa may present either as ulcers or heaped-up masses of friable tissue. In some instances, they are contiguous with cutaneous lesions (82). An unusual early cutaneous manifestation of systemic blastomycosis is a pustular eruption that may be widespread (85) or largely acral in distribution (86) (Fig. 23-11A).

Histopathology. Early lesions of blastomycosis demonstrate a dermal inflammatory infiltrate of polymorphonuclear leukocytes with numerous organisms. After a few weeks, occasional giant cells may be seen. Later, a verrucous histologic pattern with pseudoepitheliomatous hyperplasia is characteristic (Fig. 23-11B). The regional lymph nodes show a granulomatous reaction with numerous giant cells, in which the organisms are predominantly located.

A biopsy from the active border of a verrucous lesion will best demonstrate diagnostic histopathology. There is considerable downward proliferation of the epidermis, often amounting to pseudocarcinomatous hyperplasia. Intraepidermal abscesses often are present. Occasionally, multinucleated giant cells are completely enclosed by the proliferating epidermis. The dermis is permeated by a polymorphous infiltrate. Neutrophils usually are present in large numbers and form small abscesses. Multinucleated giant cells are scattered throughout the dermis. Usually, they lie alone and not within groups of epithelioid cells. Occasionally, there are tuberculoid formations, although without evidence of caseation necrosis. In the ulcerative lesions, the dermal changes are the same as in the verrucous lesions, but the epidermis is absent.

The spores of *B. dermatitidis* are found in histologic sections often only after a diligent search, usually in clusters of neutrophils or within giant cells (Fig. 23-11C). One or several spores may lie within a giant cell, where they are easily spotted even in H&E-stained sections. Unstained, the spores resemble small, round holes punched out of the cytoplasm of the giant cells. On high magnification, the spores are seen to have a thick wall, which gives them a double-contoured appearance. They measure 8 to 15 μm in diameter (average, 10 μm). Occasionally, spores show a single broad-based bud. As in most fungal infections, many more spores are visualized in sections stained with the PAS reaction or with methenamine silver than in routinely stained sections.

Pathogenesis. The diagnosis of *B. dermatitidis* is based on finding physical evidence of the organism, because reliable serologic tests are not available and clinical examinations are nonspecific. Fine needle aspiration or wet prep of wound fluid fixed in 95% alcohol and stained with Papanicolaou and H&E is a rapid means to find diagnostic broad-based budding forms (87,88). Also of great value is the demonstration of the spores of *B. dermatitidis* in tissue sections either by direct immunofluorescence (89) or by immunoperoxidase (90). The required antiserum is prepared in rabbits with pure cultures of fungi and is conjugated either with fluorescein isothiocyanate or with horseradish peroxide. The antiserum can be applied to fresh as well as to formalin-fixed, paraffin-embedded tissue sections. Prior staining with H&E does not interfere with the procedure.

Corresponding antisera are valuable also for the demonstration of the spores of *Sporothrix schenckii, Cryptococcus neoformans (90), C. albicans, Candida tropicalis, Candida krusei, Aspergillus,* and *Histoplasma capsulatum* (91).

Differential Diagnosis. The verrucous lesions of systemic blastomycosis must be differentiated from other deep fungal infections, tuberculosis verrucosa cutis, halogenodermas, and squamous cell carcinoma. Mucicarmine staining, which highlights the capsule of *C. neoformans*, allows its differentiation from the spores of *B. dermatitidis*, and the narrow-necked budding forms of *H. capsulatum* can be distinguished from the broader-based buds of *B. dermatitidis* without special stains. Tuberculosis verrucosa cutis shows no spores in the tissue, the number of neutrophils is smaller, and areas of caseation necrosis usually are present. Halogenodermas may be difficult to differentiate from a deep fungal infection without obvious organisms, but the presence of intraepidermal abscesses, a mixed dermal inflammatory

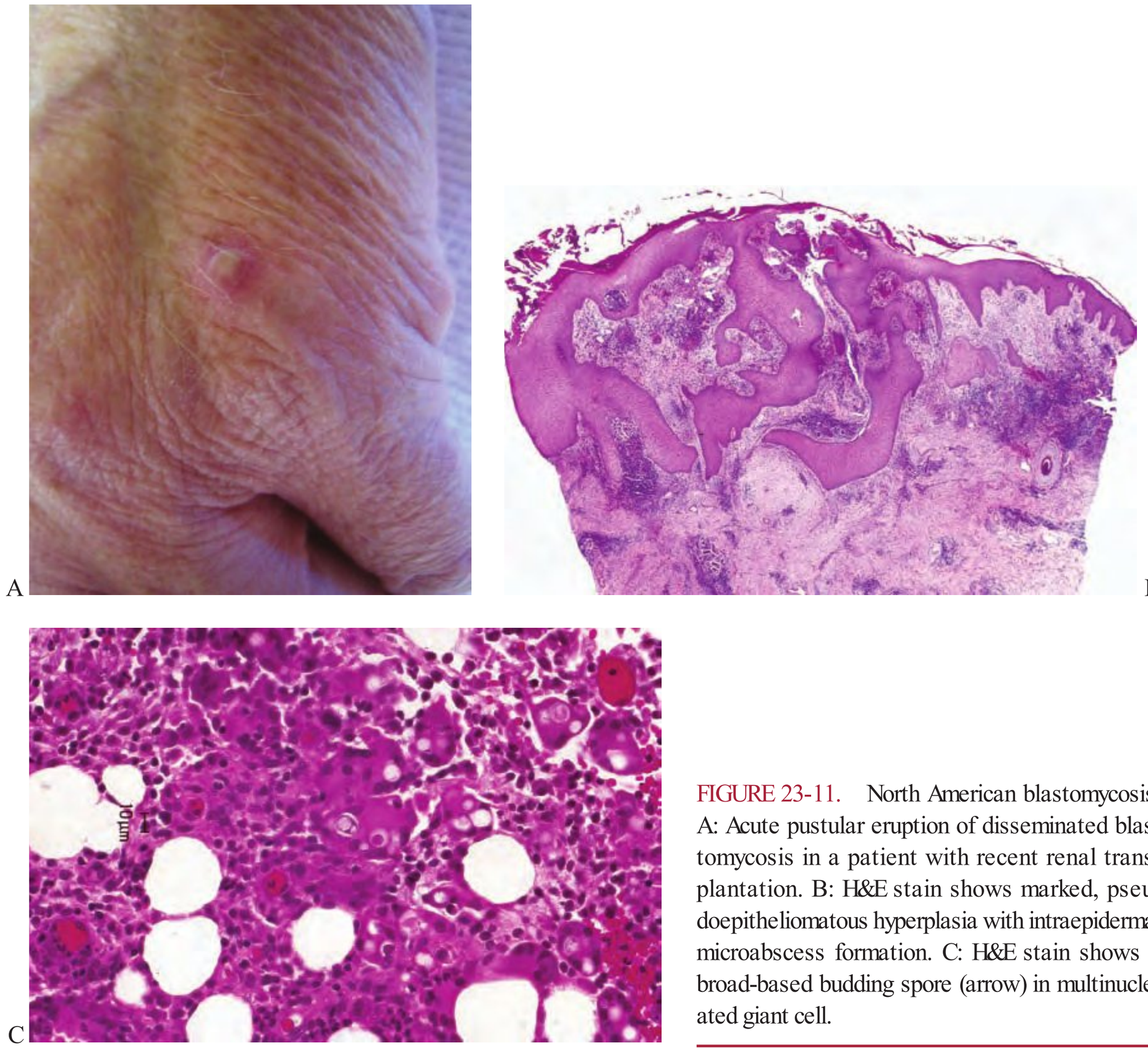


FIGURE 23-11. North American blastomycosis. A: Acute pustular eruption of disseminated blastomycosis in a patient with recent renal transplantation. B: H&E stain shows marked, pseudoepitheliomatous hyperplasia with intraepidermal microabscess formation. C: H&E stain shows a broad-based budding spore (arrow) in multinucleated giant cell.

infiltrate, and multinucleated giant cells is usually sufficient to rule out squamous cell carcinoma. Keratoacanthoma shares morphologic features with blastomycosis, including a verrucous architecture and intraepidermal abscesses. However, keratoacanthoma has a high degree of keratinization, a glassy appearance of the keratinocytes, and an abrupt cut-off between the central crater and adjacent epidermis.

PARACOCCIDIOIDOMYCOSIS

Paracoccidioidomycosis, also called *South American blastomycosis* because it occurs almost exclusively in South and Central America, is a chronic granulomatous disease caused by *Paracoccidioides brasiliensis*.

P. brasiliensis almost always gains entrance into the human body through inhalation and infects the lungs, where there is a subclinical infection that can be recognized only through a positive paracoccidioidin skin test (92). The typical patient with clinical disease is an adult male with an indolent, slowly progressive course. The first clinical manifestation is usually lesions in the oropharynx and on the gingivae. The lesions in the mouth begin as papules and nodules that then ulcerate. Subsequently, extensive granulomatous, ulcerated lesions develop in the mouth, nose, larynx, and pharynx. Extensive cervical lymphadenopathy develops, with suppuration of some of the lymph nodes. The oral lesions may extend to the neighboring skin, with formation of similar granulomatous, ulcerated lesions around the mouth and nose (92).

Through both lymphatic and hematogenous spread, the disease may subsequently involve many lymph nodes, both subcutaneous and visceral, and the lower gastrointestinal tract. In cases with wide dissemination, the lungs are clinically involved, presenting a picture greatly resembling chronic pulmonary tuberculosis (93). Adrenal insufficiency due to destruction of the adrenal glands, uncommon in other systemic mycoses except histoplasmosis, is not infrequent (94). Rarely, widely scattered cutaneous lesions resulting from hematogenous spread are observed during the stage of dissemination. The lesions may be papular, pustular, nodular, papillomatous, or ulcerated (95).

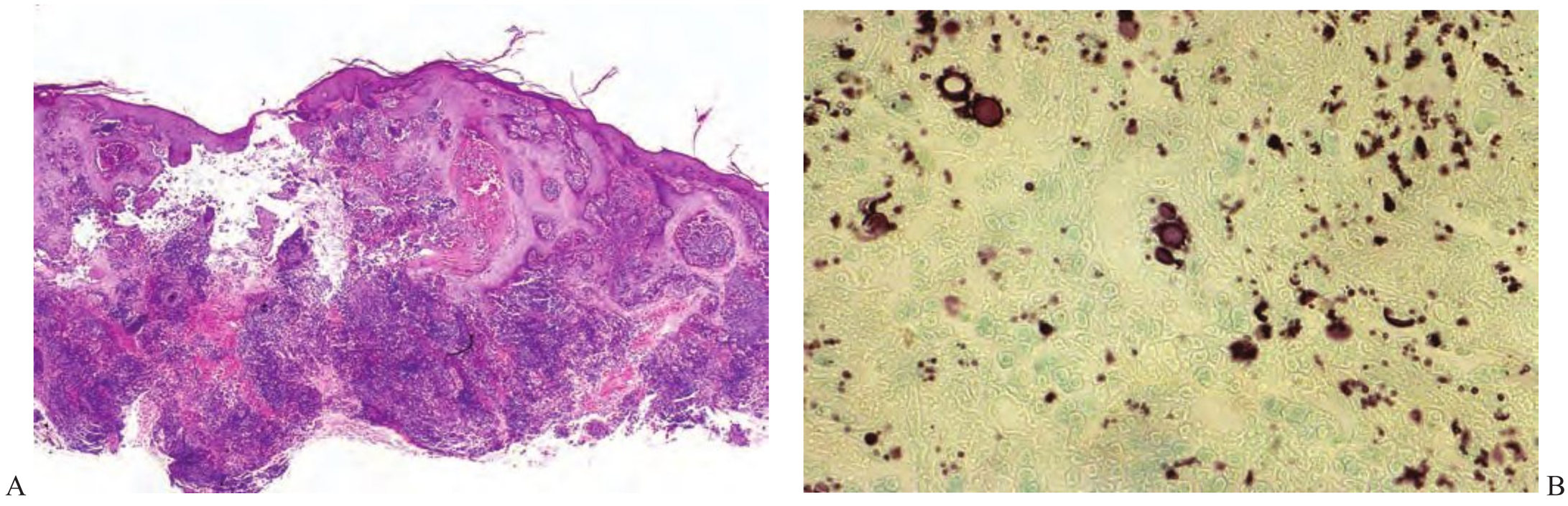


FIGURE 23-12. Paracoccidioidomycosis. A: H&E stain shows marked pseudoepitheliomatous epidermal hyperplasia with microabscess formation and a mixed dermal infiltrate. B: GMS stain shows variably sized yeast, some with multiple buds.

The disease develops and disseminates more rapidly in children and is then termed the *subacute progressive juvenile form* (96). Although experience is limited, it appears that there is little effect on the course of paracoccidioidomycosis in early HIV infection but that HIV patients with severe immunosuppression are at risk for a more fulminant course (97).

Histopathology. Examination of cutaneous or mucosal lesions reveals a granulomatous infiltrate showing epithelioid and giant cells in association with an acute inflammatory infiltrate and abscess formation (98). Spores may lie within giant cells or free in the infiltrate, especially in the abscesses. They are best demonstrated with the PAS reaction or methenamine silver. Pseudoepitheliomatous hyperplasia may be marked (Fig. 23-12A).

Many of the spores present in the tissue show only single, usually narrow-based buds or no buds at all (95). In the rare spores with multiple budding, peripheral buds are distributed over the whole surface of the ball-shaped fungus cell (Fig. 23-12B). Because of protrusion of the peripheral buds, such yeast cells in cross-sections have the appearance of a marine pilot's wheel. Whereas nonbudding or singly budding spores measure from 6 to 20 μm in diameter, spores with multiple budding may measure up to 60 μm in size.

Differential Diagnosis. *B. dermatitidis* and *C. neoformans* may be difficult to distinguish from paracoccidioides when only single budding organisms are seen. North American blastomycosis is distinguished by its thick refractile wall and broad-based blastospores. The capsule of C. *neoformans* stains with mucicarmine and is thus specifically identified.

LOBOMYCOSIS

Lobomycosis is an extremely indolent fungal infection characterized by asymptomatic, usually smooth, nodular lesions that resemble keloids on the ear, face, or extremity. The lesions may coalesce to form plaques but generally are limited to one area. Although the lesions persist, the condition is limited to the skin, except for occasional involvement of a regional lymph node (99). The infection, which is probably caused by a minor local injury, occurs sporadically in the South American tropics and Panama (100). The causative fungus is designated as *L. loboi*.

Histopathology. The dermis shows an extensive infiltrate of macrophages and large giant cells separated from a usually atrophic epidermis by a grenz zone. Scattered lymphocytes and plasma cells are present, but neutrophils are not typically present. Numerous fungus spores lie both within these cells and outside of them, and because the fungus does not stain with H&E, there may be so many unstained areas that the section may have a sievelike appearance (Fig. 23-13).

On staining with the PAS reaction or methenamine silver, the fungus spores average 10 μm in diameter. They possess a

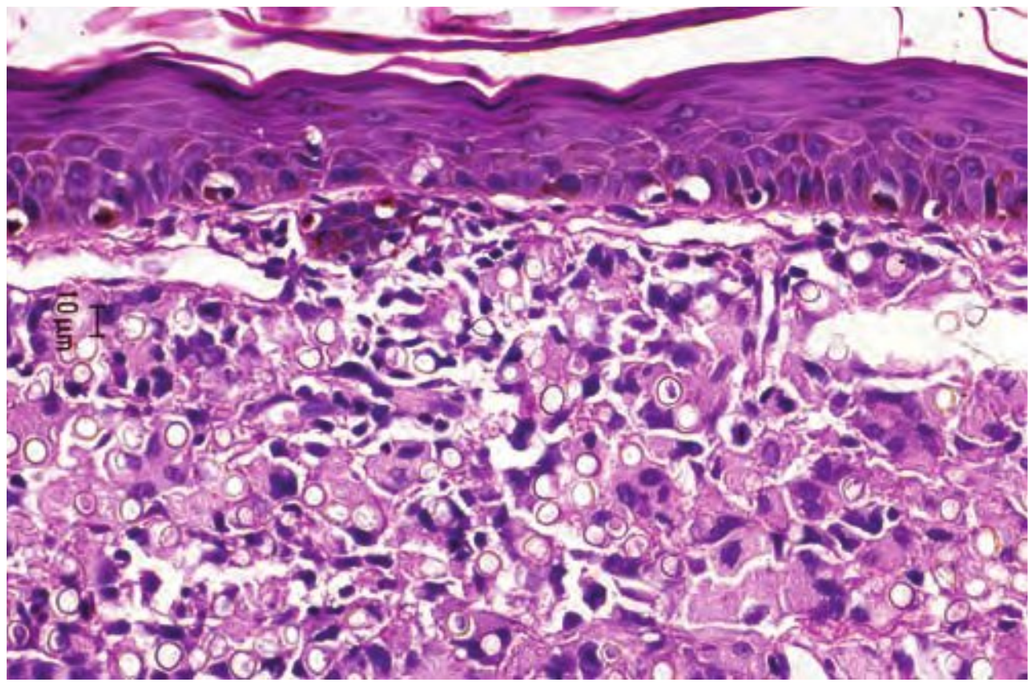


FIGURE 23-13. Lobomycosis. A diffuse dermal infiltrate of multinucleated giant cells containing spores is present beneath a flattened epidermis (H&E stain).

thick capsule, about 1 μm in thickness, with a tip that gives the organisms a distinctive "lemon-like" appearance. The spores occasionally show single budding (100) and often form single chains joined together by small, tubular bridges (101).

Pathogenesis. The macrophages contain abundant PAS-positive granular material that appears to consist of fragments of fungal capsules, indicating that the host macrophages are unable to digest the glycoproteins in the capsules (102).

CHROMOMYCOSIS

Chromomycosis is a slowly progressive cutaneous mycosis caused by pigmented (dematiaceous) fungi that occur as round, nonbudding forms in tissue sections. Inasmuch as budding is absent, the designation chromo*blasto*mycosis is somewhat inappropriate. In the past, the related term *chromomycosis* has also been used for cutaneous infections as well as for subcutaneous and cerebral infections by dematiaceous fungi in which hyphal forms almost always predominate. These two latter types of infections are clinically and histologically distinct and usually are classified as phaeohyphomycoses (103).

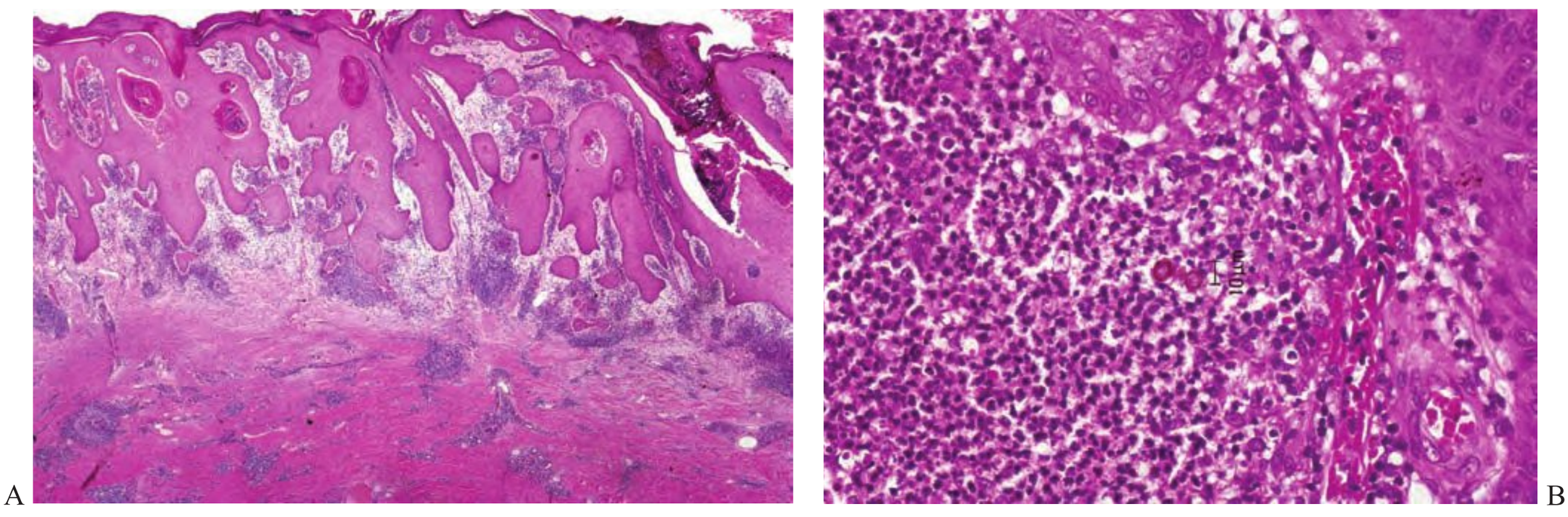
Chromomycosis is most often caused by one of five closely related species: *Phialophora verrucosa*, *Fonsecaea pedrosoi*, *Fonsecaea compactum*, *Exophiala* (*Fonsecaea*, *Wangiella*) *jeanselmei*, *Exophiala spinifera*, *Rhinocladiella aquaspersa*, and *Cladosporium carrionii* may each produce chromomycosis (104). These fungi are saprophytes and thus can be found growing in soil, decaying vegetation, or rotten wood in subtropical and tropical countries. The primary lesion is thought to develop as a result of traumatic implantation of the fungus into the skin (105).

The cutaneous lesions generally arise on the lower extremities and are variably pruritic, papular, nodular, verrucous, or plaquelike lesions (104,105). While some of the lesions heal with scarring, new ones may appear in the vicinity as a result of spreading of the fungus along superficial lymphatic vessels or autoinoculation (103). Lymphatic disruption with elephantiasis may occur.

Hematogenous dissemination may cause extensive cutaneous lesions (106), but it is a rare event, even in immunocompromised persons, and the disease is not as aggressive as other systemic fungal infections that secondarily involve the skin (107).

Histopathology. Cutaneous chromomycosis resembles North American blastomycosis in that both demonstrate a lichenoid-granulomatous inflammatory pattern. In chromomycosis, there is pseudoepitheliomatous epidermal hyperplasia and an extensive dermal infiltrate composed of many epithelioid histiocytes (108). Other components of the infiltrate include multinucleated giant cells; small abscesses and clusters of neutrophils; and variable numbers of lymphocytes, plasma cells, and eosinophils. Tuberculoid formations may be present, but caseation necrosis is absent.

Fungi are found within giant cells as well as free in the tissue, especially in the abscesses. They appear as conspicuous, dark brown, thick-walled, ovoid or spheric spores varying in sizes from 6 to 12 μm that are likened to "copper pennies" and that may lie either singly or in chains or clusters (103) (Fig. 23-14). Because of their brown pigmentation, the spores can be seen easily without the use of special stains. Reproduction is by intracellular wall formation and septation, not by budding, and cross walls can be seen in some of the spores. In cases demonstrating marked hyperplasia of the epidermis, fungal spores can be seen within microabscesses or giant cells, as in North American blastomycosis. Transepidermal elimination of fungal spores may be observed, resulting in clinically visible black dots (109,110).



A B

FIGURE 23-14. Chromoblastomycosis. A: H&E stain shows pseudoepitheliomatous epidermal hyperplasia with microabscess formation and a mixed inflammatory infiltrate. B: Pigmented spores (adjacent to scale marker) resembling "copper pennies" are surrounded by a neutrophilic infiltrate (H&E stain).

Pathogenesis. Although percutaneous inoculation of the fungus is widely accepted as the mode of infection, the fact that the cutaneous manifestations show no chancriform syndrome but rather a granulomatous infiltrate resembling that of North American blastomycosis suggests that the cutaneous lesions of chromomycosis may arise by hematogenous dissemination from a silent primary pulmonary focus. Although this view is supported by occasional reports of hematogenous dissemination and by the observation of multiple areas of calcification in the chest x-ray film of a patient with chromomycosis (111), convincing evidence is lacking. In support of the concept that cutaneous inoculation may cause cutaneous chromomycosis, pigmented fungal elements were found on embedded wood splinters associated with a foreign body reaction and in direct contact with the surrounding dermis in two patients (112), and one patient developed classic cutaneous chromomycosis caused by *F. pedrosoi* after trauma with a tree branch containing the same organisms (113).

COCCIDIOIDOMYCOSIS

Coccidioidomycosis, also known as *Valley fever*, is caused by the dimorphic fungus *Coccidioides immitis*. Like blastomycosis, it occurs in three forms: primary cutaneous inoculation coccidioidomycosis, pulmonary coccidioidomycosis, and systemic coccidioidomycosis. This soil-dwelling organism is endemic in the southwestern United States, especially in the San Joaquin and Sacramento valleys, southern Arizona, and Mexico (114). The vast majority of infections with *Coccidioidomycosis* result from inhalation of the aerosolized arthrospores. Approximately 60% of those infected are asymptomatic, and of the symptomatic patients, 90% to 99% experience only mild flulike symptoms (114).

Primary cutaneous inoculation coccidioidomycosis is very rare. In a few instances, as in primary cutaneous inoculation blastomycosis, it has occurred as a laboratory or an autopsy room infection (115,116); but unlike primary cutaneous inoculation blastomycosis, it has also been found as a naturally occurring infection through injuries by contaminated thorns or splinters (117,118). A tender, ulcerated nodule forms within 1 to 3 weeks at the site of inoculation and may enlarge into a granulomatous, ulcerated plaque. This is followed, as in the case of accidental inoculation with *B. dermatitidis*, by regional lymphangitis and lymphadenitis. Healing usually takes place within a few months, but meningitis developed in one reported patient, requiring prolonged intrathecal treatment with amphotericin B (118).

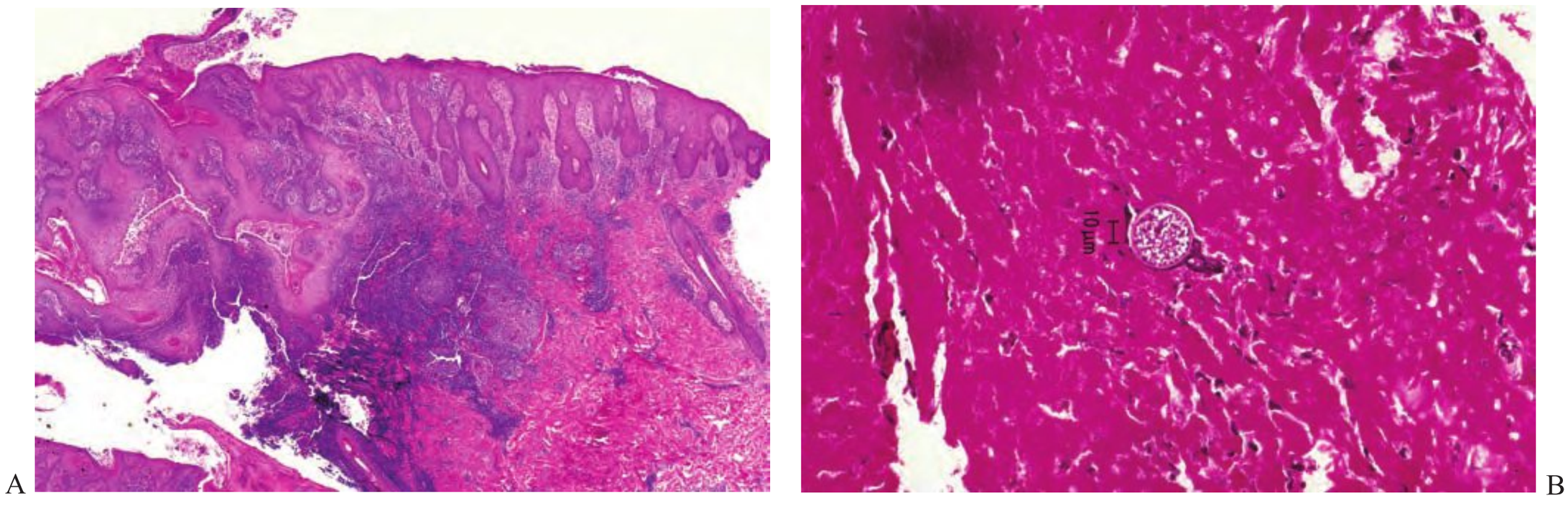
Pulmonary coccidioidomycosis is the most common form of the infection; epidemiologic skin test studies suggest that between 30% and 90% of the population in the southwestern United States have been infected (119–121). The fungus is resident in the soil of these arid or semiarid areas, and arthrospores are inhaled by the host when the soil is disturbed. Most immunocompetent infected individuals are asymptomatic, although about 40% will develop transient symptoms of an acute respiratory infection. The development of erythema nodosum is not uncommon, and most individuals recover without serious sequelae (122). In 2% to 8% of cases, however, the pulmonary lesions progress to chronic disease with cavity formation before finally healing.

Systemic coccidioidomycosis follows the primary pulmonary infection in only about 1 in 10,000 cases in otherwise immunocompetent whites. However, Mexicans are about 5 times, blacks 25 times, and Filipinos 175 times more likely to acquire systemic disease than whites, which has a mortality rate of about 50% when untreated (114). Studies of this difference have focused on human leukocyte antigen (HLA) genes, which produce molecules responsible for antigen presentation to T cells, the portion of the immune system important in elimination of fungi. Some studies have shown HLA subtypes -A9 and -B5 as well as ABO blood group B to be associated with disseminated coccidioidomycosis, and each occurs with greater frequency in blacks and Filipinos than in whites. The risk of dissemination and a fatal outcome is also greater in HIV-infected patients, particularly those with AIDS (123,124). Disseminated coccidioidomycosis may occasionally represent the first manifestation of AIDS (123). Immunosuppressive therapy may cause activation of a latent pulmonary infection of coccidioidomycosis. Dissemination of the infection after iatrogenic immunosuppression is frequently explosive and may be fatal. Therefore, all patients with a history of travel or residence in endemic areas should receive a coccidioidin skin test and have a chest roentgenogram before immunosuppressive therapy is initiated (125). In systemic coccidioidomycosis, many organs, especially the meninges, lungs, bones, and lymph nodes, may be involved (126). Coccidioidal fungemia often occurs in severe, acute forms of systemic coccidioidomycosis and is associated with a high mortality (123,126).

The coccidioidin skin test, which consists of the intradermal injection of 0.1 mL of a 1:100 dilution of coccidioidin, is of value in diagnosing early infection. The test converts from negative to positive within a few weeks of the primary pulmonary infection, even before a blood test would be positive. Patients with erythema multiforme or nodose lesions are exquisitely sensitive to coccidioidin, and even higher dilutions have been recommended for use in such cases (127). The test is helpful when positive; however, those patients with anergy or disseminated disease tend to have a persistently negative skin test (116).

Cutaneous lesions occur in 15% to 20% of cases of systemic coccidioidomycosis. They may consist of verrucous papules, nodules, or plaques, or of subcutaneous abscesses, which may break through the skin to form draining sinuses. One or a few cutaneous nodules or plaques may occasionally be the only clinical manifestation of systemic coccidioidomycosis, heralding a relatively good prognosis (125). A rare manifestation is the sudden widespread appearance of small pustules on an erythematous base (126), just as described in North American blastomycosis.

Histopathology. In primary cutaneous inoculation coccidioidomycosis, a dense dermal inflammatory infiltrate of neutrophils, eosinophils, lymphoid cells, and plasma cells with an occasional giant cell can be observed. Small abscesses may be



A B

FIGURE 23-15. Coccidioidomycosis. A: The low-power pattern is similar to that of North American blastomycosis with pseudoepitheliomatous epidermal hyperplasia and a mixed inflammatory infiltrate (H&E stain). B: A large, round, thick-walled spore with granular cytoplasm is present in a background of necrotic tissue (H&E stain).

seen (115). Spores, and in some cases also hyphae, are present. The regional lymph nodes show a well-developed granulomatous reaction consisting of epithelioid and giant cells. Spores are found within and outside the giant cells.

The verrucous nodules and plaques of the skin in systemic coccidioidomycosis histologically resemble those of North American blastomycosis (Fig. 23-15A). However, they show less of a tendency toward abscess formation, and caseation necrosis may occur. The causative organisms are found as spores, free in the tissue and within multinucleated giant cells, and as a rule, they are present in large numbers.

The subcutaneous abscesses show a central area of necrosis surrounded by a granulomatous infiltrate that is tuberculoid in type and composed of lymphoid cells, plasma cells, epithelioid cells, and some giant cells. Numerous spores are present extracellularly as well as intracellularly in the giant cells. The pustules seen in a few cases show the presence of spores within them (128).

The nodose skin lesions occurring in primary pulmonary coccidioidomycosis have the same histologic appearance as those in idiopathic erythema nodosum (128).

The spores of *C. immitis* vary in size from 10 to 80 µm (Fig. 23-15B), with the average size being about 40 µm. Thus, the fungi of *Coccidioides* are much larger than those of *Blastomyces, Cryptococcus,* or *Phialophora.* The spores are round and thick walled and have a granular cytoplasm. Multiplication takes place by the formation of endospores, which may be seen lying inside the larger spores. The endospores are released into the tissue by rupture of the spore wall. Endospores may measure up to 10 µm in diameter.

CRYPTOCOCCOSIS

Cryptococcosis is an infection caused by the yeast *C. neoformans,* which occurs throughout much of the world. *C. neoformans* is found in the excreta of birds, mainly pigeons and chickens, and in soil contaminated by them. The yeast is spread by aerosol, and transient colonization of the respiratory tract and skin of humans is not rare (129). Primary cutaneous (inoculation) cryptococcosis is extremely rare (130,131). The organism generally enters the body through the respiratory tract, where it can cause symptomatic or asymptomatic infection, either of which may be followed by hematogenous spread (132). Although clinical disease occurs in some apparently normal individuals, it usually develops in immunocompromised hosts, especially those with AIDS (133) (Fig. 23-16A), but also in patients taking corticosteroids (134,135) and in patients with hematopoietic malignancies (136,137) or sarcoidosis (137–139).

Meningitis is the most common clinical manifestation of systemic infection. Symptom onset is insidious. Patients report a dull headache, most commonly with little fever until late in the disease. Other signs of meningeal irritation such as nuchal rigidity are absent (132). In addition, there may be osseous lesions and involvement of the kidneys and prostate. Cutaneous lesions are found in 10% to 15% of the cases of systemic cryptococcosis (140). In rare instances, lesions of the oral mucosa also occur (136). Without adequate treatment, mortality with the systemic form is 70% to 80%; untreated cerebromeningeal cryptococcosis is almost invariably fatal. Cryptococcemia is an extremely grave prognostic sign (132,141).

In some instances of systemic cryptococcosis, central nervous system involvement is not seen, and there are only one or a few lesions in the skin, lymph nodes, bones, or eyes. In cases in which only cutaneous lesions are present, the disease may take a benign course, ending with healing of the lesions, even without treatment (142,143). However, cutaneous lesions may be the presenting sign of systemic cryptococcosis and may be followed by wide dissemination of the disease with a fatal ending (132,141).

Cutaneous lesions are variable and may consist of papules, pustules, herpetiform vesicles, nodules, infiltrated plaques, subcutaneous swellings or abscesses, or ulcers (140). Lesions resembling those of molluscum contagiosum, Kaposi's sarcoma, or acne have been described in patients with AIDS

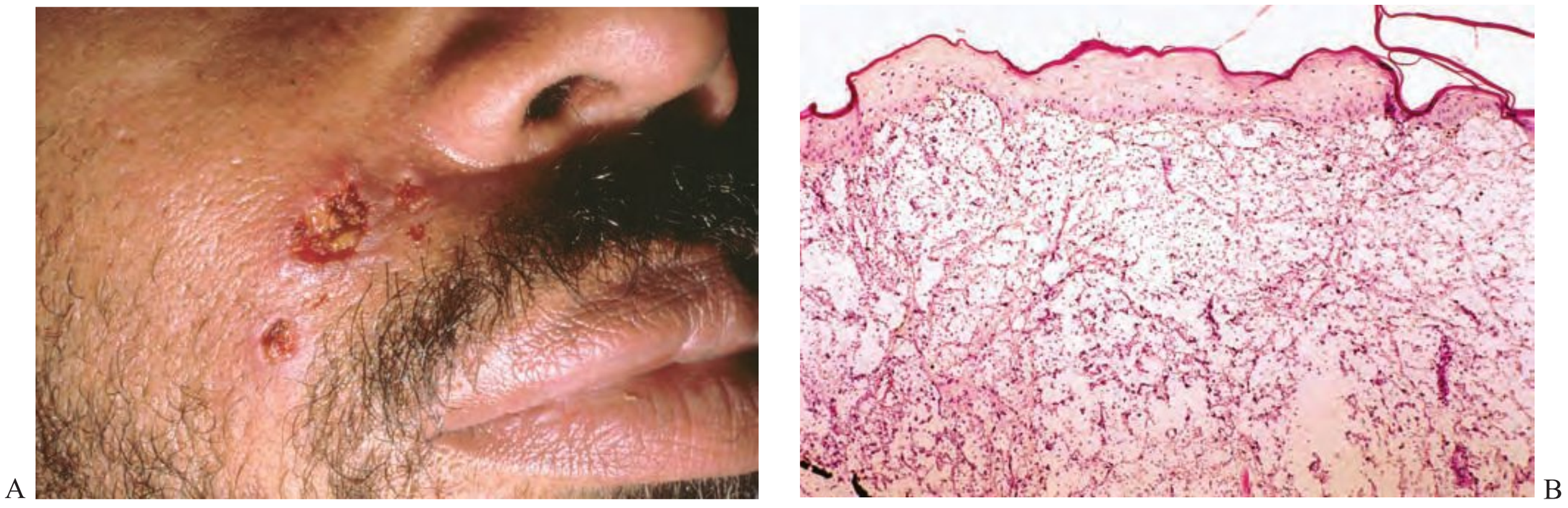


FIGURE 23-16. Cryptococcosis. A: Ulcerated papules and plaques of crytococcal infection in a HIV-positive male. B: H&E stain shows spores surrounded by wide capsules with relatively little inflammatory reaction. C: Spores, but not their capsules, can be visualized in routine stained sections (H&E stain).

(144–146) (Fig. 23-16A). In infections limited to the skin, generally only one or possibly two lesions are present, but in cases with widespread systemic infection, there are often multiple cutaneous lesions (134,140).

Cryptococcal cellulitis is a variant form that may occasionally be limited to the skin. This form has an abrupt onset and spreads rapidly. There may be multiple sites of involvement. It is seen only in markedly immunosuppressed hosts, especially in renal transplant patients (147).

Histopathology. Two types of histologic reaction to infection with *C. neoformans* may occur in the skin as well as elsewhere: gelatinous and granulomatous. Both types may be seen in the same skin lesion (132,135). Gelatinous lesions show numerous organisms in aggregates and only very little tissue reaction (Fig. 23-16B). In contrast, granulomatous lesions show a pronounced tissue reaction consisting of histiocytes, giant cells, lymphoid cells, and fibroblasts. Areas of necrosis may also be seen, and the organisms are present in a much smaller number than in gelatinous lesions, found mainly within giant cells and histiocytes or occasionally free in the tissue (148).

C. neoformans, a round to ovoid spore, measures from 4 to 12 μm in diameter in the gelatinous reaction but often only 2 to 4 μm in the granulomatous reaction (148) (Fig. 23-16C). The spore stains with the PAS reaction or methenamine silver and shows a dark brown or black color with the Fontana-Masson stain, which completely disappears with melanin bleach (149). Like *B. dermatitidis,* it multiplies by budding. In the gelatinous reaction pattern, a broad capsule surrounds the fungus, and there is very little infiltration of inflammatory cells. The capsule does not stain with H&E or the PAS reaction, but because of the presence of acid mucopolysaccharides, it stains metachromatically purple with methylene blue, blue with Alcian blue (150), and red with mucicarmine. When the Alcian blue stain and PAS reaction are combined, the yeast cell stains red and the surrounding capsule blue. However, when the yeast cells do not form a capsule, an intense granulomatous inflammatory reaction of histiocytes, giant cells, lymphocytes, and fibroblasts is elicited (149).

Cryptococcal cellulitis shows nonspecific acute and chronic inflammation in which cryptococcal organisms can be demonstrated with the PAS and mucicarmine stains (147).

Pathogenesis. *C. neoformans* is inhaled as a relatively small, nonencapsulated organism measuring approximately 3 μm in diameter. Under favorable nutrient conditions in the human host, the size of the organism increases up to 12 μm, and a wide gelatinous capsule forms. The lack of a tissue reaction to encapsulated *C. neoformans* is best explained by the fact that the thick capsule prevents contact of the organism with the host tissue and thus inhibits phagocytosis of the organism (148). Failure of the organism to form a capsule probably is the result of a defect in one of its metabolic pathways (149).

On electron microscopy, the mucinous capsule of *C. neoformans* is seen to consist of radially arranged fibrillary material, with the fibrils intertwining and having a beaded appearance (151).

Ever since cases of cryptococcosis with only one or a few cutaneous lesions have been described, some authors have assumed that a purely cutaneous form of cryptococcosis produced by cutaneous inoculation exists (152). However, the fact that purely cutaneous lesions show no chancriform syndrome with regional lymphadenopathy speaks against the theory of primary inoculation of the skin (134). It has been recommended that all cases seeming to be purely cutaneous cryptococcosis should be considered potentially disseminated (153). Cultural studies should include the spinal fluid, sputum, prostatic fluid, and urine to rule out disseminated disease (154). Of note, there are multiple reports of cross-reactivity of *Cryptococcus* with unrelated fungi with the use of agglutination kits (155,156). Confirmation of a positive capsular antigen test with a second test helps to limit false positives.

Differential Diagnosis. In the granulomatous type of reaction, *C. neoformans* may have no capsule, may be small with an average diameter of only 3 μm, and is found largely within macrophages and giant cells. Histologic differentiation from *B. dermatitidis,* which also reproduces by budding; *H. capsulatum*; and other fungi may then be difficult. However, only *C. neoformans* stains black with the Fontana-Masson stain (149).

HISTOPLASMOSIS

Histoplasmosis is found throughout the world, but the largest endemic focus is in the central eastern United States, especially the Ohio and lower Mississippi river valleys, where 85% to 90% of the population have positive skin tests for histoplasmin. It has been estimated that 40 million persons have undergone pulmonary infection with *H. capsulatum* and that there are 200,000 new cases annually in the United States (157,158).

Like blastomycosis and coccidioidomycosis, histoplasmosis may occur in three forms: primary cutaneous inoculation histoplasmosis, primary pulmonary histoplasmosis caused by inhalation, and disseminated histoplasmosis.

Primary cutaneous inoculation histoplasmosis, a very rare event, is benign and self-limited in duration. It generally occurs as a laboratory infection and presents as a chancriform syndrome, with a nodule or ulcer at the site of inoculation and associated lymphangitis and lymphadenitis (159,160).

Primary pulmonary histoplasmosis, the common form of infection, is usually asymptomatic, although acute pulmonary histoplasmosis with symptoms resembling those of influenza may develop in a minority of patients. Chronic pulmonary histoplasmosis usually occurs in patients with preexisting lung disease and may result in the formation of cavities. It develops in about 1 in 2,000 infections, resembles pulmonary tuberculosis in its symptoms, and may end fatally unless treated. Reactivation of pulmonary histoplasmosis following treatment with infliximab (Remicade) has been reported and should be considered when fever and pulmonary symptoms develop in these patients (161).

Before the advent of HIV, disseminated histoplasmosis developed in only 1 in 50,000 infections (162) and was usually found in infants, patients with lymphoma (163), or those receiving immunosuppressive treatment (164). Although not as frequent in the general AIDS population as coccidioidomycosis and cryptococcosis (165), disseminated histoplasmosis can be the most frequent opportunistic infection in AIDS patients living in highly endemic areas (166,167).

Disseminated histoplasmosis presents a variable clinical picture, depending on the degree of parasitization. Cases with severe degrees of parasitization (acute disseminated disease) occur principally in infants and immunosuppressed patients and may be fatal. There is often high, persistent fever and extensive involvement of the reticuloendothelial system with hepatosplenomegaly; anemia, leukocytopenia, and thrombocytopenia may also be seen. Cases with moderate degrees of parasitization (subacute disseminated disease) occur in both adults and infants, who if adequately treated may survive. Fever, hepatosplenomegaly, and bone marrow depression are mild or moderate. Adrenal involvement leading to adrenal insufficiency, as well as gastrointestinal ulceration, meningitis, and endocarditis, are common. Cases with mild degrees of parasitization (chronic disseminated disease) are associated with destructive focal lesions in a number of organs and occur almost exclusively in adults. There may or may not be fever, hepatosplenomegaly, bone marrow depression, adrenal insufficiency, meningitis, or endocarditis. In the chronic disseminated form, the response to treatment generally is good (159). If no cutaneous or oral lesions are present, the most useful diagnostic method is a bone marrow biopsy and occasionally also biopsy of the liver or a palpable lymph node (164).

Cutaneous lesions occur in only 6% of patients with disseminated histoplasmosis but may rarely be the presenting sign (168–170). Cutaneous lesions occur in a wide variety of forms, none of which can be said to be characteristic. Most commonly, they consist of primary ulcers, often with annular, heaped-up borders (169,171). They may also consist of papules, nodules, or large plaquelike lesions (168,172). Papules may umbilicate, causing a resemblance to lesions of molluscum contagiosum (173). Lesions may be purpuric or crusted or may develop pustular caps and ulcerate. There may be tender, red nodules due to panniculitis (174). A rare cutaneous manifestation is a generalized pruritic erythroderma (175,176). In addition, there may be a number of nonspecific cutaneous manifestations associated with histoplasmosis, including erythema nodosum and erythema multiforme.

In contrast to the rarity of cutaneous lesions, lesions of the oral mucosa occur in about half of all cases of disseminated histoplasmosis and are not infrequently the presenting sign of the disease (168). Lesions of the oral mucosa often start as painless papular swellings and usually ulcerate. The contiguous skin may also be involved. Biopsy of a mucosal or cutaneous lesion may be the most rapid method of arriving at a specific

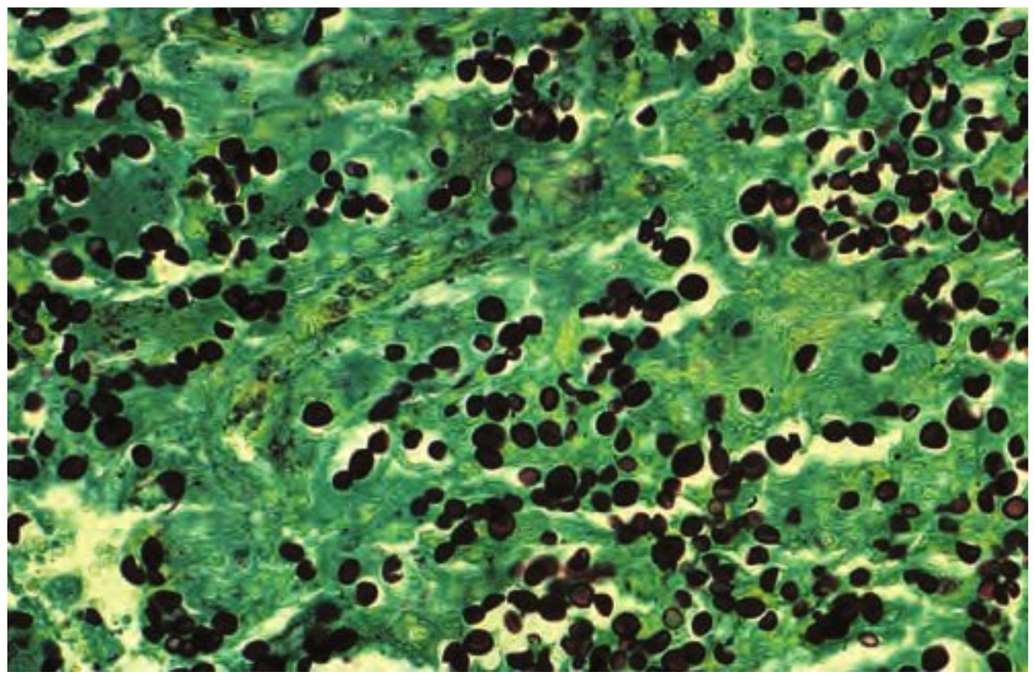


FIGURE 23-17. Histoplasmosis. Large spores of H. capsulatum var. duboisii are seen extracellularly and in giant cells (GMS stain).

diagnosis of disseminated histoplasmosis and may allow for the rapid institution of lifesaving therapy as culture may require up to a 4-week incubation period (177).

Histopathology. The diagnostic feature in all types of cutaneous histoplasmosis is the presence of tiny 2- to 4-μm spores within the cytoplasm of macrophages and variably within giant cells (172,178). The spores of *H. capsulatum* are visualized in sections stained with H&E, Gram, or Giemsa (Fig. 23-17). They appear as round or oval bodies surrounded by a clear space that was originally interpreted as a capsule, giving rise to the name *H. capsulatum*. The spores, not including the clear space surrounding them, measure from 2 to 4 μm in diameter. Silver impregnation stains and electron microscopic studies show that *H. capsulatum* does not possess a capsule and that the inner portion of the clear space represents the cell wall of the fungus and the clear space itself is filled with granular material that separates the cell wall of the fungus from the cytoplasm of the macrophage (178). On electron microscopy, it can be seen that each spore of *H. capsulatum*, including its halo, is located within a phagosome that is lined by a trilaminar membrane (178).

In acute disseminated histoplasmosis, lesions consist mostly of heavily parasitized histiocytes with relatively little surrounding tissue reaction. Cutaneous lesions in the chronic form of the disease tend to be composed of better-differentiated macrophages with fewer organisms (168). A suppurative granulomatous pattern may develop, especially in ulcerated lesions. There may be foci of necrosis, and giant cells may also be present. Although well-developed tubercles are characteristic of pulmonary histoplasmosis, they are unusual in the skin. Oral lesions, especially when ulcerated, may show a more mixed infiltrate with neutrophils and eosinophils.

Pathogenesis. *H. capsulatum* is a dimorphous fungus that grows in culture at temperatures below 35°C and on natural substrates in soil as a mycelial fungus elaborating macroaleuriospores (8 to 16 μm) and microaleuriospores (2 to 5 μm). When inhaled, the latter sprout and transform into small budding yeasts that are 2 to 5 μm in diameter. In cultures at a temperature of 37°C, the organism also grows in the yeastlike form (179).

Differential Diagnosis. The histologic appearance of histoplasmosis, characterized by the presence of parasitized macrophages within a chronic inflammatory infiltrate, is much like that of rhinoscleroma, granuloma inguinale, and cutaneous leishmaniasis. *H. capsulatum* is the only pathogen to parasitize macrophages that stains with the usual fungal stains, such as the PAS reaction and methenamine silver. *Histoplasmosis* does not possess a true capsule and can thus be distinguished from *C. neoformans*, particularly when the latter is noted to stain black with Fontana-Masson stain.

African Histoplasmosis

In addition to classical histoplasmosis caused by *H. capsulatum*, there is a form of histoplasmosis that is caused by *H. capsulatum* var. *duboisii*, and that has been called *African histoplasmosis* because it occurs almost exclusively in Central Africa. The portal of entry is not known. It usually occurs as a relatively indolent form involving the skin as well as the subcutaneous tissue, bones, and lymph nodes (180,181). This organism relatively rarely causes a disseminated form of disease that involves many internal organs and may be fatal, thus resembling more classical disseminated histoplasmosis (182).

The cutaneous lesions may be one, a few, or many. They consist of papules, nodules, and plaques that often ulcerate (183). There may be large, subcutaneous granulomas that develop into fluctuant, nontender abscesses (179). Purulent bone lesions may result in draining sinus tracts extending through the skin (181).

Histopathology. The cutaneous lesions show a dense, mixed cellular infiltrate containing numerous giant cells and scattered histiocytes, lymphocytes, and plasma cells. There are focal aggregates of neutrophils forming small abscesses (183). Numerous yeast cells, 8 to 15 μm in diameter, are present mainly in the giant cells but also in histiocytes and extracellularly (181).

Pathogenesis. Despite the fact that African histoplasmosis differs in its clinical character and in the size of the organism from classic histoplasmosis, it is clear that *H. capsulatum* and *Histoplasma duboisii* are variants of the same species, since after prolonged *in vitro* growth at 37°C, the small yeast cells of *H. capsulatum* can assume the same size as those of *H. duboisii* (181).

SPOROTRICHOSIS

Surveys with the sporotrichin skin test show a positive reaction in up to 10% of the population in certain areas, suggesting that many infections with *S. schenckii* are minor or asymptomatic and not recognized clinically (184,185). Clinical sporotrichosis usually occurs as one of two primary cutaneous forms, either

the fixed cutaneous or the lymphocutaneous form. Both result from direct inoculation at a site of minor trauma. Although the infection may rarely disseminate from either form by autoinoculation to other skin sites or by hematogenous spread (186–188), systemic sporotrichosis more commonly follows pulmonary infection. Development of systemic sporotrichosis, although rare, occurs particularly in persons with a depressed immune response, such as patients with lymphoma or persons receiving long-term systemic corticosteroids. *S. schenckii* is not a common opportunist in HIV-infected individuals, but disseminated sporotrichosis has been seen in a few patients with AIDS (189).

The lymphocutaneous form of sporotrichosis starts with a painless papule that grows into an ulcer, usually on a finger or hand. Subsequently, a chain of asymptomatic nodules appears along the lymph vessel draining the area ("sporotrichoid spread"). These lymphatic nodules may undergo suppuration with subsequent ulceration.

In the fixed cutaneous form, a solitary plaque or occasionally a group of lesions is seen, most commonly on an arm or the face. It may show superficial crusting or a verrucous surface (190–192). There is no tendency toward lymphatic spread.

Systemic sporotrichosis may be unifocal or multifocal and usually develops subsequent to pulmonary infection. Unifocal systemic sporotrichosis may affect the lungs, a single joint or symmetric joints, the genitourinary tract, or rarely the brain (193). Chronic pulmonary sporotrichosis resembles pulmonary tuberculosis (194). Multifocal systemic sporotrichosis nearly always shows widely scattered cutaneous lesions, which start as nodules or as subcutaneous abscesses and undergo ulceration. In addition, involvement of the lungs (188) or of several joints of the extremities is usually observed. The predilection of *S. schenckii* for cooler parts of the body, such as the skin, lungs, and joints of the extremities, has been attributed to the fact that the organism grows best at temperatures less than 37°C.

Histopathology. Early primary cutaneous lesions of sporotrichosis usually show a nonspecific inflammatory infiltrate composed of neutrophils, lymphoid cells, plasma cells, and histiocytes (195). Longer-standing, clinically verrucous lesions show a hyperplastic epidermis with small, intraepidermal, and dermal lymphoplasmacytic infiltrate with small abscesses, eosinophils, giant cells, and small granulomas often associated with asteroid bodies (191,195). Later, through coalescence, a characteristic arrangement of the infiltrate in three zones may develop. These include a central "suppurative" zone composed of neutrophils; surrounding it, a "tuberculoid" zone with epithelioid cells and multinucleated histiocytes; and peripheral to it, a "round cell" zone of lymphoid cells and plasma cells.

The lymphatic nodules of lymphocutaneous sporotrichosis and the cutaneous nodules of multifocal systemic sporotrichosis at first show scattered granulomas within an inflammatory infiltrate predominantly in the deep dermis and subcutaneous fat (191,196). These enlarge and coalesce to form irregularly shaped suppurative granulomata, and eventually a large abscess surrounded by zones of histiocytes and lymphocytes as described for primary lesions (191).

In many instances, it is not possible to recognize the causative organisms of *S. schenckii* in tissue sections, particularly in the two common forms: the lymphocutaneous and fixed cutaneous. This seems to be true especially in cases of sporotrichosis reported from the United States (197) and Europe (196). In these areas, negative findings are common even with diastase digestion of glycogen granules prior to staining of sections with the PAS reaction. Staining with methenamine silver has not increased the frequency of positive findings (196). Even in cases with positive findings, numerous sections often have to be examined before one or a few organisms are visualized. Immunohistochemical staining using primary antibodies directed against *S. schenckii* may increase the percentage of cases in which the organism can be demonstrated to 83%, more than double that achieved with ordinary histochemical methods (198). In addition, there are apparently significant geographic differences, since in a series of cutaneous sporotrichosis reported from Japan, 98% of the cases showed spores in tissue sections on staining with the PAS reaction (199). If present, the spores of *S. schenckii* appear as round to oval bodies 4 to 6 μm in diameter that stain more strongly at the periphery than in the center (196) (Fig. 23-18). Single or occasionally multiple buds are present. In some instances, small, cigar-shaped bodies up to 8 μm long are also present (187,195). In only very few cases can clumps of branching, nonseptate hyphae be demonstrated (197,199).

Asteroid bodies may be seen in sporotrichosis, as well as in a number of other infectious processes, and sarcoidosis. Asteroid bodies are visible in sections stained with H&E, and in sporotrichosis consist of a central spore 5 to 10 μm in diameter surrounded by radiating elongations of a homogeneous eosinophilic material. The phenomenon of radiating eosinophilic material found around infectious agents, described in sporotrichosis by Splendore (200) and in schistosomiasis by Hoeppli (201) and known as the *Splendore-Hoeppli phenomenon,* has been thought to represent deposition of antigen-antibody complexes and debris from host inflammatory cells (202). Measurements of the greatest diameter of asteroid bodies in sporotrichosis vary from 7 to 25 μm, with a mean of 20 μm (191). Asteroid bodies have been observed in only a few cases of sporotrichosis occurring in the United States, and it may be difficult to demonstrate the central spore. However, asteroid bodies are found frequently in cases of sporotrichosis from South Africa, Japan, and Australia, with an incidence varying from 39% to 65% (203).

Pathogenesis. *S. schenckii* occurs throughout the world and is commonly contracted through exposure to vegetal matter, often a splinter or thorn, although transmission by insects and animals has been reported (204). In nearly all cases of sporotrichosis, even in those without demonstrable fungi in the tissue, *S. schenckii* can be grown easily on Sabouraud medium. The fungus is dimorphic: At room temperature, it grows in a mycelial form with conidiophores bearing conidia as a "bouquet" at the

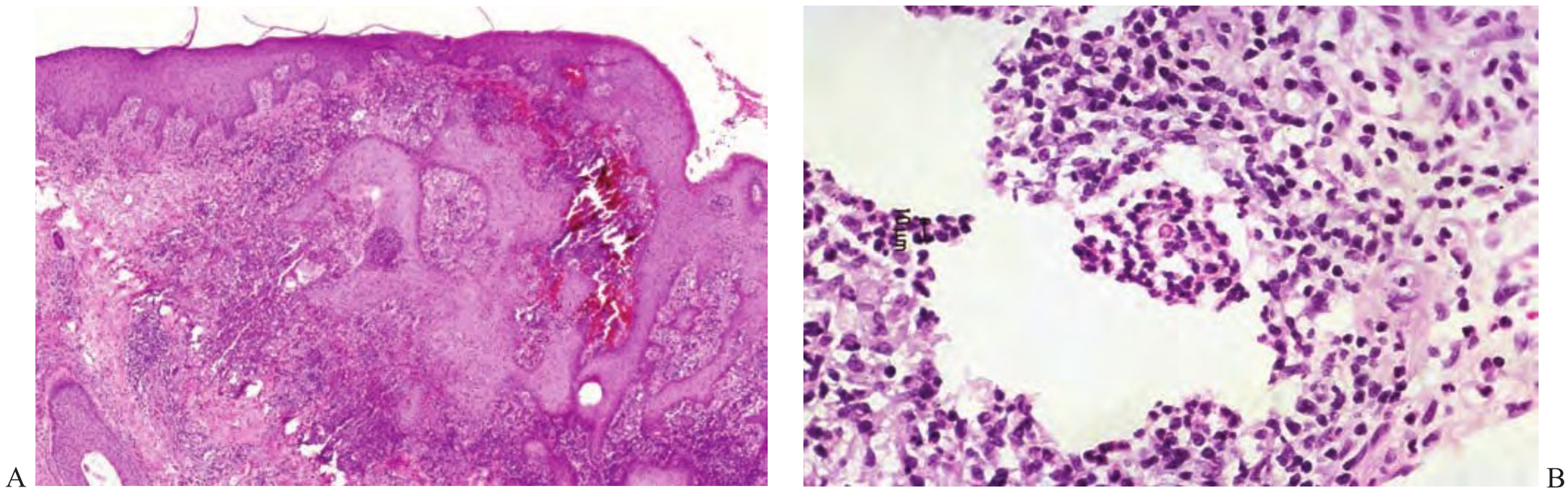


FIGURE 23-18. Sporotrichosis. A: H&E stain shows pseudoepitheliomatous epidermal hyperplasia with microabscess formation. B: H&E stain shows a round spore, staining more darkly at the periphery than centrally, surrounded by a neutrophilic infiltrate.

tip; at 37°C, it grows as a yeast (197). At 39°C, there is no growth, a fact that has led to the use of local thermotherapy (196,199).

Differential Diagnosis. If the fungus is not found in sections, a diagnosis of sporotrichosis can only be suspected; however, it can be excluded in dubious cases by a negative cutaneous sporotrichin test, which is almost always positive except in cases of disseminated disease (196). The subcutaneous abscesses of tularemia and of infections with *Mycobacterium marinum* may have the same histologic appearance as the cutaneous and subcutaneous nodules and abscesses of sporotrichosis and must be excluded.

EUMYCETOMA (FUNGAL MYCETOMA)

A number of fungi and filamentous bacteria may cause an indolent local infection, characterized by induration associated with draining sinuses. These diverse agents may have clinically identical presentations that have been collectively called *mycetoma* (205). The term *actinomycetoma* refers to such infections when filamentous bacteria cause them; they are discussed further in Chapter 21. *Eumycetoma*, however, is caused by a group of true fungi with thick septate hyphae, including *Petriellidium boydii* (*Allescheria boydii*, *Pseudallescheria boydii*), *Madurella grisea*, and *Madurella mycetomatis* (206). Although much more common in tropical regions, eumycetoma is seen occasionally in the United States, where the most common cause is *P. boydii* (207). Differentiation between actinomycetoma and eumycetoma is important, because they respond to different treatments.

Eumycetoma is a persistent, invariably progressive local infection without a tendency for systemic spread. There is no obvious association with immunosuppression. The infection starts as a subcutaneous nodule(s) usually on the foot at a site of trauma; in the past, these infections were not uncommon in the Madras region of India, and thus the term *Madura foot* has been used synonymously with mycetoma (206). The nodules eventuate in abscesses and draining sinuses (Fig. 23-19A). Gradually, the muscles and tendons are damaged and osteomyelitis develops. Grossly visible "sulfur granules" or "grains," which are tightly knit clusters of organisms, are discharged from the draining sinuses. These granules are black in cases of eumycetoma caused by the dematiaceous fungi *M. grisea* and *M. mycetomatis* (208,209), whereas they are colorless in eumycetoma caused by *P. boydii* (210).

Histopathology. Histologic examination of the indurated skin shows extensive granulation tissue containing abscesses that may lead into sinuses. The granulation tissue is nonspecific in appearance. In the early phase of the disease, the tissue surrounding the abscesses is composed of lymphoid cells, plasma cells, histiocytes, and fibroblasts, whereas in the late phase, fibroblasts may predominate. The diagnosis can be established only by finding the "sulfur granules" (Fig. 23-19B). Because they occur almost exclusively in abscesses or sinuses, an area containing purulent material should be chosen as the site for biopsy.

Most granules measure between 0.5 and 2.0 mm in diameter and are thus large enough to be visible macroscopically (208). The granules of both eumycetoma and actinomycetoma stain with the PAS reaction and methenamine silver (Fig. 23-19C). Granules of eumycetoma are composed of septate hyphae 4 to 5 μm thick, whereas the granules of actinomycetoma usually consist of fine, branching filaments or bacillary forms that are only about 1 μm thick (209). A Gram stain aids in differentiating bacterial from fungal causes of mycetoma; the filaments of actinomycetoma are gram positive, whereas the hyphae in grains of eumycetoma are gram negative (211). The study of discharged granules crushed on a slide and stained with lactophenol blue also allows differentiation between the thin filaments of actinomycetoma and the thicker hyphae of eumycetoma (211).

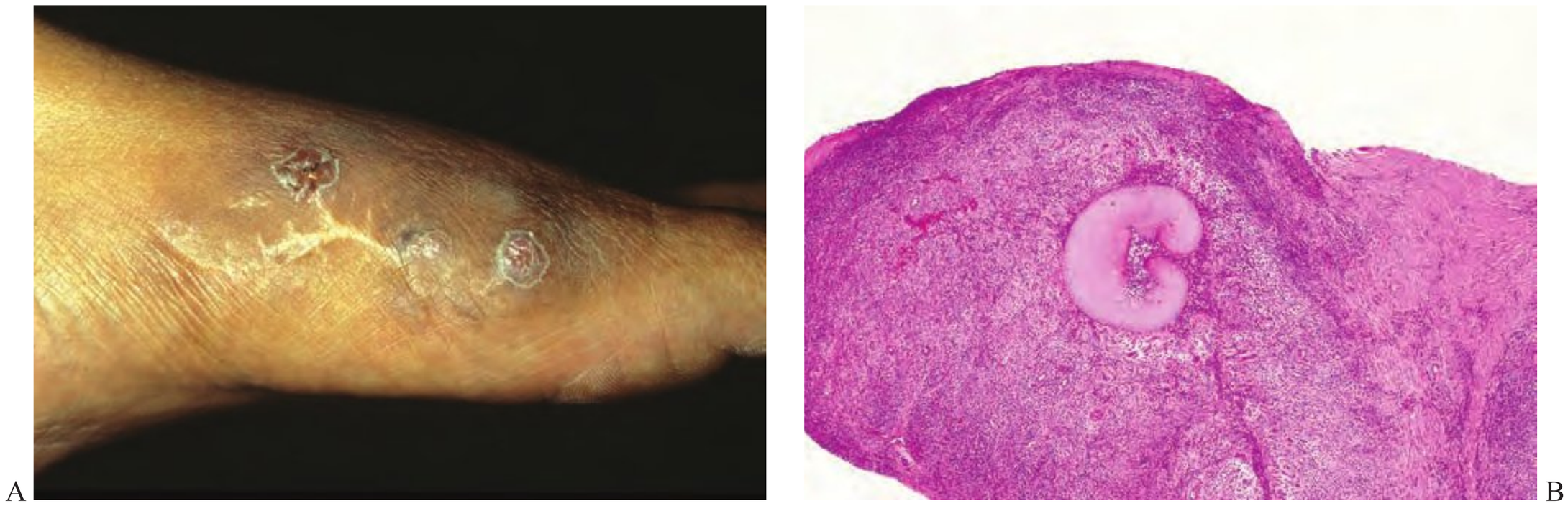


FIGURE 23-19. Eumycetoma. A: Ulcerated, indurated plaque of eumycotic mycetoma on the foot. B: H&E stain shows a "sulfur granule" in a purulent area of granulation tissue. C: The sulfur granule is composed largely of septate hyphae of P. boydii (GMS stain).

RHINOSPORIDIOSIS

Rhinosporidiosis is a chronic infection that is caused by *Rhinosporidium seeberi*. Rhinosporidiosis typically involves mucosal surfaces, most frequently the nasal mucosa, and may involve contiguous skin. This disease is seen primarily in India and Ceylon, but a number of cases have been seen in South America and a few in the United States (212).

The mode of transmission is not known. Lesions start as an often puritic papule, which grows into an erythematous polypoid mass that may cause obstruction of the nose and nasopharynx. Small cysts and pseudocysts develop and may discharge a combination of mucus, pus, and organisms, creating tiny white dots and giving lesions a characteristic strawberry-like appearance. Lesions of the ocular mucosa tend to be flatter, and skin lesions have a warty shape (212). Involvement of the genital mucosa has also been reported (213). Dissemination of the organism is extremely rare (214).

Histopathology. The epithelium is hyperplastic with papillomatosis and deep invaginations, some of which form pseudocysts (Fig. 23-20A). Numerous globular cysts of varying shape, representing sporangia in different stages of development, give the corium a distinctive "Swiss cheese" appearance. There is a surrounding dense, mixed inflammatory infiltrate with lymphocytes and histiocytes, including occasional giant cells, plasma cells, neutrophils, and eosinophils.

R. seeberi is a large, endosporulating organism with a distinctive morphology that can usually be recognized in H&E-stained sections (Fig. 23-20B). Sporangia develop from individual spores about the size of an erythrocyte (215). The spores develop into small uninucleate cysts that enlarge and develop a chitinous, eosinophilic wall. With increasing size, nuclear divisions lead to the development of up to 16,000 spores in a sporangium. These distinctive structures may be 300 μm in diameter. Rupture of the cyst or release of the spores through a pore in the cyst wall results in individual spores into the surrounding tissue. The organisms stain with the PAS reaction at all stages, but GMS and mucicarmine stains are not effective for organisms <100 μm in diameter (216).

Differential Diagnosis. The different clinical presentations of coccidioidomycosis and the smaller size of the spherical coccidioidal sporangia (<60 μm in diameter) allow for an easy distinction of that disease from rhinosporidiosis.

CUTANEOUS PROTOTHECOSIS

Prototheca is a genus of algae that causes cutaneous infections in humans. Discussion of *Prototheca* is included in this chapter because this organism may be isolated on Sabouraud's medium and has traditionally been discussed in mycology texts as well as because this text has no separate chapter for diseases caused by algae. Although there is one report of cutaneous infection in

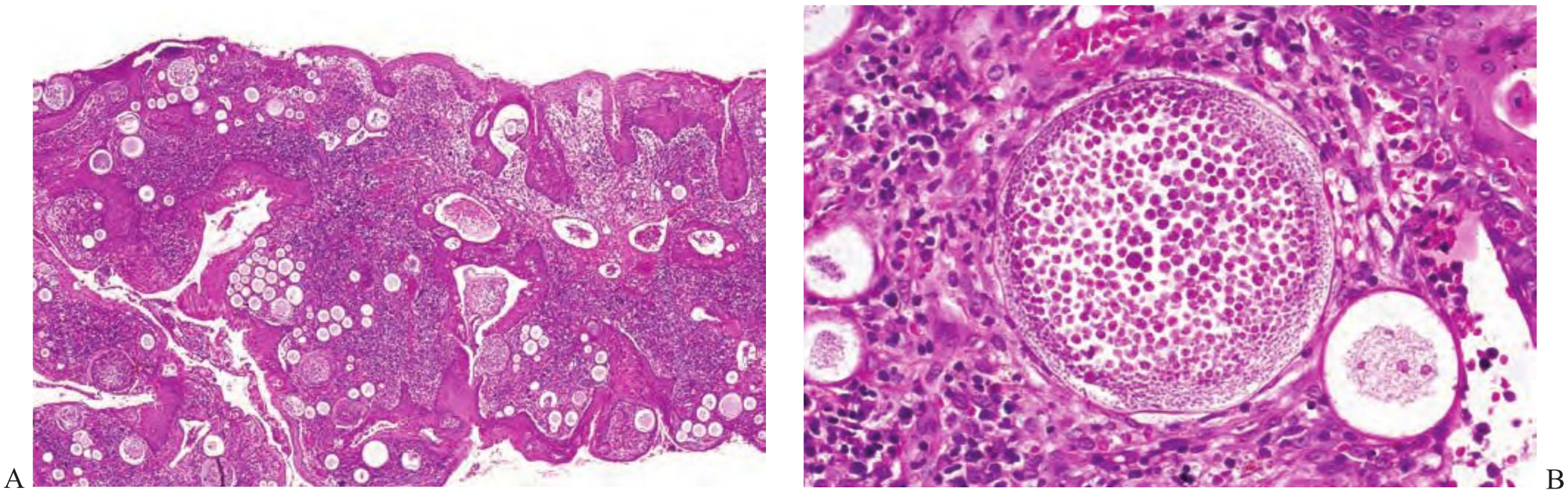


FIGURE 23-20. Rhinosporidiosis. A: H&E stain shows marked papillomatosis and deep invaginations of the nasal mucosa. B: A sporangium contains many individual spores (H&E stain).

a patient also infected with HIV (217), cutaneous protothecosis usually occurs in otherwise healthy persons following trauma and wound contamination with water (218). Lesions develop very slowly and may be single or multiple papules, plaques, or nodules with smooth, verrucous, or ulcerated surfaces (218–222).

Histopathology. The histologic appearance, like the clinical appearance, is not characteristic, so the diagnosis depends on the finding of the organisms. Usually, there is a mixed inflammatory infiltrate with areas of necrosis and fairly numerous giant cells (Fig. 23-21). In sections stained with H&E, the organisms stain faintly or not at all. On staining with PAS or silver methenamine, however, the organisms stain well and are seen both within giant cells and free in the tissue (219).

Individual organisms are spheric and measure 6 to 10 μm in diameter (222). However, as the result of septation, many contain endospores and then are considerably larger. Further subdivision of daughter cells within the parent cell leads to the formation of "sporangia" containing as many as 50 cells lying clustered together as morula-like structures (218). Ultimately, such a sporangium breaks down into individual organisms.

Pathogenesis. *Prototheca* is a genus of saprophytic, achloric (nonpigmented) algae. These organisms reproduce asexually by way of internal septation, producing autospores identical to the parent cell. *Prototheca* forms creamy, yeastlike colonies on Sabouraud's medium between 25°C and 37°C. These colonies become visible within 48 hours (219).

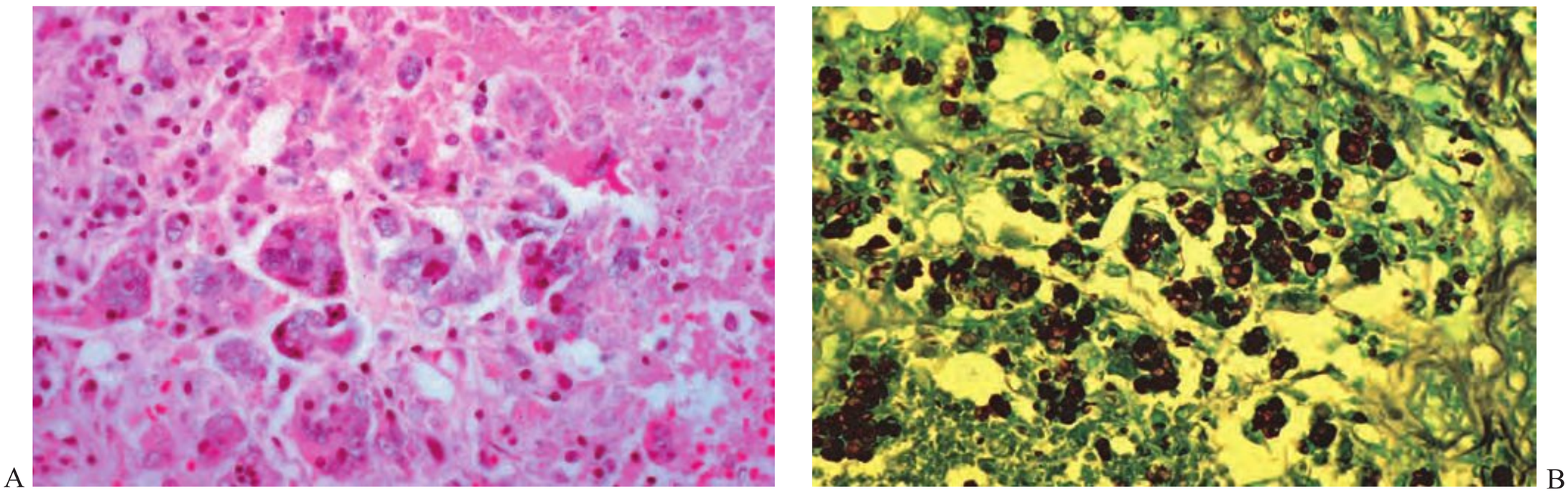


FIGURE 23-21. Protothecosis. A: H&E stain shows individual cells and clusters of organisms within giant cells. B: The morula-like clusters in multinucleated giant cells are highlighted by silver impregnation (GMS stain).

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CHAPTER 24

Klaus Sellheyer
Eckart Haneke

Protozoan Diseases and Parasitic Infestations

The increase in international travel from endemic regions has brought diseases to North America and Europe that were once thought of as being confined to tropical countries. Furthermore, HIV infection has become an important cofactor in acquiring diseases that are normally rare in the developed world. In particular, leishmaniasis is considered to be an emerging opportunistic disease particularly in HIV-infected individuals (1). Immigrants from Asia, Africa, and South America represent another contingent of patients afflicted by diseases that are normally not prevalent in the United States and Western Europe.

LEISHMANIASIS

Leishmaniasis is a protozoan disease with a prevalence of 12 million cases and an incidence of almost 2 million new cases worldwide, making it, together with malaria, helminthic infestations of the gastrointestinal tract, and HIV infection, one of the most common infectious diseases worldwide (2). The inciting organism belongs to the order Trypanosomatida, which comprises two genera pathogenic to humans: *Trypanosoma* and *Leishmania* (3).

Leishmania species primarily affect cells of monocyte-macrophage lineage and exist in two forms during their life cycle: a flagellar (promastigote) and an aflagellar (amastigote) stage. The former is found in the intestines of sandflies, which function as the arthropod vector to *Leishmania* species. In the Old World the sand flies belong to the genus *Phlebotomus*, and in the New World to the genera *Lutzomia* and *Psychodopygus* (3). After the promastigotes enter the skin of the human host via the bite of infected sandflies, they transform into amastigotes within histiocytes. If the histiocytic response to *Leishmania* species remains confined to the skin, cutaneous lesions develop; if dissemination of the protozoa occurs, internal organs become involved.

At the center stage of all of the different forms of leishmaniasis is a disruption of macrophage activation with the subsequent avoidance of intracellular killing mechanisms (4). The parasites do so by inhibiting lysosomal phosphatases and protein kinase C. Substrates of protein kinase C are involved in cytoskeletal rearrangements and vacuolar trafficking and are thus important in cellular signaling. *Leishmania* species also inhibit the synthesis of proinflammatory and increase the production of antiinflammatory cytokines, thereby preventing their elimination from the human host.

Classification of Leishmaniasis

The former simplistic classification dividing leishmaniasis into cutaneous, mucocutaneous, and visceral forms has been abandoned in favor of a classification that recognizes the overlap in the clinical spectrum of the different types of leishmaniasis (1,5–8):

- Localized (acute) cutaneous leishmaniasis
- Diffuse (acute) cutaneous leishmaniasis (= disseminated anergic cutaneous leishmaniasis)
- Chronic cutaneous leishmaniasis (including leishmaniasis recidivans or lupoid leishmaniasis)
- Post–kala-azar dermal leishmaniasis
- Mucocutaneous leishmaniasis
- Visceral leishmaniasis
- Viscerotropic leishmaniasis

Each form of leishmaniasis is associated with a different type of *Leishmania* species and has a specific predilection for a geographic location (Table 24-1).

Localized (Acute) Cutaneous Leishmaniasis

Representing the most common form of skin involvement, localized acute cutaneous leishmaniasis affects primarily the exposed parts of the body, such as face, scalp, and arms (9–11). It appears initially as a painless, erythematous papule that enlarges over a period of 4 to 12 weeks to a nodule or a plaque measuring up to 2 cm in diameter (Fig. 24-1A). Ulceration is common. After several months the lesion spontaneously regresses, starting from the center and progressing outward. The end stage is represented by a scar accompanied by hypo- or hyperpigmentation (1,5,8,12). New World leishmaniasis commonly presents with a single lesion and Old World leishmaniasis with multiple ones (1,5).

Histopathology. The characteristic changes are noted throughout the dermis and consist of a dense, diffuse infiltrate of histiocytes admixed with lymphocytes and few plasma cells (Fig. 24-1B) (1,5,7–13). Eosinophils and neutrophils are rare;

TABLE 24-1 Leishmania Species and Geographic Locations Associated with the Different Clinical Forms of Leishmaniasis

Form of disease	New World parasite	Old World parasite	Geographic location
Localized (acute) cutaneous leishmaniasis	L b. braziliensis, L b. guyanensis, L b. panamensis, L m. mexicana, L m. amazonensis, L donovani chagasi	L major, L tropica, L aethiopica, L infantum	North Africa, India, Middle East, China, southern Russia, Pakistan, Mediterranean, Central and South America, Texas, Caribbean region
Diffuse (acute) cutaneous leishmaniasis	L m. amazonensis, L mexicana, L m. pifanoi	L aethiopica	Venezuela, Bolivia, Mexico, Dominican Republic, Brazil, Ethiopia
Leishmaniasis recidivans	L braziliensis	L tropica	Central and South America, Middle East
Post–kala-azar dermal leishmaniasis	L donovani chagasi	L donovani, L tropica L infantum	India, Bangladesh, East Africa, Sudan
Mucocutaneous leishmaniasis	L b. braziliensis		Brazil, Venezuela, Peru, Ecuador, Colombia
Visceral leishmaniasis	L donovani chagasi	L donovani, L infantum, L tropica	China, India, Bangladesh, Asia, Sudan, Africa, eastern Russia, Mediterranean, South America
Viscerotropic leishmaniasis		L tropica	Iraq, Kuwait

Note: New World parasites have a species and subspecies name; Old World parasites have only a species name.
L b. braziliensis, Leishmania braziliensis braziliensis; L m. mexicana, Leishmania mexicana mexicana.
Adapted and slightly modified from Grevelink SA, Lerner EA. Leishmaniasis. J Am Acad Dermatol 1996;34:257.

the latter are more numerous if the lesion is ulcerated (12). The cytoplasm of the histiocytes is filled with numerous dull blue-gray, round to oval bodies measuring 2 to 4 μm in diameter and exhibiting a round basophilic nucleus and a rod-shaped paranuclear kinetoplast, a specialized mitochondrial structure containing extracellular DNA (Fig. 24-1C). These intracellular bodies stain red or dark blue with Giemsa but not with periodic acid-Schiff (PAS) and Grocott's methenamine silver (GMS) because of a lack of a capsule and represent amastigotes, known as Leishman-Donovan bodies. When numerous, they can also be seen extracellularly. The number of leishmania organisms decreases with time and is often inversely related to the amount of plasma cells.

The epidermal changes are nonspecific and consist of hyperkeratosis, parakeratosis, and epidermal atrophy or hyperplasia (1,5,7,9,11,13). Ulceration is also noted. The basal cell layer may show hydropic degeneration and the follicular ostia may display plugging with compact orthokeratotic material (13).

Differential Diagnosis. The organisms of histoplasmosis do not exhibit a kinetoplast and do stain with (PAS) and (GMS) stains. *Klebsiella rhinoscleromatis*, the inciting agent of rhinoscleroma, also resides in macrophages and measures 2 to 3 μm in diameter. In contrast to leishmaniasis, rhinoscleroma reveals a large number of plasma cells with formation of Russell bodies. Granuloma inguinale, caused by *Calymmatobacterium granulomatis*, displays numerous small abscesses throughout the inflammatory infiltrate (see Chapters 21 and 23).

Diffuse (Acute) Cutaneous Leishmaniasis

Diffuse acute cutaneous leishmaniasis, also known as disseminated anergic cutaneous leishmaniasis, is a rare variant of localized cutaneous leishmaniasis and is due to a lack of a *Leishmania*-specific cellular immune response (14). It begins as a single lesion and then spreads diffusely all over the body, characteristically as nonulcerated nodules, often involving upper and lower extremities, buttocks, and face (Fig. 24-2) (1,5,14). In atypical cases ulceration of the nodules is noted (15).

Histopathology. The histopathologic changes of the individual lesions are the same as those seen in localized acute cutaneous leishmaniasis except for a larger number of Leishman-Donovan bodies and a relative lack of accompanying lymphocytes

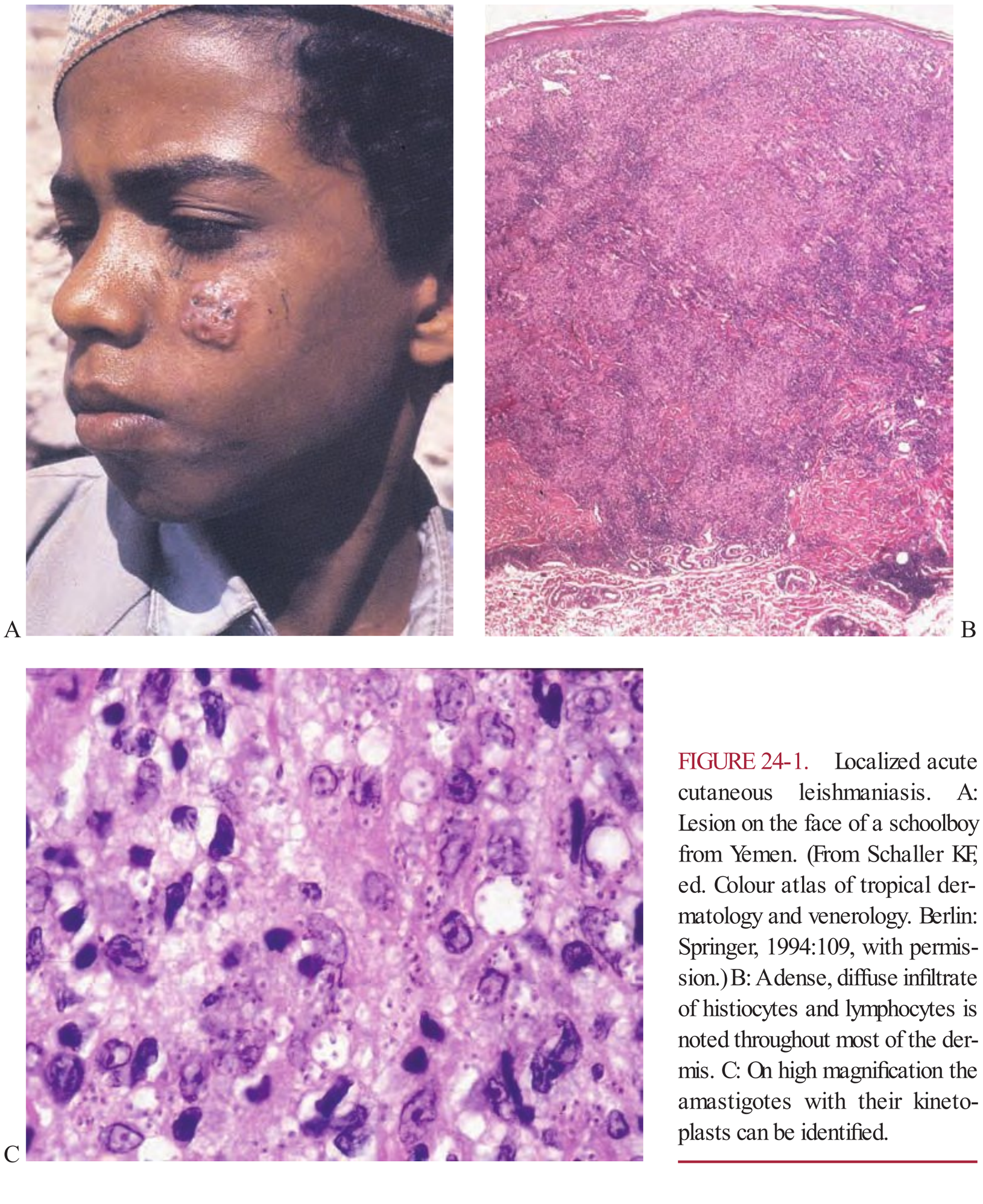


FIGURE 24-1. Localized acute cutaneous leishmaniasis. A: Lesion on the face of a schoolboy from Yemen. (From Schaller KF, ed. Colour atlas of tropical dermatology and venerology. Berlin: Springer, 1994:109, with permission.) B: A dense, diffuse infiltrate of histiocytes and lymphocytes is noted throughout most of the dermis. C: On high magnification the amastigotes with their kinetoplasts can be identified.

(1,5,14,16). In the rare ulcerated lesions of diffuse cutaneous leishmaniasis, eosinophils are predominant within the inflammatory infiltrate and reveal ultrastructural characteristics of parasitocidal activity (15).

In reactivated, previously dormant leishmaniasis in a kidney transplant recipient, a subcutaneous inflammatory infiltrate with numerous intracellular amastigotes was seen; the dermis was not involved (17).

Chronic Cutaneous Leishmaniasis

If the lesions do not resolve within 1 to 2 years, the condition is termed chronic cutaneous leishmaniasis (8,18). Two subtypes are noted: nonhealing chronic cutaneous leishmaniasis and leishmaniasis recidivans (the latter is also called lupoid leishmaniasis, relapsing chronic cutaneous leishmaniasis, or recurrent cutaneous leishmaniasis) (18–20). In the former the original lesion of localized (acute) cutaneous leishmaniasis persists, clinically presenting as an erythematous plaque of several years' duration and no evidence of healing (18). Leishmaniasis recidivans refers to the appearance of new lesions in the center or at the periphery of an atrophic scar derived from a previous lesion of localized (acute) cutaneous leishmaniasis (5,18,19). It carries great clinical resemblance to lupus vulgaris and presents with erythematous papules, often coalescing into crust-covered plaques, in association with a scar. The face is the area of predilection (19,20). It is either due to reactivation of persistent organisms or exogenous reinfection (5).

Histopathology. Both subtypes of chronic cutaneous leishmaniasis reveal essentially the same histopathologic changes, except for the presence of scar tissue in leishmaniasis

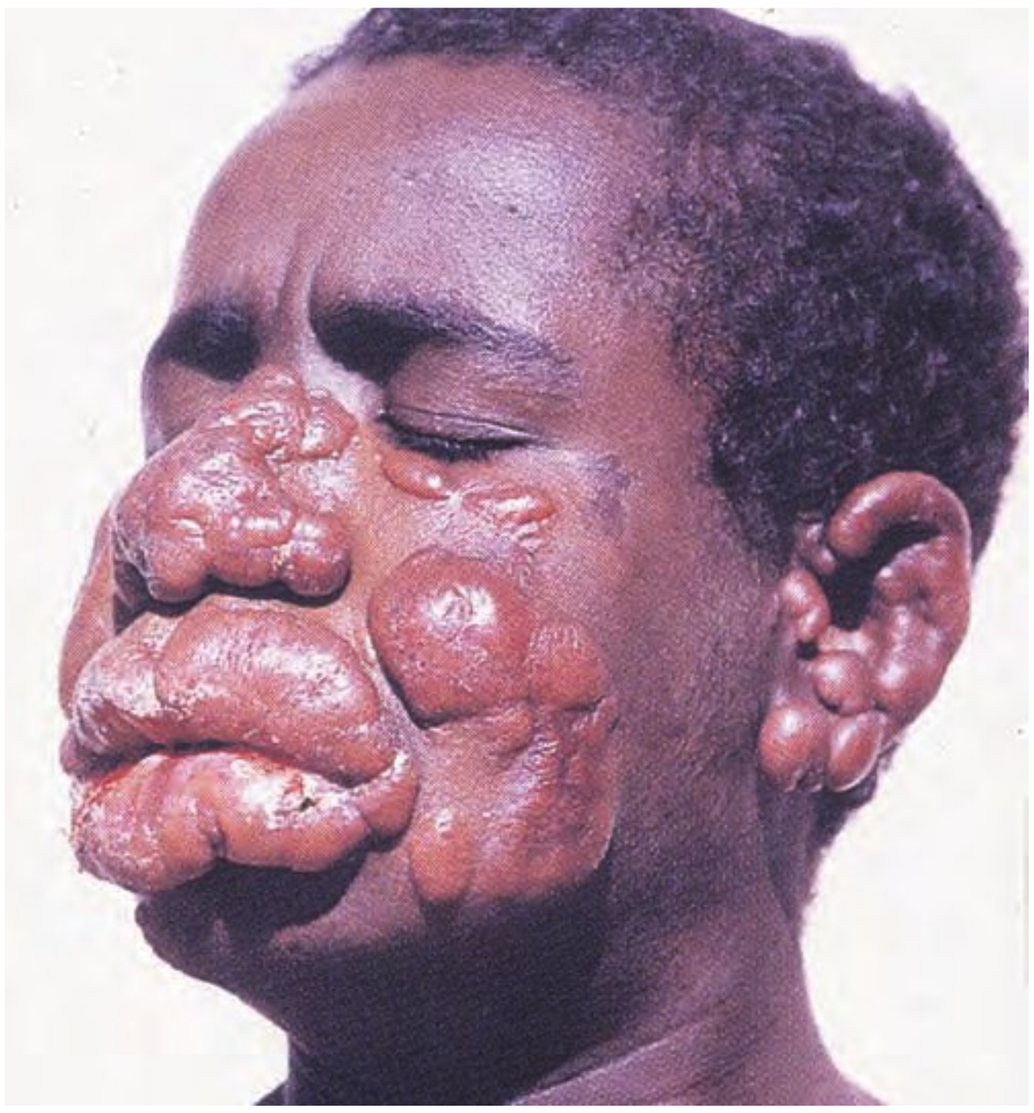


FIGURE 24-2. Diffuse acute cutaneous leishmaniasis. Ethiopian patient with pseudolepromatous appearance. (From Schaller KF, ed. Colour atlas of tropical dermatology and venerology. Berlin: Springer, 1994:113, with permission.)

recidivans in contrast to nonhealing chronic cutaneous leishmaniasis (19).

The histopathologic hallmark of chronic cutaneous leishmaniasis is a dense, diffuse, or nodular infiltrate composed of epithelioid cell granulomas within the superficial and deep dermis (7,13,20–22). The granulomas are tuberculoid in nature, made up of epithelioid histiocytes and Langhans giant cells surrounded by lymphocytes and plasma cells. Necrosis at the center of the granulomas is exceedingly rare (7,13,20,22), although it is occasionally documented (20). Leishman-Donovan bodies are either absent or very small in number. There is an inverse relationship between the number of organisms and the age of the lesion (23). The epidermal changes are nonspecific.

Differential Diagnosis. Other granulomatous dermatitides, especially lupus vulgaris, have to be differentiated from chronic cutaneous leishmaniasis (20,21). This may require the use of ancillary techniques such as immunohistochemistry with *Leishmania*-specific antibodies (24) or the polymerase chain reaction (25).

Post–Kala-azar Dermal Leishmaniasis

Post–kala-azar dermal leishmaniasis occurs 1 to 5 years after successful treatment of visceral leishmaniasis (1,5,8,18). It presents initially as hypopigmented macules over the trunk and extremities. The macules become progressively erythematous and evolve into nonulcerated papules and nodules with marked involvement of the face, clinically resembling lepromatous leprosy (1,5,8,18,26,27). The human host is apparently able to confine *Leishmania* to the skin but cannot eradicate the organisms from the body (26).

Histopathology. Reports on the histopathology of post–kala-azar dermal leishmaniasis are sparse. Hypopigmented macules display a superficial perivascular lymphocytic infiltrate with admixed plasma cells without evidence of granuloma formation (26). The amount of epidermal melanin is decreased (7).

The nonulcerated papules and nodules show a dense, diffuse infiltrate composed of histiocytes, lymphocytes, and plasma cells within the dermis with sharply defined margins and a narrow grenz zone (26,27). Granulomas are not reported, and organisms are sparse. This is in contrast to earlier studies, which described the presence of well-formed epithelioid cell granulomas in nodular lesions of post–kala-azar dermal leishmaniasis (28,29). The overlying epidermis is often atrophic, and the hair follicles show prominent keratotic plugging (27).

Mucocutaneous Leishmaniasis

Mucocutaneous leishmaniasis, most commonly seen in South America, affects the upper respiratory tract and usually develops subsequently to healed localized (acute) cutaneous leishmaniasis (1,5,18,23). The mucosal lesions usually appear within 2 years of the initial skin involvement but may take as long as 30 years to develop (23). They often begin in the nasal septum, which becomes inflamed and later perforates. The lips (especially the upper lip), oral cavity, the pharynx, and even the trachea and bronchi can become involved, imposing a severe life-threatening condition. South American mucocutaneous leishmaniasis probably develops secondary to hematogenous or lymphatic dissemination from primary cutaneous lesions or occasionally from direct extension of nearby skin lesions (5).

Histopathology. The histopathologic changes of mucocutaneous leishmaniasis are subdivided into an edematous, a granulomatous proliferative, and a granulomatous necrotizing stage (30). In the early edematous stage parasites are scanty, a lymphohistiocytic infiltrate with admixed plasma cells in the superficial and deep dermis is noted, and the overlying epidermis is thin. When the patient develops proliferative lesions, parasites become obvious, tuberculoid granulomas can be seen, and pseudocarcinomatous epidermal hyperplasia develops. These changes characterize the granulomatous proliferative phase. In clinically destructive lesions areas of necrosis with numerous neutrophils and abundant Leishman-Donovan bodies constitute the granulomatous necrotizing phase.

Visceral Leishmaniasis

Visceral leishmaniasis is a systemic disease characterized by fever, lymphadenopathy, hepatosplenomegaly, ascites, pancytopenia, and emaciation (1,5,18). The Indian name *kala-azar*

(meaning "black fever") refers to the diffuse darkening of the skin, most pronounced on the face, hands, and feet, which is seen, however, only in a small proportion of patients and peculiarly confined to those from the Indian subcontinent (18). The initial cutaneous lesion of visceral leishmaniasis—the leishmanioma—is rarely seen. Although generally being devoid of cutaneous involvement during the course of the active visceral disease, patients coinfected with HIV can present with skin lesions. The lesions comprise erythematous papules, often confluent to plaques, and, less often, hypo- and hyperpigmented macules with a tendency to localize symmetrically on acral zones (31). These lesions have to be differentiated from those seen in post–kala-azar dermal leishmaniasis, which appear after the patient has been successfully treated for visceral leishmaniasis.

Histopathology. The cutaneous lesions in HIV-infected patients consist of a perivascular infiltrate within the superficial dermis composed of lymphocytes and histiocytes with numerous intracytoplasmic organisms within the latter (31). Leishman-Donovan bodies are also found extracellularly (31,32) and, in one case in eccrine sweat glands, suggesting transepithelial elimination (32). Parasitization of Kaposi's sarcoma by *Leishmania* species (32,33) and a leishmanial cutaneous spindle cell pseudotumor (32,34) have also been reported.

Viscerotropic Leishmaniasis

Originally thought of as causing cutaneous lesions only, *L. tropica* was recently found as the inciting agent of a visceral form of leishmaniasis in veterans of Operation Desert Storm (35). The condition was termed viscerotropic leishmaniasis. No skin involvement is documented.

ACANTHAMOEBIASIS

Among the three free-living genera of amoebae capable of producing cutaneous lesions (*Acanthamoeba* species, *Entamoeba histolytica*, and *Balamuthia mandrillaris*), acanthamoebiasis recently surfaced as the most common one, seen mostly in conjunction with the AIDS epidemic. It also causes keratitis in nonimmunocompromised individuals who wear soft contact lenses. Granulomatous amebic encephalitis, a fatal disease, is another manifestation of *Acanthamoeba* species infection; like cutaneous acanthamoebiasis, it affects primarily immunoincompetent patients (36–38). In disseminated acanthamoebiasis, other organ systems, such as bones (causing osteomyelitis), can be affected (39).

Acanthamoeba species exist in two forms. The amebic cysts, measuring 13 to 19 μm in diameter (36), are resistant to desiccation and excyst to trophozoites only in a favorable environment such as the human host; the second form, between 10 and 20 μm in size (40), reveals slender acanthopodia for slow movement and represents the infectious and invasive form of *Acanthamoeba* species (37).

The cutaneous lesions in acanthamoebiasis are nonspecific and consist of papules, nodules, and chronic, nonhealing ulcers, tender or nontender, ranging from 0.5 to 3 cm in diameter, with the ulcers being sometimes larger (37–43). The skin may serve either as the initial port of entry or may become secondarily involved via hematogenous spread (42,43).

Histopathology. Depending on the number of organisms, a nodular or diffuse inflammatory infiltrate composed mostly of neutrophils and histiocytes admixed with extensive tissue necrosis is noted, sometimes evolving into abscess formation (36,39,42). Cutaneous lesions can also present under the histopathologic picture of a leukocytoclastic vasculitis with fibrin deposits within the vessel wall and leukocytoclasis (36,40–42). Lobular panniculitis with necrotizing vasculitis is another form of presentation (38).

Mixed within the inflammatory infiltrate are the round trophozoites projecting acanthopodia and revealing a vacuolated cytoplasm with a centrally placed nucleus and a single prominent nucleolus (Fig. 24-3). Despite often being numerous, the trophozoite forms are inconspicuous and can be missed easily, closely resembling macrophages (37,39,42). The cyst forms, also being present, display a double wall; the outer wall is wavy and wrinkled in appearance, and the inner wall is shallow and scalloped surrounding the cytoplasm. The cyst walls stain with PAS and GMS (39,42).

Differential Diagnosis. The yeast forms of *Blastomyces dermatitidis* are slightly smaller and have characteristically thick cell walls and broad-based buds; often an overlying epidermal hyperplasia with neutrophilic microabscesses is present (39,42). The cysts of *Entamoeba histolytica* are negative for GMS and do not display an undulating double membrane (42).

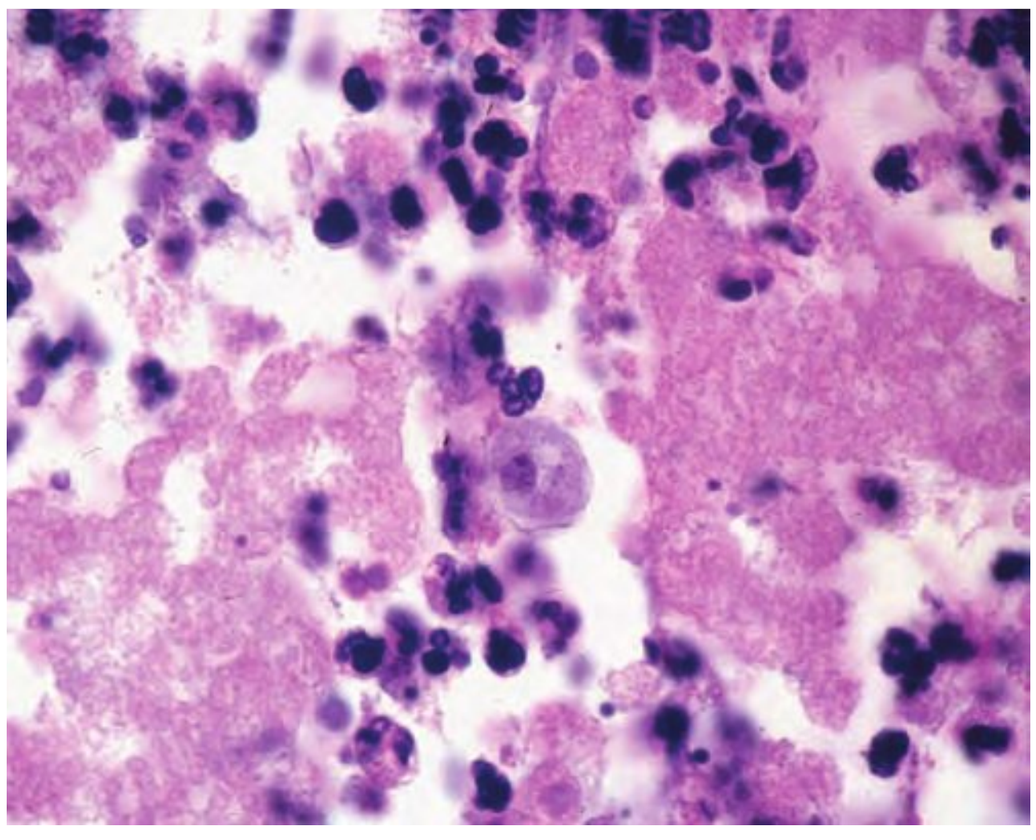


FIGURE 24-3. Acanthamoebiasis. In the center the trophozoite with a large nucleus and basophilic cytoplasm is noted among necrotic debris. (Specimen courtesy of Khalil G. Ghanem, MD, Johns Hopkins Hospital, Baltimore, Maryland.)

SCABIES

Acarid mites produce several skin manifestations in humans, the most common one represented by scabies, which is caused by the eight-legged itch mite *Sarcoptes scabiei* var. *hominis*, also referred to as *S. sarcoptes scabiei*. Animal pathogenic mites also affect the skin, although only transiently because the mites do not survive for an extended period of time (3).

Burrows are the pathognomonic lesions of scabies and are found mostly in the florid, papulovesicular type of sarcoptic acariasis (Fig. 24-4A). They are produced by female mites and occur mainly on the palms and plantae, the palmar and lateral aspects of the fingers and toes, the interdigital spaces, the flexor surfaces of the wrists, the nipples of women, the genitals of men, and, to a lesser extent, on the buttocks and axillae. Characteristically, the head is spared, except in newborns and infants (44). The burrows appear as fine, tortuous, blackish threads a few millimeters long. A vesicle may be visible near the blind end of the burrow. The mite is situated in this vesicle and may be visible as a tiny gray speck by dermatoscopy. Although pathognomonic, the burrow is not the most common lesion seen in scabies. Small, erythematous, often excoriated papules are more frequent (44).

In some patients, itching nodules persist for several months after successful treatment, and therefore are named nodular scabies or persistent scabietic nodules. They are found most commonly on the scrotum and are believed to result from a prolonged response to persistent scabies antigens (45).

In a third, rare variant, the so-called Norwegian scabies or crusted scabies, innumerable mites are present. Patients with this variant show widespread erythema, hyperkeratosis, crusting, nail thickening, and subungual hyperkeratosis but no obvious burrows.

Histopathology: A definitive diagnosis of scabies can be made only by demonstration of the mite or its products. A very superficial epidermal shave biopsy of an early papule or, preferably, of an entire burrow may be carried out with a #15 scalpel blade (46). Local anesthesia is not required. The biopsy specimen is placed on a glass slide, and a drop of immersion oil and then a cover slip are placed on top of it (Fig. 24-4B). This technique yields a higher percentage of positive preparations than the often performed mere scraping of a suspicious lesion with a scalpel blade.

Histologic examination of a specimen containing a burrow reveals that the burrow in almost its entire length is located within the horny layer (47). Only the extreme, blind end of the burrow, where the female mite is situated, extends into the stratum malpighii (48). The mite has a rounded body and measures about 350 to 450 μm in length and 250 to 350 μm in width (Fig. 24-4C) (3).



FIGURE 24-4. Scabies. A: Numerous pustules and papules are noted on the back of the foot and the toes of this infected child. B: Adult female mite found in skin scrapings. C: The female mite is located in the upper portion of the epidermis underneath the stratum corneum.

In the papulovesicular form of scabies, spongiosis is present in the stratum malpighii near the mite to such an extent that formation of a vesicle is often the result. Even if no mite is found in the sections, the presence of eggs containing larvae, of egg shells, or of fecal deposits (scyballa) within the stratum corneum is indicative of scabies (47,49). The dermal infiltrate in sections containing mites shows varying numbers of eosinophils.

In nodular or persistent nodular scabies, there is a dense, chronic inflammatory, often pseudolymphomatous infiltrate in which many eosinophils may be present. Vasculitis is considered by some as being frequent (49) but by others as representing a rather uncommon event (45). These different findings may be related to the duration of the scabietic nodules and the timing of the biopsy (45). The nodules are rich in indeterminate cells, sometimes misleading to the diagnosis of Langerhans cell histiocytosis based on light microscopy and immunophenotyping alone (50). Atypical mononuclear, $CD30^+$ cells may be found (51), and in some instances, the nodules show, as in persistent arthropod bites or stings (see later discussion), a histologic picture resembling that of lymphoma (52). Viable mites are hardly ever found in the nodules. However, mite parts are seen in up to 22% of cases (45).

In Norwegian scabies, the thickened horny layer is riddled with innumerable mites, so that nearly every section shows several parasites (49).

Pathogenesis. Earlier scanning electron microscope studies revealed the keratinocytes around the burrow to be compacted, indicating that the mite physically forces its way in between the keratinocytes rather than chewing a passage (48). More recent studies, however, also using transmission electron microscopy, have found that the secretion of cytolytic substances by the mite as a contributing factor in advancing the parasite body through the skin in addition to mere compression (53). The cellular damage was greatest around the body, especially the mite capitulum.

Both cell-mediated and humoral immune responses are activated in scabies. The acute eczematoid reaction in the epidermis is indicative of cell-mediated hypersensitivity. A role for humoral hypersensitivity is suggested by the presence of immunoglobulin M and the third component of complement in vessel walls (45,54). Besides being reported in mentally deficient and physically debilitated patients, Norwegian scabies is observed generally in patients who are severely compromised in their immune responses, including those with leukemia, lymphoma, and the acquired immunodeficiency syndrome (55).

HOOKWORM-RELATED CUTANEOUS LARVA MIGRANS

Cutaneous larva migrans is caused by skin-penetrating larvae of nematodes, most commonly of the cat and dog hookworm *Ancylostoma braziliense*, *A. caninum, A. tubaeformis, Uncinaria stenocephala*, and *Bunostomum phlebotomum* (3,56–58). Other forms of cutaneous larva migrans are caused by human- and animal-type *Strongyloides* species and are then known as larva currens (see later discussion). *Gnathostomum spinigerum* does not belong to the hookworm family but to the group of spiruriids and can also evoke cutaneous larva migrans (3).

Hookworm-related cutaneous larva is the most common variant. The infestation occurs through contact with soil contaminated with the larvae. The exposed parts of the body, most commonly the feet but also the buttocks in vacationers, for example, who lie nude in the sand, are most commonly involved. Creeping eruption represents the clinical manifestation of cutaneous larva migrans and is manifested by an irregularly linear, thin, raised, serpiginous burrow that is 2 to 3 mm wide (Fig. 24-5A). The larva moves a few millimeters per day. The eruption is self-limited because humans are accidental hosts, leaving the hookworm incapable of sexually maturing.

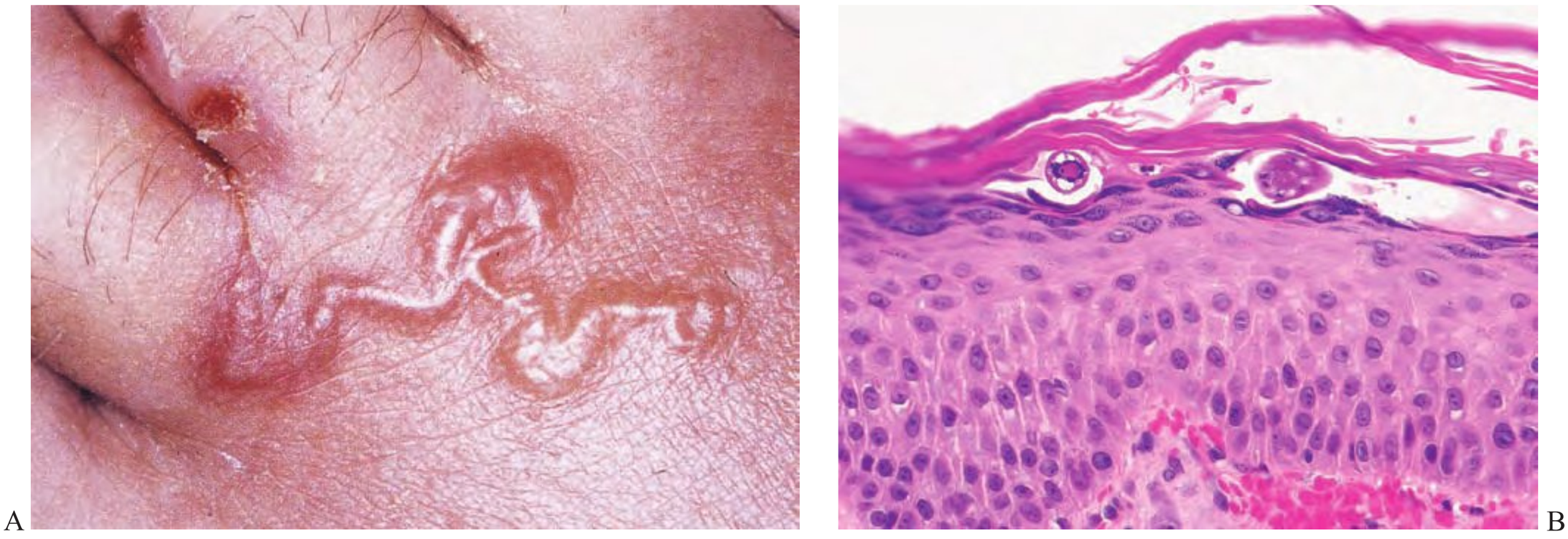


FIGURE 24-5. Cutaneous larva migrans. A: This curvilinear superficial burrow is the prototypical clinical manifestation. B: The organism is found underneath the stratum corneum in the upper portion of the stratum malpighii. (Specimen courtesy of Mandi Sachdeva, MD, and Rajiv Patel, MD, Cleveland Clinic Foundation, Cleveland, Ohio.)

Histopathology. The visible track does not correlate with the exact location of the larva and represents an inflammatory response composed of lymphocytes admixed with many eosinophils in the epidermis and upper dermis (3,57,58). The parasite is found 1 to 2 cm ahead of the visible track within a burrow located in the upper layers of the epidermis (Fig. 24-5B) (59). The lesion, aside from the larva, which is often not observed in the biopsies, shows spongiosis and intraepidermal vesicles in which necrotic keratinocytes can be seen. Numerous eosinophils in the superficial and deep reticular dermis are also commonly observed. A specific subtype of hookworm-related cutaneous larva migrans is known as hookworm folliculitis, in which the organism is associated with the hair follicle (60). It is important to recognize this variant because it is typically more difficult to treat.

Pathogenesis. The tissue penetration and the movements of the hookworm larvae within the epidermis are at least in part due to active production and secretion of proteases by the parasite (61). However, with the exception of hookworm folliculitis, these enzymatic activities are typically not adequate to allow penetration into the dermis, and hence the nematode is located in the upper portion of the epidermis (62).

STRONGYLOIDIASIS

Strongyloides stercoralis is a small intestinal nematode that is mainly endemic in the tropics and subtropics but is also found in the southeastern United States (especially eastern Kentucky, rural Tennessee, southern Virginia, and western North Carolina and South Carolina) (63). It is a geohelminth contracted by humans through cutaneous penetration of filariform larvae. A unique cycle includes traveling of the larvae via the venous system to the lungs, the patient coughing up and subsequently swallowing the larvae, and the parasite finding its final habitat in the small intestine (3). Three forms of strongyloidiasis can be delineated clinically: a not well characterized acute form, a chronic form, and a disseminated form (63). The chronic type presents with gastrointestinal and pulmonary symptoms and the pathognomonic larva currens. The latter represents a linear or serpiginous urticarial tract moving at a rate of 5 to 15 cm/hour caused by rapidly migrating larvae and is a subtype of cutaneous larva migrans (see previous discussion). It is believed to derive from autoinoculation with intestinal larva in the perineal area. The disseminated variant of strongyloidiasis occurs in the setting of severe immunodepression and is commonly fatal. Patients with advanced hyperinfection present with a purpuric skin eruption, often located periumbilically (64,65). Other cutaneous manifestations of strongyloidiasis include chronic urticaria, prurigo nodularis, and lichen simplex chronicus (64–66).

Histopathology. The serpiginous urticarial lesions believed to represent the migrating path of larvae are consistently negative for organisms (64). In contrast to hookworm-associated cutaneous larva migrans, the migratory tracts of larva currens are not located in the epidermis but in the dermis (3). It is only in the disseminated variant of strongyloidiasis that organisms can be found. They occur in the form of filariform larvae, measuring from 9 to 15 μm in diameter, which can be seen at all levels of the dermis, commonly associated with vascular damage producing purpura and petechiae, which are likely due to vascular damage by the filariform larvae migrating through the vessel wall (Fig. 24-6A–C) (64,65,68,69). These changes often do not provoke a dermal inflammatory response, probably because these patients are severely immunocompromised (64,65,70) (Fig. 24-6A). Changes of leukocytoclastic vasculitis are also not noted (68–70). Eosinophil-rich granulomata around *Strongyloides* larvae are, however, occasionally described (63,69).

SUBCUTANEOUS DIROFILARIASIS

Dirofilariasis is a zoonosis most commonly seen on the North American continent in the southeastern United States, with 75% of almost all cases being reported from Florida, which thus represents the epicenter of the infestation (71). The definite hosts of *Dirofilaria* species are dogs, cats, and raccoons, but hosts also include bears and porcupines (the two last ones are seen in the northern United States and Canada, from where dirofilariasis cases have also occasionally been reported).

Subcutaneous infection of humans by *Dirofilaria* species is rare and usually caused in North America by *D. tenuis, D. ursi*, or *D. subdermata* and in Europe, Africa, and Asia by *D. repens* (72,73). Mosquitoes transmit microfilariae from infected animals to humans, who act as a terminal host. In humans, the parasite never reaches the sexually mature adult stage capable of producing microfilariae, thereby rendering human-to-human transmission impossible (74).

Over the course of the infestation, one or, occasionally, several well-defined, firm, slightly red, tender nodules measuring 1 to 2 cm in diameter and clinically often mistaken for lipomas (72) develop in areas not covered by clothes, especially the head. Multiple lesions usually result from migration of a single worm (71).

Histopathology. At the center of the subcutaneous nodule, there is a tightly convoluted worm seen in multiple transverse and diagonal sections. Transverse sections measure from 50 to 300 μm in diameter, with the male worms being smaller than the female ones (71). The parasite possesses a thick, laminated cuticle displaying longitudinal ridges and transversal striae in *D. repens* and *D. tenuis* (Fig. 24-7) and a smooth cuticle in the dog heartworm *D. immitis*, the cause of pulmonary dirofilariasis in humans, allowing for species identification on histologic sections (72). It is imperative to thoroughly section the tissue block so as not to miss the helminth (75). The worm is embedded in eosinophilic material and surrounded by an inflammatory reaction that includes many eosinophils, mononuclear cells, and often foreign-body giant cells. Unlike fungal infections, fat necrosis is conspicuously absent (75). The extent of

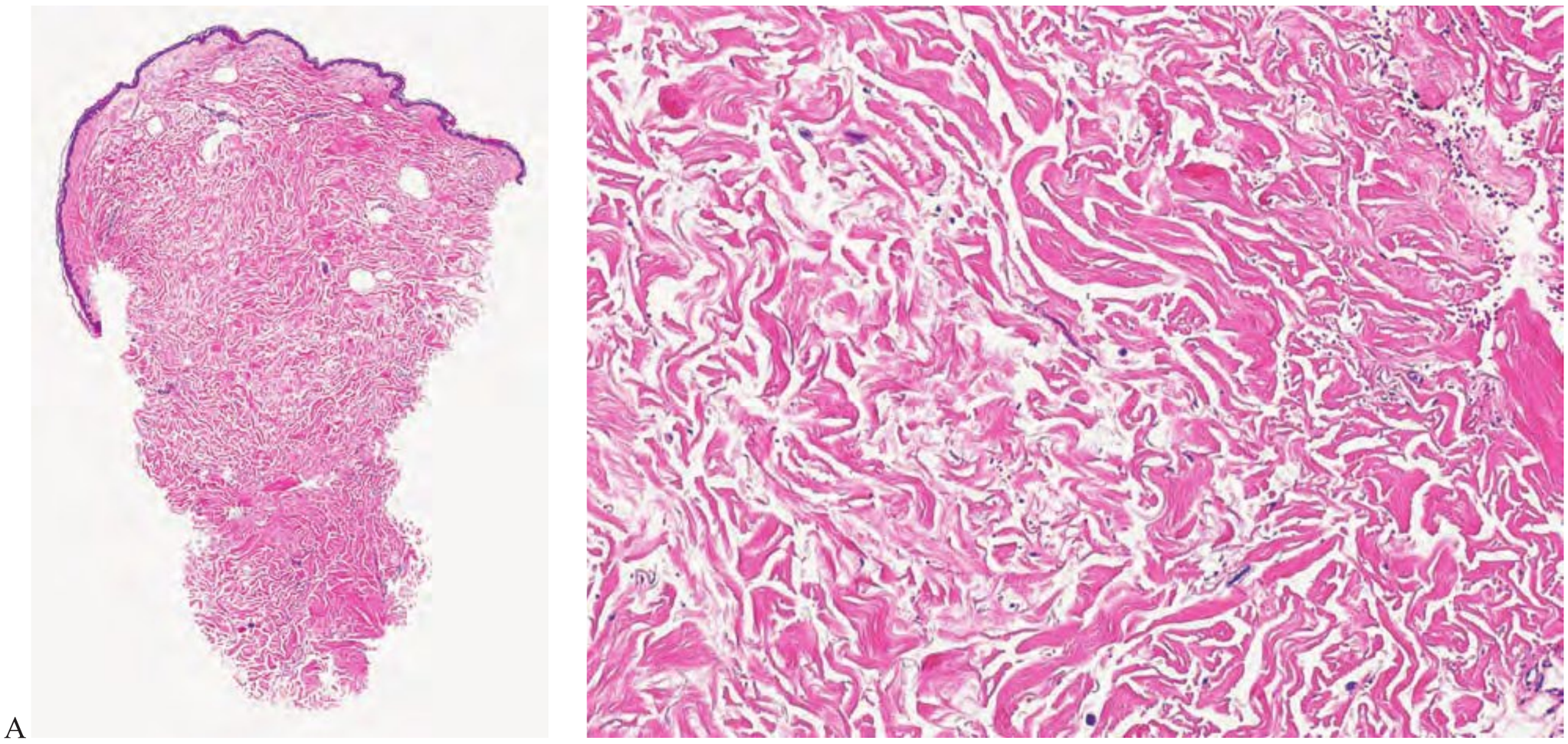


FIGURE 24-6. Strongyloidiasis. A: On scanning magnification, the punch biopsy from the periumbilical purpuric eruption shows no obvious histopathologic changes. The patient died from disseminated strongyloidiasias. B: On medium-power magnification, extravasated erythrocytes are noted (upper right corner) and basophilic linear and round structures become apparent. C: On rare occasions an entire nematode cut at the right angle is seen percolating between the collagen bundles. Note extravasated erythrocytes at the top of the micrograph. (A, B: Specimen courtesy of Arlene S. Rosenberg, MD, MetroHealth Medical Center, Cleveland, Ohio. C: Courtesy of Catherine M. Stefanato, MD, and Eduardo Calonje, MD, St. John's Institute of Dermatology, London, U.K.)

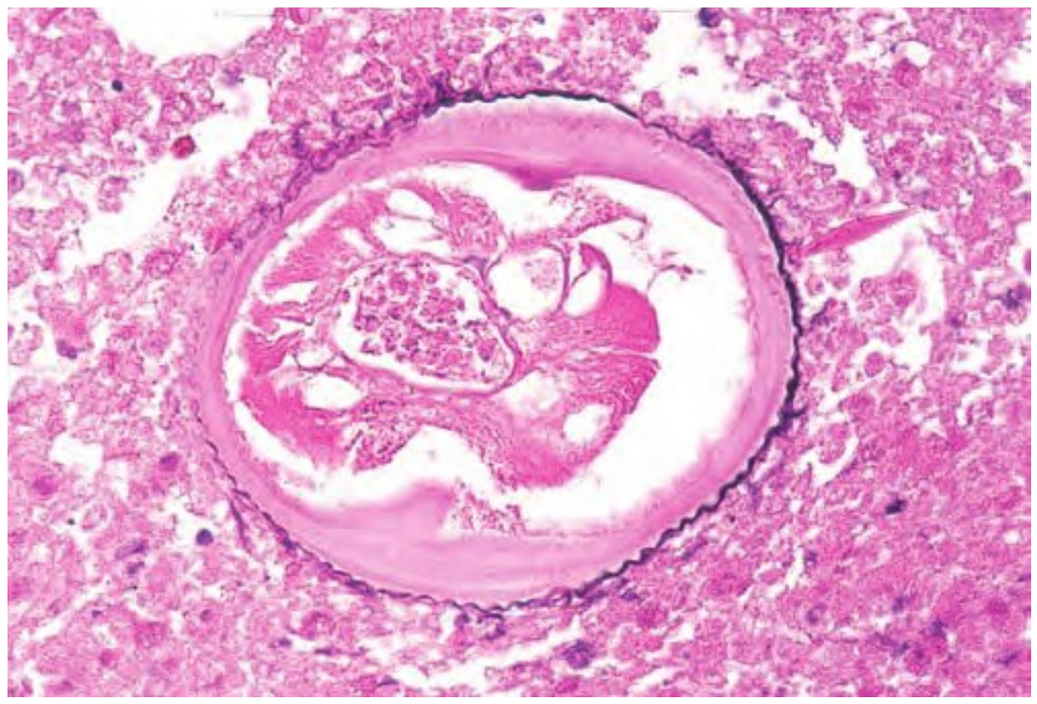


FIGURE 24-7. Dirofilariasis. The helminth is surrounded by necrotic debris within the subcutis. This organism represented Dirofilaria tenuis. (Courtesy of Yezid Gutierrez, MD, PhD, Cleveland Clinic Foundation, Cleveland, Ohio.)

fibrosis in the surrounding tissue correlates with the extent to which the parasite is degenerated (71).

Differential Diagnosis. Although having an identical clinical presentation to the infestation with *D. tenuis,* subcutaneous sparganosis, caused by the larval stage of the tapeworm *Spirometra* species, can affect any organ system. The larva in sparganosis has the typical histology of a pseudophyllidian tapeworm, consisting of a tegument, a cellular subtegument, and mesenchymal tissues with numerous large, longitudinal muscle cells and excretory canals (71). However, it still can be histologically mistaken for *Dirofilaria* species (71,75).

ONCHOCERCIASIS

Onchocerciasis is common in certain regions of Central America, Venezuela, and tropical Africa. It is transmitted by black flies of the genus *Simulium*, which breed in fast-flowing rivers;

through their probosces, the infective larvae of *Onchocerca volvulus*, a filarial nematode, enter the human skin. They mature to the adult stage in the subcutaneous tissue. The adult worms live in the deep dermis and subcutis and become clinically apparent as asymptomatic subcutaneous nodules called onchocercomas, of which there are usually only a few, ranging in size from 0.5 to 2.0 cm (Fig. 24-8A). The adult worms do not cause any harm; however, their progeny, consisting of millions of microfilariae, live in the dermis and the aqueous humor of the eyes, where they provoke inflammatory changes after several years. In the eyes, keratitis, iridocyclitis, chorioretinitis, and optic atrophy ultimately result in blindness (76). On slit-lamp examination, the microfilariae in the anterior chamber of the eyes may be seen to be moving actively (76). Clinically, onchocercal dermatitis is characterized by itching, edema, lichenification, and pigment shifting ("leopard skin") (Fig. 24-8B) (77–79). Later, the skin becomes atrophic. A clinical classification and grading system of the cutaneous changes in onchocerciasis has been proposed but is not yet universally accepted (77). *Onchocerca volvulus*, like *Wuchereria bancrofti*, may also be a cause of lymphatic filariasis, in which massive numbers of microfilariae may occlude lymphatics and result in elephantiasis (81). Lymphadenopathy and so-called hanging groins (adenolymphoceles) are other manifestations of the disease (81).

Histopathology. The onchocercomas show a chronic inflammatory infiltrate and fibrosis at their peripheries. Their centers consist of dense, fibrous tissue containing transverse and diagonal sections of adult worms measuring from 125 to 450 μm in



FIGURE 24-8. Onchocerciasis. A: African patient with onchocercoma on the head. B: African patient with onchocercal dermatitis. C: In an onchocercoma, multiple cross sections of the adult organism can be seen surrounded by dense fibrosis. D: On high magnification the microfilariae within the female adult worm become obvious. When released by the female worm, the microfilariae evoke the changes seen in onchocercal dermatitis. (A, B: From Schaller KF, ed. Colour atlas of tropical dermatology and venerology. Berlin: Springer, 1994:127, with permission. C, D: Specimen courtesy of Yezid Gutierrez, MD, PhD, Cleveland Clinic Foundation, Cleveland, Ohio.)

transverse diameter and up to 500 mm in length in females and 42 mm in males (Fig. 24-8C, D) (81). Some of them are alive at the time of biopsy. Dead worms are surrounded by an inflammatory reaction containing foreign-body giant cells. Microfilariae, hatched by female worms, are occasionally observed within lymphatic vessels of the onchocercomas, through which they are disseminated in the skin. They are from 5 to 9 μm in diameter and from 220 to 360 μm in length (81).

In early, untreated onchocercal dermatitis, many undulating microfilariae are present within the dermis, mainly close to the epidermis (78). Their number decreases greatly with time, and thus they may be difficult to find in old lesions (79). In early infections, reactive changes in the dermis are minimal, but in the course of years, chronic inflammatory cells including eosinophils accumulate around the vessels, and, ultimately, fibrosis of the dermis, especially perivascularly, results (78). Hyperorthokeratosis, parakeratosis, epidermal hyperplasia (in the late-stage flattening of the epidermis), tortuosity of dermal vessels, and pigment incontinence are other features of long-standing onchocercal dermatitis (78).

Pathogenesis. The slow development of the cutaneous changes and also of the ocular changes suggests that microfilariae, as they gradually disintegrate, act as a source of foreign protein and that the dermatitis and the various forms of eye involvement are the result of a coordinated response by the cellular and humoral immune system (78,79,81). Indeed, while alive, microfilariae do not evoke a strong inflammatory response. Only when dying or dead, either during the natural course of their life span or therapeutically induced, do microfilariae produce a prominent inflammatory reaction, with eosinophils being essential in the process (78,79,81).

SCHISTOSOMIASIS

Schistosomiasis is caused by trematodes of the genus *Schistosoma* and affects 180 to 200 million people in 71 countries, making it the most important trematode pathogenic to humans worldwide (82). It is acquired through exposure to skin-penetrating cercariae, a stage in the life cycle of the parasite. The cercariae emerge from a freshwater snail, which functions as an obligate intermediate host to the fluke. The cercariae burrow through the skin and migrate to venous plexuses, where they mature.

Three species of *Schistosoma* are pathogenic to humans. *S. mansoni* is common in the Caribbean islands and in northeastern South America; *S. japonicum* is found in Eastern Asia; and *S. haematobium* is common in the Middle East and in Africa. The usual habitats of *S. mansoni* are the portal circulation and mesenteric venules of the large intestines, with discharge of the eggs in the stool. The usual habitat of *S. japonicum* is the small gut, also resulting in discharge of the eggs with the stool. The usual habitats of *S. haematobium* are the pelvic and vesical venules, with passage of the eggs with the urine. *S. mansoni* and *S. japonicum,* through granulomas in the liver, may cause portal hypertension and esophageal varices, and *S. haematobium,* through granulomas in the bladder, may lead to hematuria and hydronephrosis (83). In Africa, mixed infections with both *S. mansoni* and *S. haematobium* are not uncommon (84,85).

The cutaneous manifestations of schistosomiasis can be divided into three types, depending on the life cycle of the trematode (82,86).

Dermatitis schistosomica (swimmer's itch) is caused by the initial penetration of the skin by human or nonhuman cercariae and manifests as a pruritic maculopapular eruption usually lasting several hours, sometimes days, and, rarely, weeks, depending on previous sensitization. Cercariae of nonhuman *Schistosoma* species (usually avian species primarily affecting ducks or other water birds) can penetrate the skin but subsequently die. The dermatitis produced by anthropophilic *Schistosoma* is milder than that caused by nonhuman species (82).

The second cutaneous manifestations of schistosomiasis, also transitory, are the *bilharzides* or *schistosomides.* Several weeks after penetration, the cercariae have matured into worms 15 to 25 mm in length. The female then releases thousands of eggs into the bloodstream. Their release may be accompanied by anaphylactoid reactions manifested by a combination of fever, urticaria, and sometimes purpura known in Japan as Katayama's syndrome and in China as Yangtze fever (82,86).

A specific cutaneous involvement (known as *bilharziasis cutanea tarda*) represents the third cutaneous manifestation of schistosomiasis and is caused by ectopic deposition of eggs within the dermis when ova have become dislodged from their natural habitat in the venous circulation. Most commonly seen in *S. haematobium*, it is a rare event and presents as papular, verrucous, ulcerative, or granulomatous lesions usually of the genital or perianal skin (82,86,87). In rare instances, the thorax, abdomen, and, even less commonly, the face or scalp are involved (84,88–90).

Histopathology. Bilharziasis cutanea tarda represents the main persistent cutaneous lesion of schistosomiasis. Its pathologic hallmark is a palisading, necrotizing granulomatous inflammation within the dermis consisting of histiocytes, lymphocytes, plasma cells, and rare multinucleated giant cells surrounding complete or degenerated schistosomal ova located in the central area of necrosis (Fig. 24-9) (84,87,88). A predominant population of eosinophils as part of the inflammation is also described (87,90). In older lesions the eggs are calcified and surrounded by fibrosis; the inflammatory infiltrate is sparse or absent (82). The overlying epidermis often reveals pseudocarcinomatous hyperplasia (87,88,91,92). Transepithelial elimination of the ova is described (92).

The ova measure up to 1 mm in greatest dimension and possess a chitinous outer shell staining positively with the PAS stain. However, only *S. mansoni* but not *S. haematobium* or *S. japonicum* is acid fast-positive (84,88,90). The presence and position of a spine on the shell of the ova permit their classification within the tissue. *S. haematobium* ova have a spine in

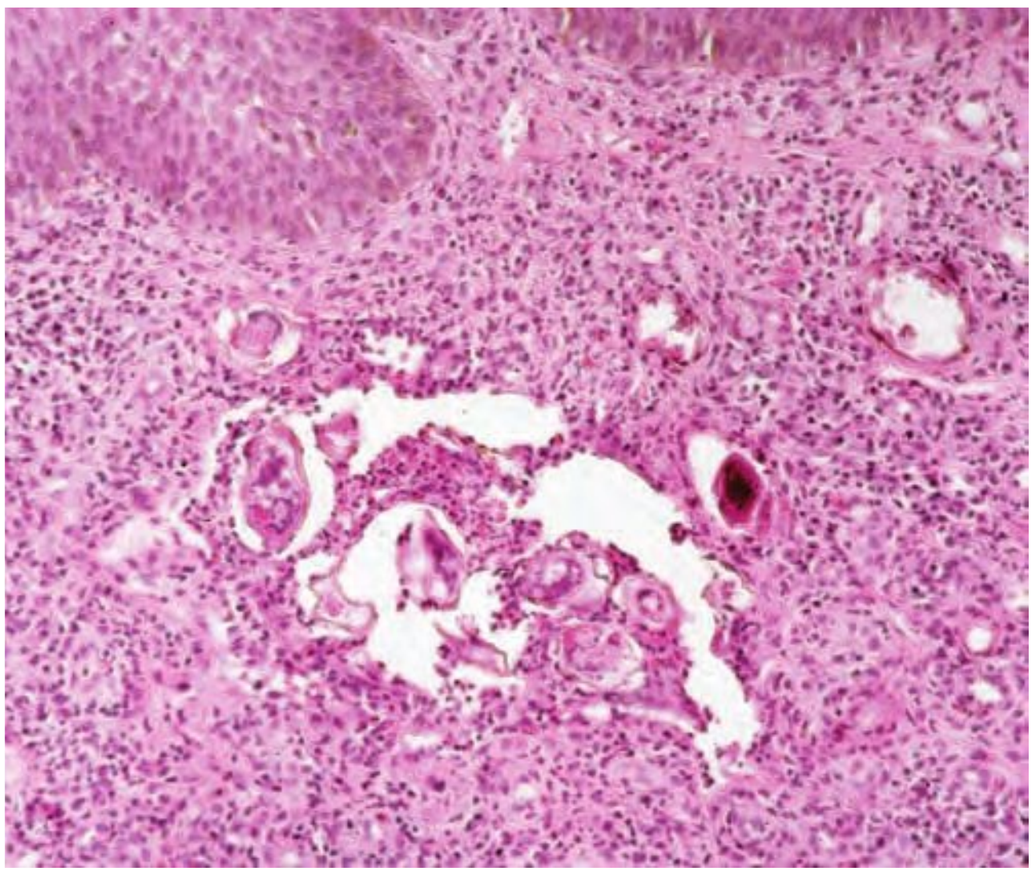


FIGURE 24-9. Schistosomiasis. In bilharziasis cutanea tarda (see text) the schistosomal eggs provoke a granulomatous reaction within the dermis. (Courtesy of Yezid Gutierrez, MD, PhD, Cleveland Clinic Foundation, Cleveland, Ohio.)

the apical position, whereas the spine of *S. mansoni* ova is on the lateral aspect, and *S. japonicum* ova have no spine. In rare instances, one may also see adult worms within distended blood vessels in the dermis (88).

Pathogenesis. The eggs and embryos are said to release soluble substances that act as antigens sensitizing T lymphocytes. These, in turn, release lymphokines, leading to migration of macrophages and eosinophils and to granuloma formation (82).

SUBCUTANEOUS CYSTICERCOSIS

The pork tapeworm *Taenia solium* develops in the human intestinal tract after the ingestion of inadequately cooked pork containing *T. solium* larvae. The tapeworm discharges its eggs in the feces. When eggs with the encysted larvae are ingested by humans, usually through contamination of hands and food by the subject's own feces but also by regurgitation of eggs from the intestinal tract into the stomach by reverse peristalsis (93), they hatch, and larvae entering the bloodstream invade various tissues, where they develop into cysticerci. Whereas the infestation with an egg-producing adult tapeworm confined to the intestines (taeniasis) imposes little harm to the patient, cysticerci can have deleterious effects by evoking cerebral cysticercosis, which is the most common parasitic infestation of the central nervous system worldwide (94). More than 1,000 cases per year are reported in the United States (95).

Subcutaneous cysticercosis is considerably less frequent. Clinically, one, several, or, rarely, numerous firm, asymptomatic nodules are present in the subcutaneous tissue. They usually measure 1 to 2 cm in diameter and can persist for many

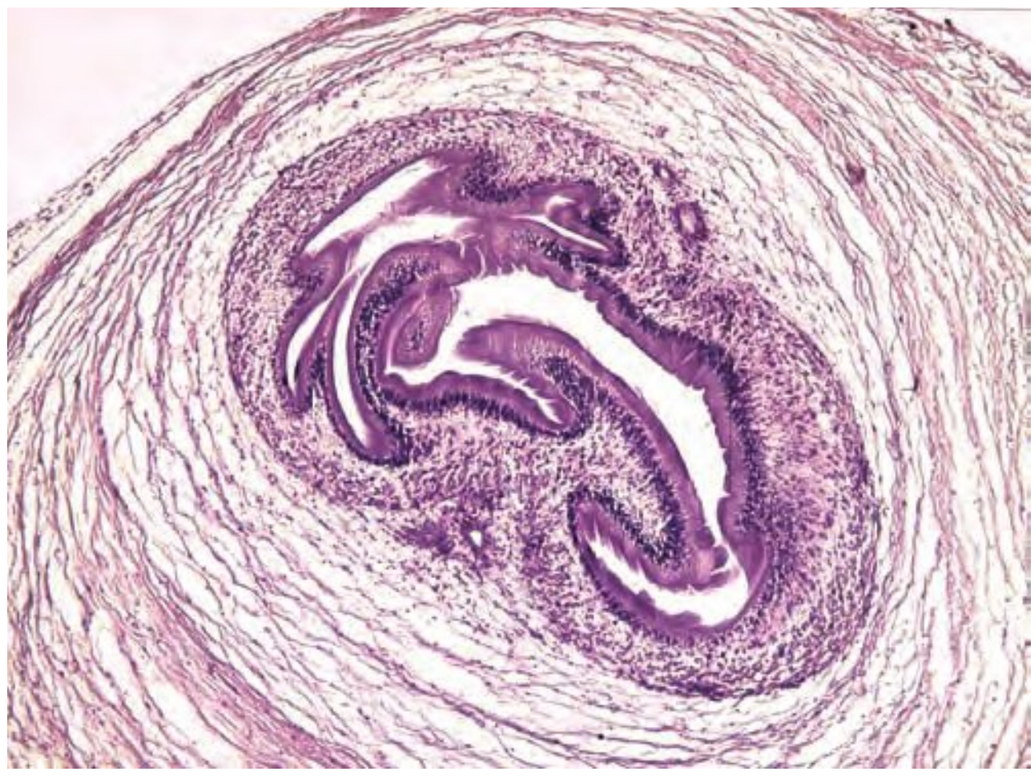


FIGURE 24-10. Subcutaneous cysticercosis. This cysticercus larva was found in a cavity within the subcutis surrounded by granulation tissue and necrotic debris. (Specimen courtesy of Dieter Krahl, MD, Institut für Dermatohistologie, Heidelberg, Germany.)

years (93,96,97). The subcutaneously located cysts of cysticercosis do not carry any risk to the patient's health but are of great value in the diagnosis of cerebral cysticercosis, which causes seizures (94).

Histopathology. A thick, fibrous capsule covered by several layers of epithelioid cells admixed with a few Langhans giant cells but without caseous necrosis surrounds a cystic cavity containing clear fluid and a white, irregularly shaped membranous structure representing a cysticercus larva (98). Eosinophilic infiltration of the capsule is present (89). Step sections reveal the scolex of the larva with suckers and hooks (Fig. 24-10) (93,96).

MYIASIS

The order Diptera (having two wings) includes flies, gnats, and mosquitoes. When fly larvae inhabit the human body, the condition is called myiasis (from the Greek word for fly, *myia*). The distribution of myiasis is worldwide, with greater abundance of cases and of causative species in the tropics.

The cutaneous manifestations of myiasis can be subdivided into three clinically recognized subcategories: wound myiasis, furuncular myiasis, and creeping myiasis (not to be mistaken with the creeping eruption caused by cutaneous larva migrans) (99–101).

In wound myiasis, which may be caused by many different fly species, including the common housefly *Musca domestica*, the fly larvae (maggots) are deposited on necrotic flesh.

Furuncular myiasis occurs mostly in the tropics and is caused in Africa by the tumbu fly *Cordylobia anthropophaga* and in the American tropics by the human botfly *Dermatobia hominis*. The latter has a unique life cycle. The female fl y

captures blood-sucking insects such as mosquitoes or other flies in the air and deposits a number of eggs on their abdomen. When these vectors come in contact with a human host, the *Dermatobia* larvae hatch and enter the skin, where they cause a furuncular lesion known as a "warble." Within 6 to 12 weeks an adult fly develops and leaves the human host through its breathing orifice.

In creeping myiasis, larvae of *Gasterophilus* species or *Hypoderma* species—flies parasitic to horses or cattle—burrow into the skin and cause a migratory pattern. In contrast to the creeping eruption seen in larva migrans, the movements are more restricted and proceed more slowly.

Histopathology. In wound myiasis the larvae generally remain superficial, are usually alive, and can be recognized grossly at the time of biopsy (100). In furuncular myiasis, there is an intense mixed inflammatory infiltrate composed of neutrophils, eosinophils, lymphocytes, plasma cells, and Langerhans giant cells surrounding the cavity, which is occupied by the larva (Fig. 24-11) (99,102,103). In creeping myiasis due to *Hypoderma* species, the inflammatory response is very minimal (100).

Pathogenesis. Both *Dermatobia hominis* and *Cordylobia anthropophaga* secrete a bacteriostatic fluid that prevents secondary bacterial infection of the larval cavity (99,104,105).

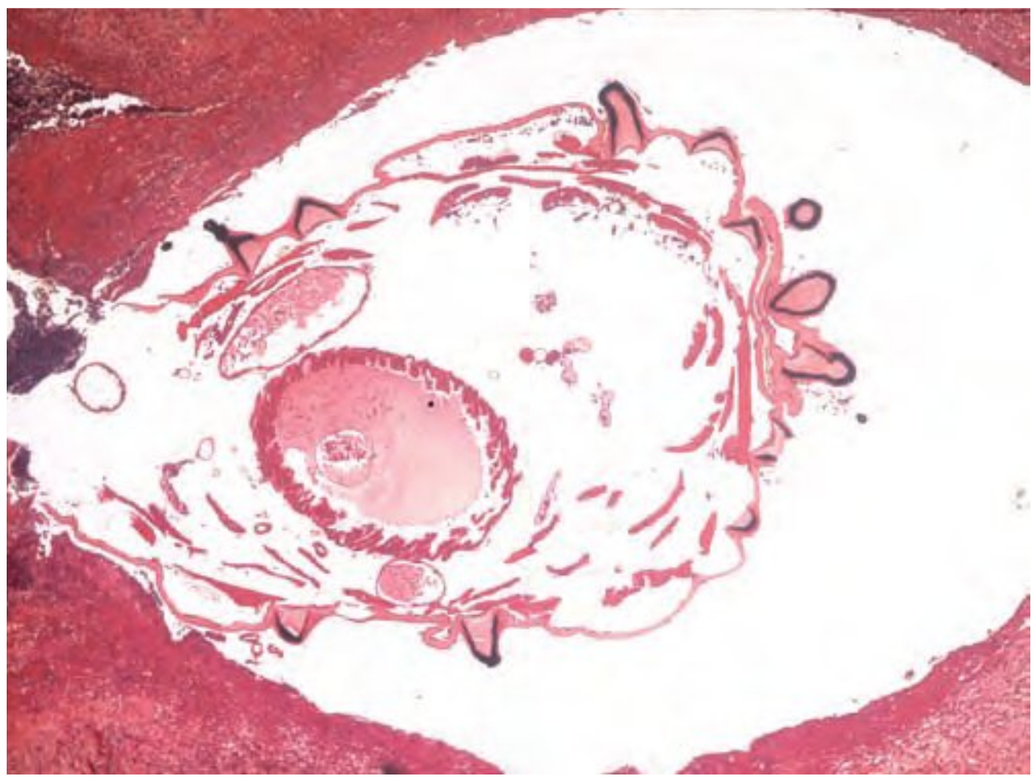


FIGURE 24-11. Myiasis. An intense inflammatory reaction surrounded this larva seen in a case of furuncular myiasis. (Specimen courtesy of Dieter Krahl, M.D., Institut für Dermatohistologie und Oralpathologie, Heidelberg, Germany.)

TUNGIASIS

Tungiasis is a cutaneous infestation by the gravid female sand flea *Tunga penetrans*, which is endemic in the Caribbean region, Central and South America, sub-Saharan Africa, and the Indian subcontinent (106,107).

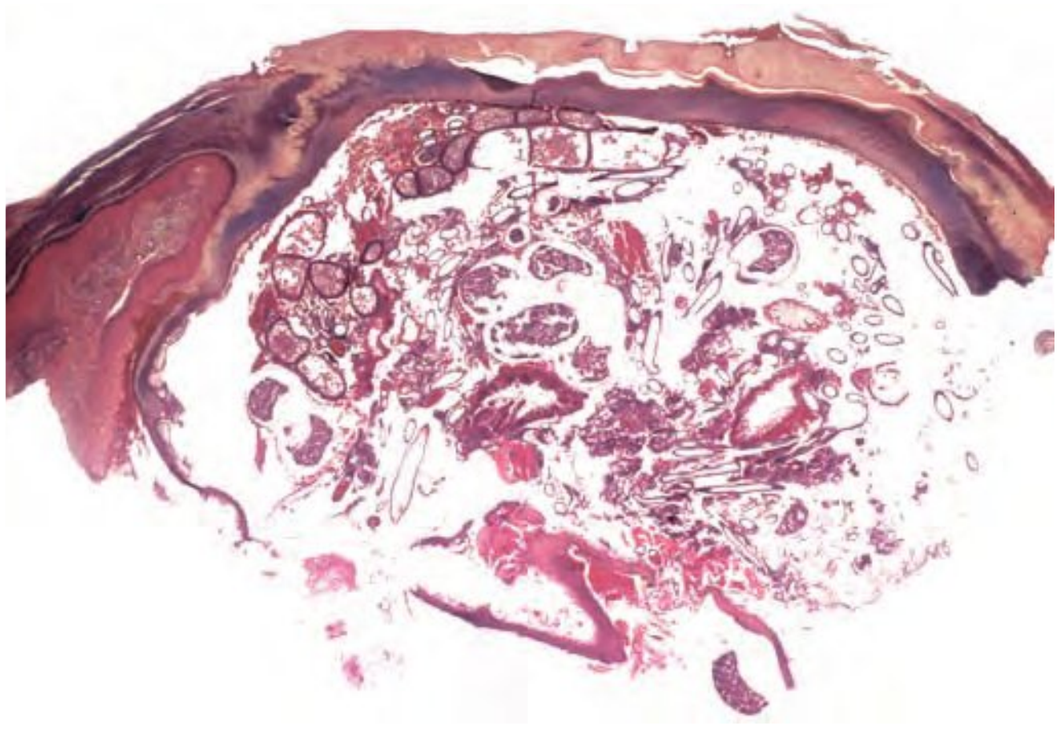
Only the female fleas are capable of penetrating the skin. They burrow a cavity with the head turned toward the dermis, feeding on the host. The gravid female eliminates its eggs through an apical opening of the cavity to the outside and dies soon thereafter, exhibiting a total life span of approximately 1 month (106).

The condition is acquired by walking barefoot. Characteristically, the lesions are located on the toes, the interdigital spaces, and the soles and heels. They are mostly single and consist of a tender nodule 5 to 6 mm in diameter with a black-to-brown central tip representing the posterior end of the parasite.

Histopathology. The flea is located in the epidermis and upper dermis inside a cavity (Fig. 24-12A, B). In its apical



A



B

FIGURE 24-12. Tungiasis. A: This scanning electron micrograph shows the swollen abdomen of the female sand flea feeding on human blood. (From Schuller-Petrović S, Mainitz M, Bohler-Sommeregger K. Tungiasis–eine immer häufigere Urlaubsdermatose. Hautarzt 1987;38:162–164, Fig. 3, with permission.) B: On hematoxylin and eosin–stained section, the typical superficial intradermal location of the flea is noted.

portion it is surrounded by a hyperplastic epidermis. In the absence of bacterial superinfection any perilesional inflammatory infiltrate is usually minimal and consists of lymphocytes, neutrophils, and eosinophils (106). Inside the cavity, portions of the exoskeleton, hypodermal layer, trachea, and digestive tract identify the organism as an arthropod. The uniformly present developing eggs are likely the most useful to differentiate *T. penetrans* from other organisms (108).

ARTHROPOD ASSAULT REACTIONS

Arthropod bites and stings are common afflictions in humans. They induce a localized or a widespread and often also a systemic reaction, depending on the type of the assaulting species and the capacity of the body to react.

Most stings evoked by mosquitoes, bees, wasps, hornets, or bedbugs are characterized initially by a localized urticarial reaction, often followed by the development of a papule and papulovesicle associated with intense pruritus. Frequently, a central punctum can be recognized. In more intense reactions, most commonly seen on the legs, the lesions are bullous (Fig. 24-13A) (109). Typically they resolve without sequelae within days. In rare cases, however, they may persist for weeks or months and are then referred to as a persistent arthropod assault reaction (110,111).

Bites by the brown recluse spider *Loxosceles reclusa* are common in the south central United States. Often painless initially, they are capable of inducing significant skin necrosis (necrotic arachnidism) (112).

Hypersensitivity to insect bites, especially from fleas, gnats, mosquitoes, or bedbugs, may result in papular urticaria, also known as lichen urticatus or strophulus infantum. It is characterized by grouped urticarial papules and papulovesicles with a tendency to spread. Spontaneous resolution within several days is usual (113). The condition cannot be reliably distinguished from arthropod bites (114).

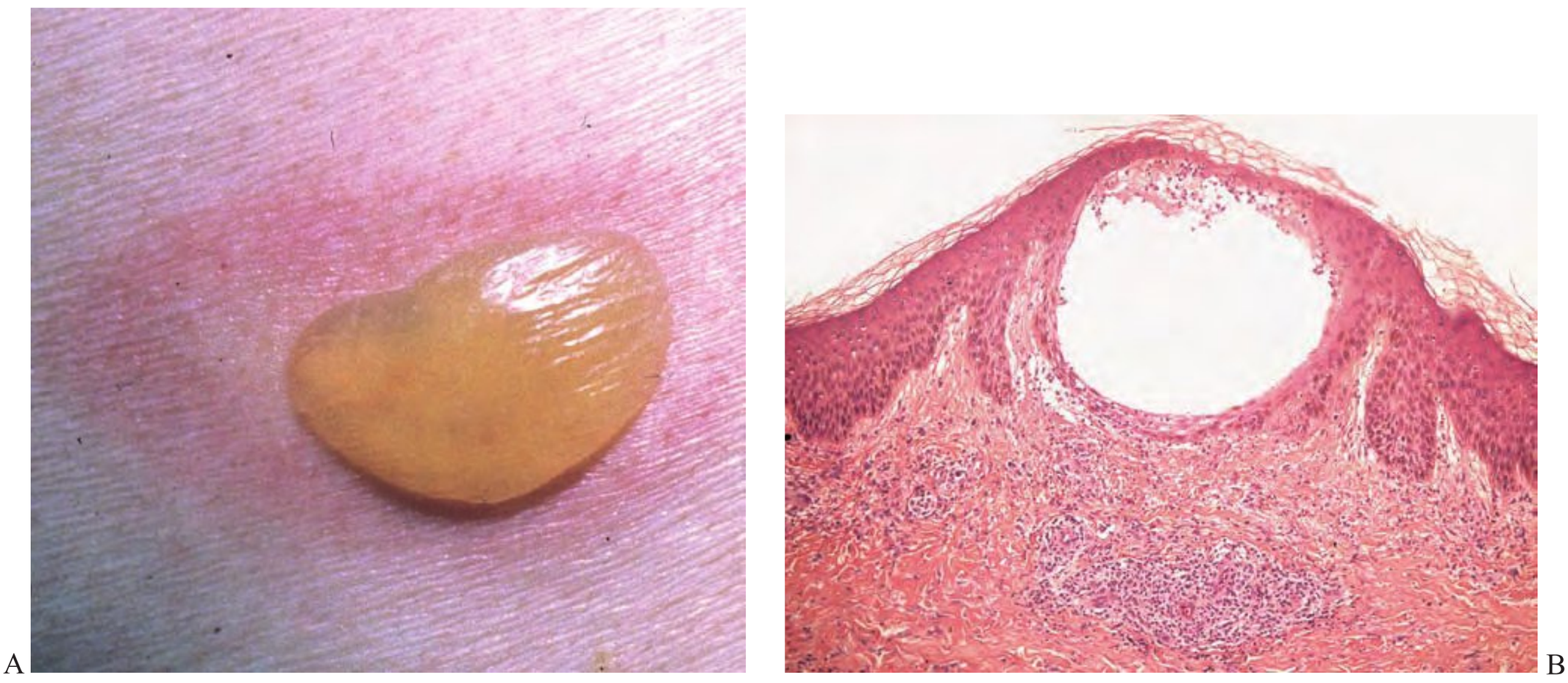
Histopathology. The classical histopathologic hallmark of an arthropod bite is a wedge-shaped, superficial and deep, perivascular and interstitial inflammatory dermal infiltrate composed of lymphocytes and eosinophils, often in association with an overlying focus of spongiosis, sometimes evolving into a vesicle or even progressing to epidermal necrosis (Fig. 24-13B) (115). These changes are indistinguishable from those of papular urticaria (114).

Mosquito bites initially show mainly neutrophils, mostly vasculocentric, and later a predominantly mononuclear infiltrate of lymphocytes and plasma cells. Eosinophils are few or absent (116,117).

Bites of the brown recluse spider initially show a neutrophilic perivasculitis with hemorrhage. Later, in cases of necrotic ulcers, one finds arterial wall necrosis and an infiltrate containing many eosinophils (118).

Some persistent arthropod assault reactions produce a dense lymphoid infiltrate, often with formation of lymphoid follicles, which has to be differentiated from lymphoma (119). In contrast to lymphomas, the lymphoid follicles in persistent arthropod reactions frequently show germinal centers and do not show evidence of clonality. Large transformed, $CD30^+$ lymphoid cells with hyperchromatic nuclei may also be found but do not represent a sign of malignancy (111).

Occasionally parts of the sting apparatus may be retained within the dermis, inducing a chronic inflammatory response,



A B

FIGURE 24-13. Arthropod assault reaction. A: Sometimes the clinical reaction to an arthropod assault is intense and results in a blister (so-called culicosis bullosa). B: On histologic sections often an intraepidermal vesicle can be seen in the center of the arthropod assault.

often with associated eosinophils, accompanied by pseudocarcinomatous epidermal hyperplasia (120). Retention of the string apparatus is more commonly seen in ticks.

Pathogenesis. The primary toxin in the brown recluse envenomation is sphingomyelinase D, which interacts with the outer plasma membrane of erythrocytes, endothelial cells, and platelets. The severe skin necrosis seen in this spider bite is a consequence of vascular damage (121).

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CHAPTER 25

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Diseases Caused by Viruses

Many viral infections have prominent skin manifestations. Characteristic skin lesions suggest a specific viral illness, the diagnosis of which can be confirmed by appropriate procedures. Viral infections of the skin are of increased significance in immunocompromised patients. Viruses are complexes of nucleic acids and proteins that have the capacity for replication in animal, plant, and bacterial cells. They are obligatory intracellular organisms that lack organelles, such as ribosomes and mitochondria. To replicate themselves, viruses use the metabolic machinery of the host cells. Virally induced alterations in cell function and antigenicity, cell death, and host responses to the presence of viruses are factors that lead to the manifestations of viral disease (1). Before viruses can enter a cell, they must attach themselves to specific receptors on the cell surface. Thus, virus infection is a receptor-mediated, species and cell type–specific process (2). Viruses enter the cytoplasm of a cell by a process called *endocytosis*, acquiring an outer coat of plasma membrane. Once inside the cell, uncoating is triggered by pH changes in endosomes. As the outer coat and the capsid are being digested, the exposed nucleoids lose their characteristic structure (3). The viruses now are in "eclipse phase" and do not become apparent until replication has taken place and new virions or viruses appear. During the process of replication, the viral proteins that are produced follow the genetic code of the specific virus nucleic acid, and the proteins formed are characteristic of the virus rather than of the host cells. Viral particles are assembled in the infected cells and released either by lysis of the cell or by budding from the cell surface.

The diameters of viruses infecting skin vary from 20 nm for the echoviruses to 300 nm for the poxviruses. Under favorable conditions, poxviruses may be recognizable under a light microscope—for example, variola viruses as Paschen bodies. As a rule, however, viruses can be resolved by light microscopy only when aggregated into inclusion bodies. *Inclusion bodies* are roughly spherical. Their average size is about 7 μm, the size of an erythrocyte. Electron microscopy has shown that inclusion bodies represent sites at which virus replication is occurring or has occurred. They are observed in three groups of viruses: the herpesvirus and papillomavirus groups, where they are found within the nuclei of cells; and in the poxvirus group, where they occur within the cytoplasm. In the nucleus, they are surrounded by a clear halo as a result of margination of the nuclear chromatin. In some viral infections, such as molluscum contagiosum, inclusion bodies contain masses of virions and are basophilic and Feulgen positive; in contrast, in other infections such as herpesvirus infection, the viruses have left the inclusion bodies, except for a few residual nucleoids, and the inclusion bodies are then eosinophilic and Feulgen negative.

There are five families of viruses that commonly affect the skin or adjoining mucous surfaces: (a) the Herpesviridae, DNA viruses that multiply within the nucleus of the host cell, including herpes simplex virus (HSV) types 1 and 2 (HSV-1, HSV-2), varicella-zoster virus (VZV), Cytomegalovirus (CMV), Roseolovirus (human herpesvirus [HHV]-6), Epstein-Barr virus (EBV; Lymphocryptovirus), HHV-7 and HHV-8; (b) the Poxviridae, which are DNA viruses that multiply within the cytoplasm, including smallpox, milkers' nodules, orf, and molluscum contagiosum; (c) the Papovaviridae, which contain DNA and replicate in the nucleus, including the various types of verrucae; (d) the Picornaviridae, which contain RNA in their nucleoids, including coxsackie virus group A, causing hand-foot-and-mouth disease; and (e) the Retroviridae, whose genetic material is RNA, including HIV, the cause of AIDS. In addition to these five families, exanthems can occur following infection with many other virus families, such as Adenoviridae, Togaviridae, Reoviridae, Parvoviridae, Paramyxoviridae, Flaviviridae, and Hepadnaviridae. Lesions from the first three DNA virus family infections contain diagnostic viral inclusions. Infections from the other virus families often produce rather histologically nonspecific changes with superficial perivascular dermatitis and occasional apoptotic cells in the epidermis.

Besides histologic examination, two other laboratory approaches can be used: virologic and serologic approaches. The virologic approach includes isolation of virus in cell culture, detection of viral particle by immunoassays or electron microscopy, and detection of viral nucleic acid by polymerase chain reaction (PCR)-based assays or labeled complementary DNA probes. The serologic approach includes demonstration of a fourfold or greater rise in antiviral immunoglobulin G (IgG) antibody using acute and convalescent sera or demonstration of virus-specific immunoglobulin M (IgM) antibody in a single late acute or early recovery phase serum. A serologic approach is still used today for certain viral infections, such as infectious mononucleosis (IM) and hepatitis. However, the virologic approach is used more frequently than before. The timing,

quality, and handling of the specimen are critical for an accurate diagnosis using the virologic approach. It is important to obtain specimens during the acute phase of a virus infection from the site of the infection. The optimal temperature for storage and transport of specimen for viral culture is 4°C in a refrigerator or on wet ice. Most of the viruses are stable at this temperature for 3 to 5 days. If a specimen needs to be stored longer than 3 to 4 days, a –70°C freezer should be used and the specimen should be transported on dry ice. With the development of molecular biology, PCR-based rapid viral detection assays have been developed and are used in clinical diagnostic laboratories.

HERPESVIRIDAE

The Herpesviridae are double-stranded DNA viruses with three subfamilies. Herpesvirus infections of humans include HSV-1, HSV-2, Varicellovirus, CMV (HHV-6), EBV (Lymphocryptovirus), HHV-7, and HHV-8.

Herpes Simplex

Two immunologically distinct viruses can cause herpes simplex: HSV-1 (orofacial type) and HSV-2 (genital type) (4). HSV is transmitted through the exchange of saliva, semen, cervical fluid, or vesicle fluid from active lesions. Primary infection with HSV-1 is often subclinical in childhood. In about 10% of the cases, acute gingivostomatitis occurs, usually in childhood and only rarely in early adult life. Primary infection may also occur in rare instances as a respiratory infection, Kaposi's varicelliform eruption, keratoconjunctivitis, or a fatal visceral disease of the newborn. Recurrent HSV-1 infections occur most commonly on or near the vermilion border of the lips (herpes labialis—"cold sores") (Fig. 25-1A). Recurrences may be triggered by sunlight, physical or emotional stress, immunosuppression, menses, hot or cold, or febrile illness (5). Besides the lips, any parts of the skin or oral mucosa can be affected by HSV-1. Herpes genitalis is one of the most common sexually transmitted diseases worldwide (6). Seroconversion for HSV-2, the most common cause of genital herpes, rarely occurs before the onset of sexual activity. Occasionally, an infant contracts HSV-2 *in utero* or by direct contact in the birth canal (7). Even though most infections of the genitalia and adjoining skin are caused by HSV-2, some infections in this area are caused by HSV-1. Genital HSV-1 infections are less likely to recur than HSV-2 infections: the rate of recurrence was 14% for HSV-1 infections compared with 60% for HSV-2 infections (8). Only 10% to 25% of individuals who are HSV-2 seropositive report a history of genital herpes (9).

Both primary and recurrent herpes simplex, in their earliest stages, show one or several groups of tiny clear vesicles on an edematous red base. If located on a mucous surface, the vesicles erode quickly, whereas if located on the skin, they may become pustular before crusting. The lesions usually heal without scarring, except in cases where secondary bacterial infection occurs. The following are special forms of cutaneous herpes simplex: eczema herpeticum (Kaposi's varicelliform eruption), herpetic folliculitis, and herpetic whitlow.

Eczema herpeticum is a potentially life-threatening herpetic infection of a preexisting skin disease (10). It occurs most commonly in patients with atopic eczema; however, it may also occur in other skin diseases such as seborrheic dermatitis, pityriasis rubra pilaris, pemphigus foliaceus, Darier's disease, and post perioral dermabrasion (11). An extensive rash with small vesicles filled with yellow pus and high fever is the common presentation of eczema herpeticum (Fig. 25-1B), which has been linked to increased interleukin (IL)-4 and decreased natural killer cells and IL-2 receptor in patients with atopic eczema (12,13). *Herpetic folliculitis* presents as painful, grouped erythematous, perifollicular vesicles that do not respond to antibacterial or antifungal agents, usually occurring in the bearded region and scalp (14). The characteristic

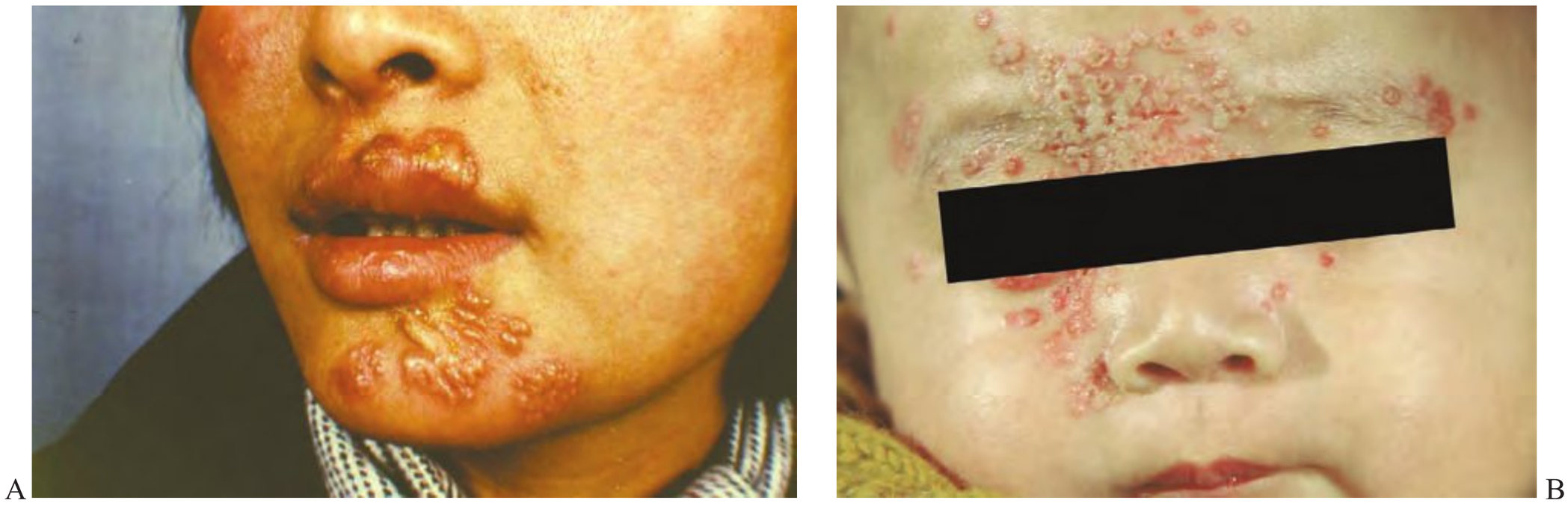


FIGURE 25-1. A: Herpes simplex. Recurrent HSV-1 infection showing grouped vesicles on an erythematous base, occurring most commonly on or near the vermilion border of the lips. B: Eczema herpeticum. This condition often occurs in atopic children.

vesiculofollicular lesions usually heal within a few weeks. *Herpetic whitlow* manifests as painful, deep-seated vesicles limited to the paronychial or volar aspects of the distal phalanx of a finger. Herpetic whitlow occurs largely in medical and dental personnel following minor injuries and may be caused by either HSV-1 or HSV-2 (15). Other forms of HSV infections include HSV keratoconjunctivitis, which is the number one cause of corneal blindness in the United States (16), and a rare necrotizing balanitis (17). Noncutaneous forms of herpes simplex infection include herpetic oropharyngitis, pneumonia, encephalitis, esophagitis, and proctitis.

Recurrent Infection. Recurrent infections of the oral cavity, skin, or genitals can result either from reactivation of a latent infection or from a new infection. Primary infection with either HSV-1 or HSV-2 is often subclinical and is followed by emergence of specific circulating antibodies and latency of the infection. In some persons infected with either HSV-1 or HSV-2, the virus can become activated intermittently and give rise to recurrent lesions. Although recurrences, particularly of HSV-2, can be due to reinfection, they are often caused by reactivation of a latent infection of the regional sensory ganglia, where the virus exists in a latent, nonreplicative state.

Herpes Simplex in Compromised Hosts

Severe primary or secondary herpetic infection with systemic involvement may occur in immunocompromised patients. Coinfection with HSV and HIV frequently occurs, probably because they potentiate each other's transmission. About 70% of HIV-positive patients are seropositive for HSV-2 (18). Three forms of herpes simplex are characteristically found in children or adults with impairment of the cellular immune system. The most common of the three forms is *chronic ulcerative herpes simplex*, and the other two are *generalized acute mucocutaneous herpes simplex* and *systemic herpes simplex*.

Chronic ulcerative herpes simplex exhibits persistent ulcers and erosions, usually starting on the face or in the perineal region (19). Without treatment, gradual widespread extension is the rule. The infection may progress into systemic herpes simplex. *Generalized acute mucocutaneous herpes simplex* follows an initial localized vesicular eruption. Dissemination associated with fever takes place, which is suggestive of smallpox or varicella infection (20). In some instances, death results without the presence of visceral lesions. *Systemic herpes simplex* usually follows oral or genital lesions of herpes simplex. Areas of necrosis, particularly in the liver, adrenals, pancreas, and brain, lead rapidly to death. In some patients, a few cutaneous lesions of herpes simplex also exist.

Congenital Herpes Simplex

Because almost 1% of patients in prenatal clinics have HSV-2 infections by culture of the vagina and one third of these have active lesions, there exists the potential of congenital herpes simplex infection. It is important, however, to distinguish primary HSV-2 infection of the mother from recurrent infection. In recurrent infection, the presence of neutralizing antibody to HSV-2 results in a low rate of attack of the fetus (21). In maternal HSV-2 *primary infection*, the mode of infection of the infant is important. Transplacental infection of the fetus occurring during the first 8 weeks of gestation produces severe congenital malformations. If infection occurs at a later time, malformations are less severe and consist of growth and psychomotor retardation; microcephaly; and a widespread, recurrent vesicular eruption that can mimic a mechanobullous disorder.

Localized herpetic lesions appearing several days after delivery are the initial manifestation if infection is acquired in the birth canal. In vertex deliveries, the scalp is a common site for the development of initial herpetic vesicles. It is rare for transplacental or neonatal infection to remain limited to the skin. It can be followed by systemic herpetic infection, such as encephalitis, hepatoadrenal necrosis, and pneumonia (22).

Herpes Simplex Associated With Erythema Multiforme

HSV is the most common identified etiologic agent in recurrent erythema multiforme (23). Molecular diagnostic methods, primarily PCR, have been used to detect herpetic DNA in the skin lesions of recurrent erythema multiforme in both adults and children (24). The association is further supported by suppression of recurrent lesions in this group by therapy directed at HSV.

Histopathology of Herpes Simplex

The earliest changes of herpes simplex lesions include nuclear swelling of keratinocytes. With hematoxylin and eosin stains, these nuclei appear slate gray and homogeneous with margination of the nuclear chromatin. A few necrotic keratinocytes in the epidermis may also be seen. The changes usually begin along the basal layer keratinocytes and then involve the entire epidermis. Later, skin herpes simplex produces profound degeneration of keratinocytes, resulting in acantholysis and vesicle formation (Fig. 25-2). Degeneration of epidermal

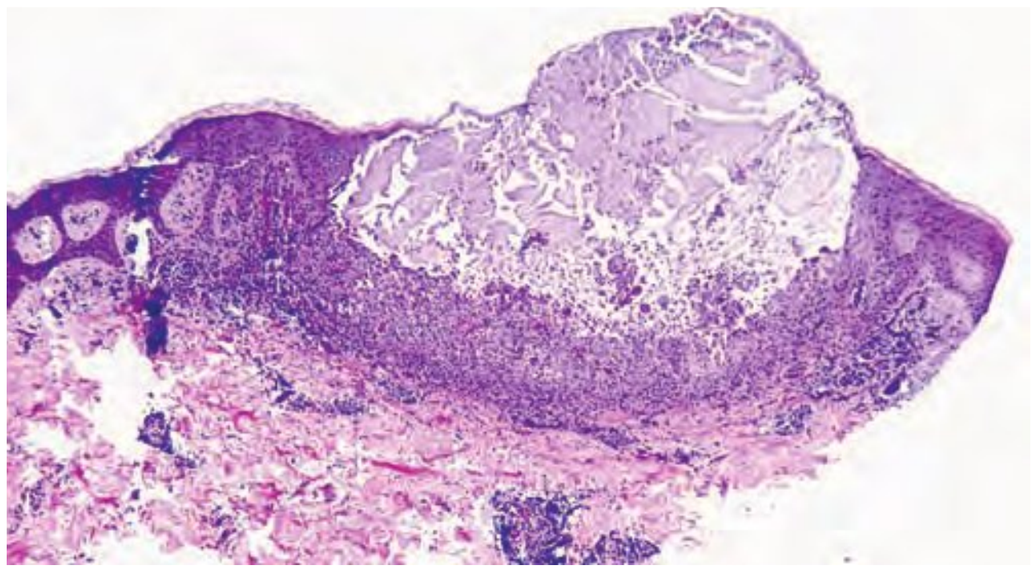


FIGURE 25-2. Herpes simplex. An intraepidermal vesicular lesion with marked acanthosis and ballooning degeneration of the cells at the floor of the vesicle (low magnification).

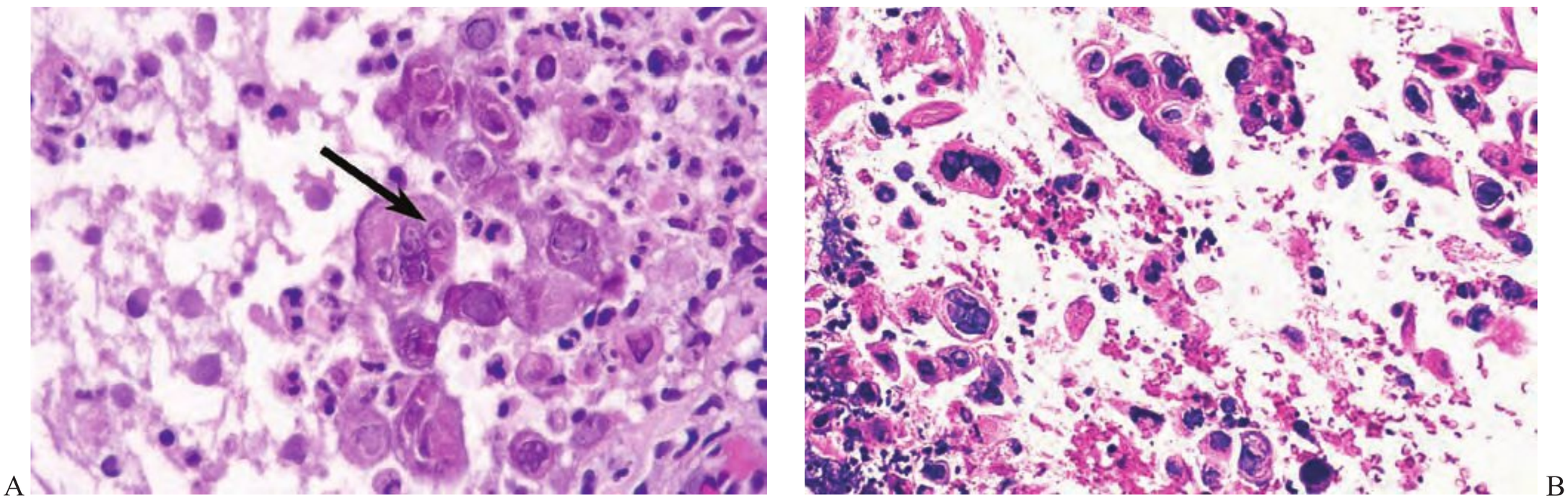


FIGURE 25-3. Herpes simplex. A: Same lesion as in Figure 25-2 but at high magnification. Balloon cells at the floor of a vesicle are shown. In the center, eosinophilic inclusion bodies surrounded by a halo lie in the nuclei of balloon cells (arrow points to the intranuclear inclusion). Other cells exhibit the more characteristic pattern of homogeneous pale chromatin without inclusion bodies. B: At high magnification, balloon cells at the floor of a vesicle are shown. These cells exhibit characteristic homogeneous pale chromatin with nuclei molding.

keratinocytes occurs in two forms: ballooning degeneration and reticular degeneration. Ballooning degeneration is swelling of epidermal keratinocytes. Balloon cells have a homogeneous, eosinophilic cytoplasm (Fig. 25-3). They may be multinucleated (Tzanck cells). Balloon cells lose their intercellular bridges and become separated from one another (secondary acantholysis), and unilocular vesicles result. Ballooning degeneration occurs mainly at the bases of viral vesicles, so the vesicle formed intraepidermally ultimately may be subepidermal. Ballooning degeneration can affect epithelial cells of hair follicles, sebaceous glands, and rarely eccrine duct cells. Reticular degeneration is the result of rupture of ballooning cells due to progressive hydropic swelling of the epidermal cells (Fig. 25-4A). Reticular degeneration occurs in the upper portions and at the peripheries of viral vesicles. Reticular degeneration is not specific for viral vesicles, because it also occurs in the vesicles of contact dermatitis. Through coalescence of cells with reticular degeneration, a multilocular vesicle may result, the septa of which are formed by residual cell membrane. In older vesicles, the cellular walls disappear. The originally multilocular portions of the vesicle may become unilocular.

Inclusion bodies are frequently observed in the centers of enlarged, round nuclei of balloon cells. The inclusion bodies are eosinophilic and surrounded by a clear space or halo (Fig. 25-3A). They measure from 3 to 8 μm in diameter. The majority of the balloon cells at the floor of a vesicle exhibit characteristic homogeneous pale chromatin and nuclei molding without inclusion bodies (Figs. 25-3B and 25-4B). Neutrophils

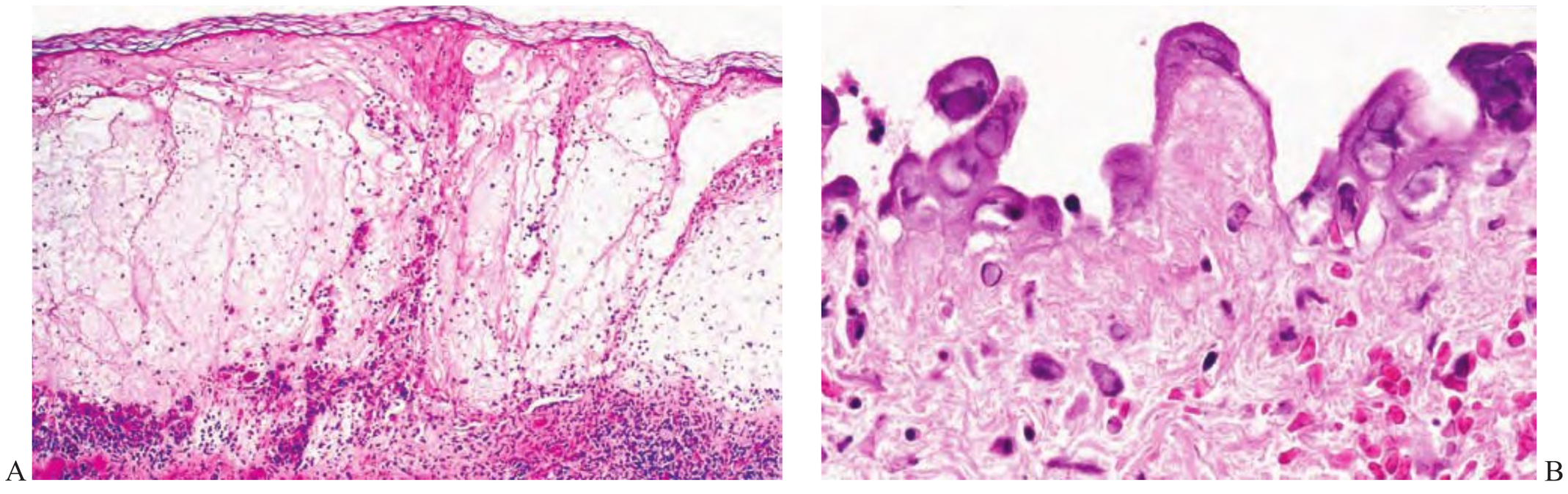


FIGURE 25-4. Varicella and herpes zoster. A: Reticular degeneration is present, especially at the top of the vesicle, resulting in a multilocular vesicle. In addition, ballooning degeneration can be seen at the floor of the vesicle. B: At high magnification, balloon cells exhibit characteristic homogeneous pale chromatin and nuclear molding. Dermal hemorrhage is common.

are often present within established vesicles. Neutrophils may be prominent in the lesions of herpetic whitlow. The upper dermis beneath viral vesicles contains an inflammatory infiltrate of variable density. In some cases of herpes simplex, vascular damage is present, showing necrosis of vessel walls, microthrombi, and hemorrhage subjacent to the vesicle. In addition, eosinophilic inclusions may be found in endothelial cells and fibroblasts. In later lesions, necrosis of epidermis is often present with abundant neutrophils. A dense mixed cell infiltrate in the upper dermis with ghosts of necrotic multinucleated acantholytic cells with slate gray nuclei may still be seen. As in all vesiculobullous diseases, an early lesion should be selected for biopsy; otherwise, secondary changes, especially invasion of inflammatory cells, may obscure the diagnostic features.

Herpetic involvement of hair follicle and pilosebaceous units is not uncommon in recurrent lesions (25). In fact, necrosis of a pilosebaceous unit is a clue to search for multinucleated cells with characteristic slate gray nuclei. In herpetic folliculitis, pilosebaceous involvement is a predominant feature. Rarely, the eccrine ducts and glands are involved by the virus. The histology of eczema herpeticum is similar to vesicles of herpes simplex, but usually with more dense neutrophilic infiltrates.

Chronic ulcerative herpes simplex may be difficult to recognize as being of viral genesis if the epidermis is absent. However, viral cytopathic changes may be observed in keratinocytes at the margin of the ulcer. Viral cultures or typing of HSV-1 and HSV-2 by direct immunofluorescence or immunoperoxidase technique can be used to prove the diagnosis. However, the most rapid and accurate method may be the use of molecular diagnostic methods such as PCR (26).

Tzanck Smear. Cytologic examination of a Giemsa-stained smear taken from the floor of a freshly opened early vesicle is often useful. The presence of many balloon cells results from the fact that the smear is taken from the floor of the blister, where ballooning degeneration is most pronounced. Many acantholytic balloon cells with one or several nuclei may be seen in herpes simplex, varicella, and zoster. The Tzanck smear cannot distinguish among HSV-1, HSV-2, and VZV.

Histogenesis and Viral Identification. HSV can be directly identified by culture, direct immunofluorescence testing, *in situ* hybridization, immunoperoxidase staining, or molecular diagnostic tests. The gold standard for diagnosis is a viral culture. For culture, material from the floor of a blister or other infected material is inoculated onto HeLa cells, human amnion cells, or fibroblasts. The virus has cytopathic effects on the cultured cells. Direct immunofluorescence examination for the presence of the viral antigen in cells infected with HSV is then performed. Herpes simplex DNA can be extracted and amplified by PCR from stained or unstained Tzanck smears, crusts, fresh tissue, and paraffin sections of suspected lesions. With appropriate primers, each herpes-type virus can be specifically identified.

For distinction between the two types of HSV, immunoperoxidase staining may be performed on sections of the lesions by using monoclonal antibodies, one directed against HSV-1 and the other against HSV-2. *In situ* hybridization can also be used for visual demonstration of viral genomic material in tissue (27). For determination of the antibody titer in the patient's serum, a complement fixation reaction is usually used. The serologic test for HSV is useful to confirm HSV infection in persons with a questionable history of herpetic disease and in those who have unrecognized or subclinical infection; thus, they may be aware of their potential to transmit the virus.

On electron microscopy, HSV is spherical. Its DNA-containing core measures approximately 40 nm in diameter. The virion has a diameter of about 100 nm and together with its outer coat measures around 135 nm (28). Ultrastructurally, the virion of herpes simplex is indistinguishable from that of varicella.

Differential Diagnosis. Viral vesicles produced by HSV and by the VZV are identical. Furthermore, an incompletely developed case of herpes zoster can mimic herpes simplex infection, both clinically and histologically. In the context of immunosuppression, chronic cutaneous forms of both viruses exist, and their specific identification may not be possible by clinical morphology or light microscopy. Molecular diagnostic methods are the quickest and most reliable way to separate and identify the specific viruses in these situations.

Kaposi's Varicelliform Eruption

Kaposi's varicelliform eruption (eczema herpeticum) is a distinct cutaneous eruption caused by HSV-1 and HSV-2, vaccinia virus, and coxsackie A16 virus, superimposed on a preexisting dermatosis (29), usually atopic dermatitis (30). Occasionally, seborrheic dermatitis or other dermatosis, such as Darier's disease, benign familial pemphigus, pemphigus foliaceus, mycosis fungoides, Sézary's syndrome, or ichthyosis vulgaris, provide the "soil" in which Kaposi's varicelliform eruption develops (11).

Eczema herpeticum is usually caused by HSV-1 and on rare occasions by HSV-2. Eczema herpeticum can occur as either a primary or a recurrent type of infection. A primary infection with HSV-1 occurs in persons without circulating HSV-1 antibodies. The great majority of patients with the primary type of eczema herpeticum are infants and children. The recurrent type of eczema herpeticum occurs in patients with circulating HSV-1 antibodies. The first attack of eczema herpeticum, whether of the primary or the recurrent type, may be the result of exogenous infection, whereas subsequent attacks may result from either reinfection or reactivation. The primary type of eczema herpeticum can be a serious disease with viremia and potential internal organ involvement resulting in death. In contrast, the recurrent type of eczema herpeticum generally shows no viremia and internal organ involvement except in immunologically compromised patients. Occasionally, secondary bacterial infection with subsequent septicemia may cause death. The mortality of eczema herpeticum is approximately 10%, with most fatalities occurring in infants and children with a primary type of herpetic infection and in adults with inadequate cellular immunity.

Clinically, all forms of eczema herpeticum and eczema vaccinatum (a condition caused by exposure to vaccinia virus, a poxvirus) look alike, but eczema vaccinatum has not been seen in modern practice because vaccinia virus has not been used, until recently, for smallpox prevention (31). Both show a more or less extensive eruption composed of vesicles and pustules that may be umbilicated. These vesicles and pustules occur chiefly in the areas of the preexisting dermatosis but also on normal skin. The face is usually severely affected and may be edematous. There may be fever and prostration.

Histopathology. Both eczema herpeticum and eczema vaccinatum show vesicles and pustules of the viral type. Even though the pustules exhibit only necrotic epidermis in their centers, reticular and ballooning degeneration at their peripheries may still be seen. In eczema herpeticum, but not in eczema vaccinatum, multinucleated epithelial giant cells often are present.

Differential Diagnosis. Because eczema herpeticum and eczema vaccinatum look alike clinically, and the histological similarity is great in the absence of inclusion bodies and of multinucleated epithelial cells, differentiation of the two diseases may have to depend on nonhistologic means, such as a history of possible exposure to the vaccinia virus. The most efficient and rapid means of identifying the viral agent is to use DNA amplification methods and appropriate probes.

Varicella and Herpes Zoster

Varicella (chickenpox) and herpes zoster (shingles) are produced by the same virus—VZV. VZV is endemic in the population but becomes epidemic during late winter and early spring (32). Varicella results from contact of a nonimmune person with this virus, whereas herpes zoster occurs in persons who have had previous varicella, either clinically or subclinically. Herpes zoster is caused by reactivation of a latent infection in either a spinal or a cranial sensory ganglion. On reactivation, the virus spreads from the ganglion along the corresponding sensory nerve or nerves to the skin.

Varicella

In varicella, a generalized eruption develops after an incubation period of about 2 weeks. Varicella is primarily a disease of childhood; 90% of cases occur in children 14 years of age or younger (33). The transmission rate of acute varicella to susceptible household contacts is estimated to be as high as 80% to 90%, making it one of the most infectious viral diseases of humans. VZV is acquired from patients with primary varicella or herpes zoster through either direct contact with infected vesicular fluid or inhalation of aerosolized respiratory secretions. Recent experiments suggest that VZV is lymphotropic, especially to T cells. After the initial viremia and a period of viral replication, a second, higher-titer viremic phase results in widespread dissemination of the virus. The rash develops as VZV-infected mononuclear cells invade vascular endothelial cells, gaining access to cutaneous tissue. After the primary varicella infection resolves, VZV enters a latent phase in the dorsal root ganglia (34). Pruritic rash of chickenpox, the hallmark of the disease, typically begins on the head and spreads to the trunk and finally the extremities; proximal involvement is greater than distal. The skin lesions of varicella begin as erythematous macules to small papules, which develop into vesicles (Fig. 25-5). In mild cases, most vesicles become crusted without changing into pustules. In severe cases, the vesicles may have slightly hemorrhagic bases ("dew drops on rose petals"). New lesions continue to develop for several days, so lesions in different stages, papules, vesicles, pustules, and crusted lesions can be observed. Typically, varicella lesions heal without scarring as new epithelium forms at the base; however, hypopigmentation, skin pitting, and keloid formation may result, especially among darker-skinned individuals. Varicella in adults is generally associated with a greater number of skin lesions, more systemic complaints, and a higher risk of such serious complications as pneumonia, encephalitis, and death. Subclinical varicella, documented by increases in antibody titer after exposure to the virus, has been estimated to occur in as much as 5% of the population (35).



FIGURE 25-5. Varicella (chickenpox). A vesicular eruption in crops with "dew drops on rose petals" appearance.

Three systemic complications can occur in varicella without the existence of immunosuppression: primary varicella pneumonia, Reye's syndrome, and varicella of the fetus and newborn. Primary varicella pneumonia occurs in approximately 14% of adults with varicella and carries a significant mortality. Reye's syndrome is an acute, severe, and usually fatal encephalopathy associated with fatty degeneration of the viscera, particularly of the liver. It follows mainly varicella but also other viral infections. Although usually observed in children, it also may occur in adults (36). Varicella in the first 20 weeks of pregnancy has a 2% risk of producing embryopathy or other congenital malformations (37). Maternal varicella late in pregnancy may be transmitted to the fetus transplacentally or may contaminate the baby during passage through the birth canal, resulting in neonatal varicella.

Varicella in Compromised Hosts

In patients with impairment of the cellular immune system, continued viral replication may lead to a prolonged course and dissemination to various organs. Varicella pneumonia is not uncommon, even in children, and death may result from dissemination. VZV may produce particularly severe problems for patients with AIDS. There may be continuous dissemination of vesicular lesions, formation of chronic vegetative lesions, and large necrotic lesions (38).

Herpes Zoster

It is known that VZV establishes latency in ganglia following the primary infection causing varicella (chickenpox) and that the virus may reactivate after years of dormancy to produce herpes zoster (shingles). It is now widely accepted that the virus is mainly latent in neuronal cells, with only a small proportion of nonneuronal cells infected. The ganglia most often involved are those of the lumbar and thoracic nerves. When the virus is reactivated, newly synthesized viruses are transported along the sensory nerve and released into the skin. Trigger mechanisms include trauma, stress, older age, cancer (especially lymphoma), and other causes of immunosuppression including therapeutic agents. The incidence of herpes zoster increases with age (39). Although herpes zoster occurs largely in adults, particularly in those of advanced age, about 5% of patients with herpes zoster are children younger than 15 years of age. The course in children without immune defects usually is mild. The eruption in herpes zoster consists of grouped vesicles on inflammatory bases and arranged along the course of a sensory nerve (Fig. 25-6). The bases of the lesions frequently are hemorrhagic, and some may become necrotic and ulcerate. Not infrequently, there are a few scattered nondermatomal lesions, and rarely there is a generalized eruption, including mucosal lesions, indistinguishable from that of varicella. The most common places of involvement include the thoracolumbar (T3-L2) and facial (V1) dermatomes. Severe neuritis with acute pain, dysesthesia, and skin hypersensitivity is common and more severe in people older than 50 years of age and in immunocompromised patients. Zoster sine herpete, or "pain without the rash," is a rare presentation of herpes zoster; dermatomal pain is present with failure to develop a rash, likely because of neural inflammation and damage caused by viral reactivation. Herpes zoster during pregnancy is not as serious a problem as primary varicella during pregnancy; it does not result in serious morbidity or intrauterine VZV infection. Transplacental transmission of the virus does not occur with maternal herpes zoster; preexisting normal immunity is thought to protect the fetus.



FIGURE 25-6. Herpes zoster (shingles). Vesicles with a characteristic dermatomal distribution.

Herpes Zoster in Compromised Hosts

Both the incidence and the severity of herpes zoster are greater in patients with impaired cellular immunity. The incidence of herpes zoster is particularly high in patients with advanced Hodgkin's disease who are receiving chemotherapy or radiation and in persons infected with HIV. In the context of HIV infection, herpes zoster may fail to resolve, may disseminate, or may produce atypical vegetative and ulcerative lesions (40). Although patients with disseminated herpes zoster but without associated serious illness have good prognoses, patients with impaired cellular immunity may develop widespread, fatal systemic manifestations, such as pneumonia, gastroenteritis, or encephalitis.

Histopathology. Lesions of varicella and herpes zoster are histologically indistinguishable from those of herpes simplex (Fig. 25-4A, B). Frequently, however, the degree of vessel damage, microthrombi, and hemorrhage are more pronounced in varicella and, particularly, in herpes zoster than in herpes simplex. Herpes zoster vasculitis may mimic giant cell arteritis (41). In severe cases of varicella and in disseminated herpes zoster, eosinophilic inclusion bodies have also been observed in the dermis within the nuclei of capillary endothelial cells and of fibroblasts bordering the affected vessels. In contrast, in localized herpes zoster, in which the virus reaches the epidermis by way of the cutaneous nerves rather than the capillaries, inclusion bodies have been demonstrated within neurilemmal cells of the small nerves in the dermis underlying the vesicles. Immunohistochemical methods using specific monoclonal antibodies may have some utility in separating VZV from HSV. Using an antibody specific for an envelope glycoprotein, Nikkels and colleagues (42) demonstrated VZV reactivity in sebaceous cells, endothelial cells, mononuclear phagocytes, and factor XIIIa-positive dendrocytes.

Tzanck Smear. Cytologic examination of the contents of vesicles is carried out for varicella and herpes zoster in the same way as for herpes simplex. It is a very useful diagnostic test, confirming the diagnosis in 80% to 100% of the cases, whereas viral cultures can confirm in only 60% to 64% (43).

Histogenesis and Viral Identification. Cultures remain the gold standard for virologic confirmation, and the virus can be cultured easily from vesicular fluid within 5 days of the onset

of symptoms or before the crusting of lesions. However, culture is not very sensitive, and in contrast with herpes simplex, VZV does not grow in ordinary tissue cultures—it only grows in human fetal diploid kidney cells or human foreskin fibroblasts. Specific antibodies are available for serologic or immunohistochemical viral identification. Electron microscopic examination of the cutaneous lesions of varicella and herpes zoster reveals virus particles in the capillary endothelium in varicella and sporadically in the axons of dermal nerves in herpes zoster. HSV and VZV are indistinguishable by electron microscopy.

CYTOMEGALOVIRUS

CMV is a herpesvirus that is ubiquitous in human populations. It has been estimated that 1% of newborns are infected transplacentally, and about 5% more acquire the infection at the time of birth. There is a steady increase with age in the number of individuals with antibodies in the serum, and this number takes a significant jump at the time of adolescence, presumably due to transfer of virus through the oral route (44). CMV may also be sexually transmitted. Owing to its ability to remain latent in peripheral leukocytes, CMV can be transmitted via transfusion. Most individuals have a mild flulike episode on initial infection; however, the virus subsequently becomes latent and persists in many tissues in the body. In immunocompromised individuals, reactivation and involvement of almost any organ of the body can take place and produce a widespread, potentially fatal, systemic infection (45).

Skin manifestation of CMV infection is rare in immunocompetent persons. Cutaneous lesions reported in the immunocompromised patients varies greatly, from genital ulceration to ulceration of the chest. A more or less widespread maculopapular rash that may become purpuric, sharply punched-out ulcers, urticaria, vesiculobullous lesions, keratotic lesions, and epidermolysis have been reported (46). In the context of HIV infection, CMV-associated viral cytopathic changes can be observed as epiphenomena in skin biopsies in that they do not appear to be the primary pathogen in the specimen and the cause of the skin eruption.

Neonates with congenital CMV infection may exhibit the clinical picture of the "blueberry muffin baby" at delivery, which is manifested by petechiae and purpuric magenta-colored macules, papules, and plaques as well as blueberry-colored ecchymoses. The hemorrhagic-purpuric looking skin lesions are thought to reflect extramedullary hematopoiesis. Ultrastructural study demonstrates that complexes of red cells in various stages of maturation occur in the skin of these patients, similar to the erythroblastic islands in the bone marrow (47). Transplacental transfer of CMV is one of the causes of *TORCH*, a congenital infection caused by Toxoplasmosis, other infections, Rubella, Cytomegalovirus, and Herpes simplex virus, with extensive damage to the developing brain, chorioretinitis, and pneumonitis (48).

Histopathology. Dilated dermal vessels exhibit, among normal endothelial cells, large, irregularly shaped endothelial cells with large, hyperchromatic, basophilic, intranuclear inclusions that are around 10 μm in size as well as small intracytoplasmic inclusions (around 3 μm in size) (Fig. 25-7). Some of the inclusions are surrounded by clear halos. A mixed inflammatory infiltrate with focal leukocytoclastic changes may also be present. In the context of HIV infection, other pathologic processes may also be present in the same tissue section.

Histogenesis and Viral Identification. CMV culture can be performed by using human fibroblasts. PP65 is a CMV viral protein that is detectable in infected peripheral mononuclear cells, which is a sensitive method to estimate the systemic viral load (49). Immunohistochemical studies using monoclonal or polyclonal antibodies to CMV antigens can be used in paraffin-embedded sections to reveal viral proteins and confirm the presence of the virus. CMV DNA can also be amplified from skin biopsy specimens with PCR by using specific primers for CMV or can be identified by *in situ* hybridization. Electron microscopy shows intranuclear viral particles approximately 110 nm in diameter. The virus greatly resembles that of herpes simplex.

Epstein-Barr Virus

EBV is thought to be responsible for a number of diseases such as infectious mononucleosis (IM), oral hairy leukoplakia, and cutaneous lymphoproliferative disorders as well as Burkett's lymphoma and nasopharyngeal carcinoma (50). Infection with the EBV develops first in the salivary gland. Large amounts of the virus are released in the saliva, enabling it to spread from one person to another. People infected with EBV will retain it for life, and most are asymptomatic. It has been estimated that the virus infects almost everyone in developing countries and >80% of people in developed countries. Most people are infected with the virus during childhood and usually are not noticeably affected. On the other hand, people infected for the first time during or after adolescence (10% to 20% of people living in developed countries) have a 50% chance of developing IM. The main site of viral persistence is within latently infected lymphocytes, although infectious virus is also released into saliva from infected cells in the oropharynx (51).

IM is a self-limited manifestation of acute EBV infection. The transient rash that occurs quite commonly in patients with IM who have received antibiotic therapy is an erythematous, maculopapular eruption, usually located on the trunk and upper extremities. The palms, soles, and oral mucosa also have been reported to be occasionally involved. The pathogenesis of the rash is believed to be secondary to polyclonal B-cell activation that occurs during EBV infection with production of polyclonal antibodies that form immune complexes capable of fixing complement (52). Oral hairy leukoplakia is another manifestation of EBV infection that occurs in immunosuppressed HIV-positive and HIV-negative individuals. In HIV-positive individuals, it serves as an indicator of disease severity and rapid progression to AIDS. The presence of oral hairy leukoplakia in an individual should prompt the clinician to perform a thorough history taking and investigation of

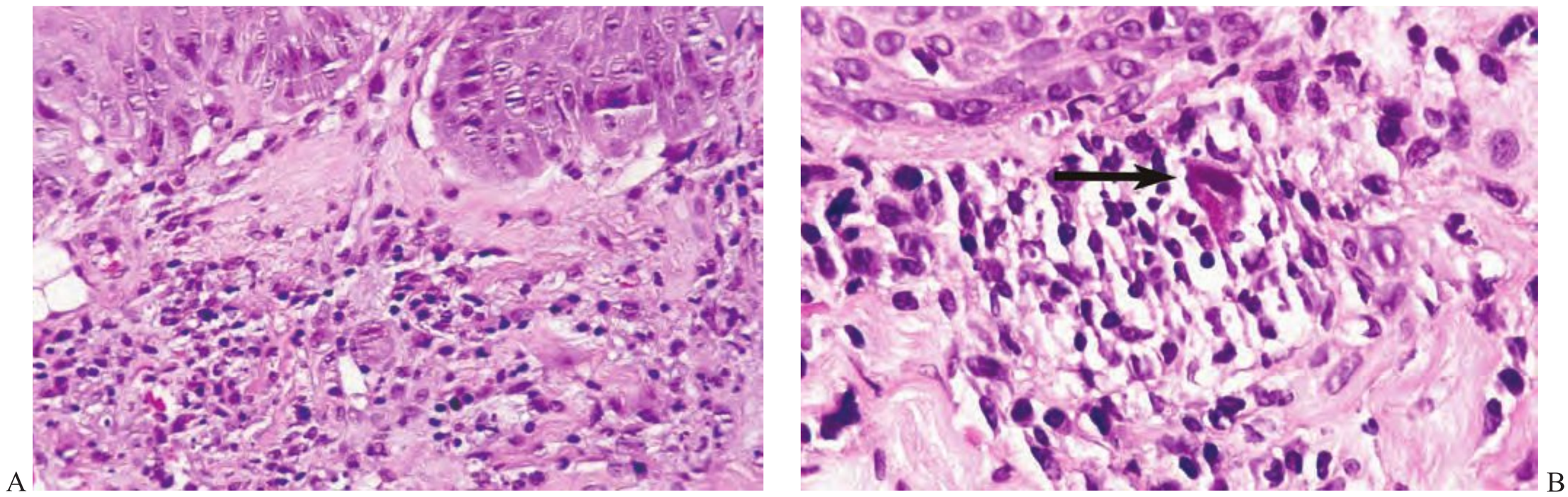


FIGURE 25-7. Cytomegalic inclusion disease. A: Scanning magnification shows superficial perivascular and diffuse inflammation with prominent vessels. Enlarged endothelial cells may be apparent at this magnification. B: At high magnification, one infected dermal cell in the center shows enlarged, hyperchromatic, basophilic, intranuclear inclusions. There is a mixed inflammatory infiltrate in the dermis. C: Dilated dermal vessel with large, irregularly shaped endothelial cells. The enlarged endothelial cells contain hyperchromatic, basophilic, intranuclear inclusions (arrow points to an inclusion). There may be basophilic cytoplasmic inclusions as well.

immune status. These lesions characteristically resemble whitish patches with a verrucous or filiform irregular surface that cannot be scraped off and are located primarily on the lateral surfaces of the tongue unilaterally or bilaterally. The condition is usually asymptomatic; however, in some cases, a burning sensation can occur, which is most likely secondary to coinfection by *Candida* (53). Lymphoproliferative disorders associated with EBV are well documented in the literature. EBV has recently been demonstrated to be associated with cutaneous T-cell lymphoma (54). EBV genome has also been detected in postrenal transplant cutaneous lymphoma, recurrent necrotic papulovesicles of the face (55), and cutaneous angiocentric lymphoma (56).

Histopathology. The histology of the macular lesion associated with IM is nonspecific and usually shows superficial perivascular lymphohistiocytic infiltrates. The histologic features that typify oral hairy leukoplakia include irregular epithelial hyperplasia with associated parakeratosis and acanthosis (Fig. 25-8A). Ballooning of keratinocytes occurs, and there are small, pyknotic nuclei with intranuclear inclusions and a clear perinuclear halo. The cytoplasm may adopt a ground-glass appearance (Fig. 25-8B). There is also a mild inflammatory infiltrate observed in the superficial dermis. Langerhans cells are noted to be absent in the epithelium. Hyphae of *Candida* are observed within the superficial epithelium of a majority of the patients with oral hairy leukoplakia and may play a role in the development of the epithelial hyperplasia observed in oral hairy leukoplakia. A leukocytoclastic vasculitis and neuropathy associated with chronic EBV infection have also been reported. EBV can be detected by *in situ* hybridization (Fig. 25-8C).

Human Herpesvirus-6, -7, and -8

HHV-6, -7, and -8 are relatively newly discovered viruses. These ubiquitous viruses may cause primary or chronic persistent infection or remain in a state of latency for many years, until a decrease in the immunologic state of the host leads to reactivation of infection (57). HHV-6 was first isolated in 1986 from patients with lymphoproliferative disorders and was classified into two variants as HHV-6A and HHV-6B. HHV-6B is the causative agent of exanthem subitum. Children start to be infected with HHV-6 at 6 months of age, and almost all get antibody by 2 years old. The transmission of HHV-6 is essentially by a salivary route (58). HHV-6 infects latently after the primary infection and reactivates especially under an immunosuppressive condition. Skin rash in the first month after allogeneic bone marrow transplant (59), generalized vesiculobullous eruptions after allogeneic bone marrow transplantation (60), papular-purpuric "gloves and socks" syndrome (61), papular acrodermatitis of childhood (Gianotti-Crosti syndrome) (62),

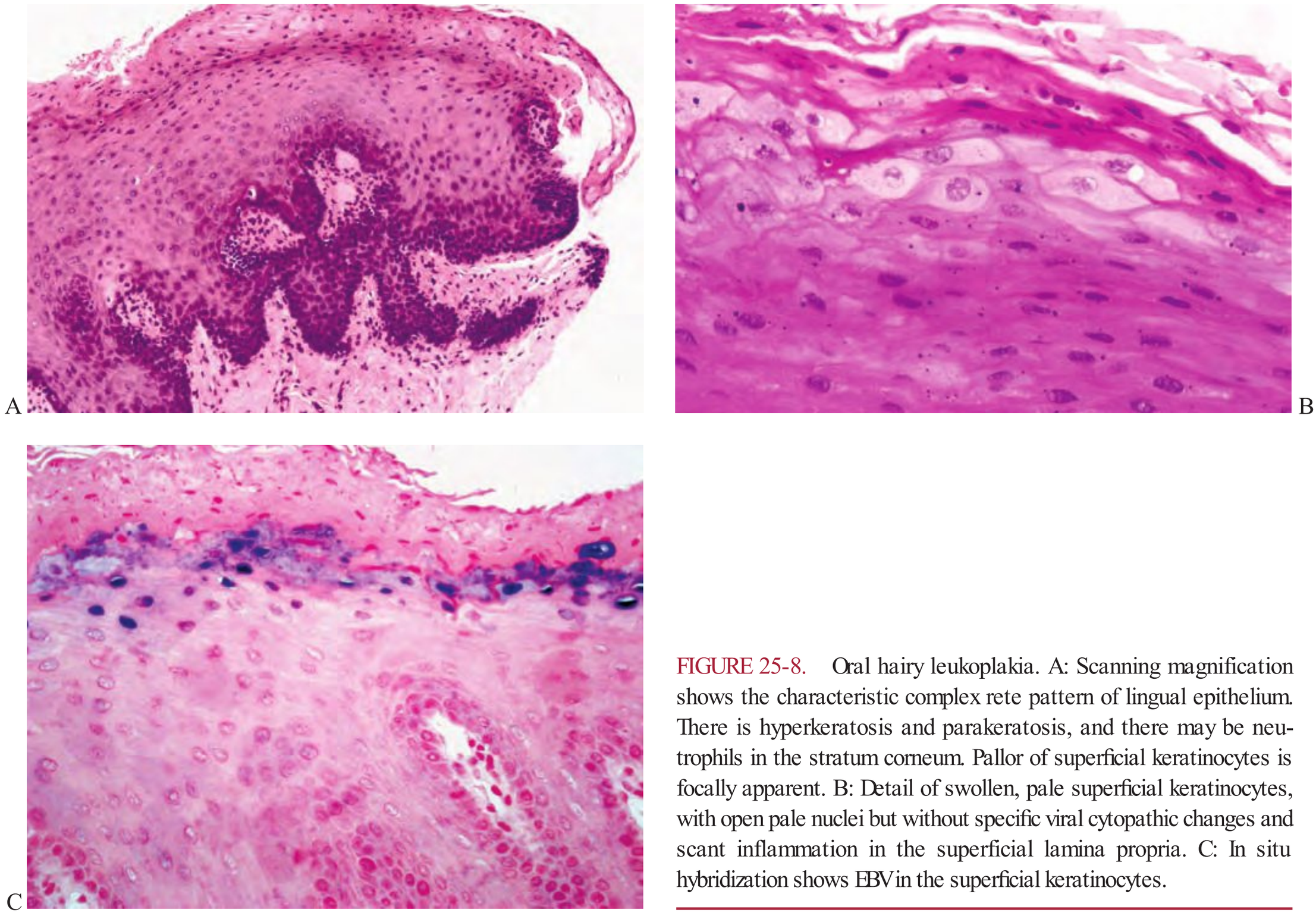


FIGURE 25-8. Oral hairy leukoplakia. A: Scanning magnification shows the characteristic complex rete pattern of lingual epithelium. There is hyperkeratosis and parakeratosis, and there may be neutrophils in the stratum corneum. Pallor of superficial keratinocytes is focally apparent. B: Detail of swollen, pale superficial keratinocytes, with open pale nuclei but without specific viral cytopathic changes and scant inflammation in the superficial lamina propria. C: In situ hybridization shows EBV in the superficial keratinocytes.

and a serious systemic reaction to a limited number of drugs called *hypersensitivity syndrome* have been associated with HHV-6 (63). HHV-6 has also been detected in skin biopsy samples of patients with graft-versus-host disease, pityriasis rosea, and lymphoproliferative malignancies.

HHV-7, isolated from $CD4^+$ T lymphocytes from the peripheral blood of a healthy individual, has been recognized as a new lymphotropic herpesvirus. Healthy adults frequently shed the virus into saliva, and children are infected at a young age but somewhat later than HHV-6B. Latency is established in peripheral blood T cells, and a persistent infection in the salivary glands is believed to be the most likely mode of transmission. The primary infection with HHV-7 is linked to febrile illness with or without rash that resembles exanthema subitum. Pityriasis rosea is thought to be associated with HHV-7; however, the association is still controversial (64).

HHV-8 was first identified in tissue samples of patients with Kaposi's sarcoma (KS) associated with AIDS in 1994. Serologic studies have demonstrated that unlike other human herpesviruses, HHV-8 is not ubiquitous; instead, its infection rates parallel the incidence of KS in the region. HHV-8 spreads through exchange of saliva and other sexual activities. HHV-8 can be found in all types of KS, whether related to HIV or not. HHV-8 seems to resemble EBV virus in its possible transforming properties, and it is clearly associated with KS, multicentric Castleman disease, and primary effusion lymphoma (65). There may be a synergistic relationship between the HIV-1 Tat protein and HHV-8 infection. Tat promotes the growth of the KS spindle cells. Like other herpesviruses, HHV-8 establishes latent and persistent infection. Only a minority of infected cells yields infectious viral particles, and their role in the development of KS and other associated diseases has not been clearly established. Presence of virus can be established in mononuclear cells of peripheral blood, endothelial cells, and spindle cells within skin lesions.

Histopathology. Exanthem subitum is linked to HHV-6 infection. It is a form of superficial perivascular dermatitis with papillary dermal edema. Exocytosis of lymphocytes is often present. Inclusions similar to those in herpes simplex infection are not seen.

POXVIRIDAE

The Poxviridae are double-stranded DNA viruses with two subfamilies and eleven genera. Poxvirus infections of humans include variola (smallpox), cowpox, vaccinia, molluscum

contagiosum, paravaccinia (milkers' nodules), and orf (ecthyma contagiosum).

Variola (Smallpox)

Before it was eradicated in 1977, smallpox was one of the most infectious and deadly diseases in the world, afflicting millions of people each year regardless of age, race, or socioeconomic status (66). There were two forms of smallpox: variola major and variola minor. Variola major had a case fatality rate of approximately 25% among those affected, while variola minor, a less virulent form, had a case fatality rate below 1%. Although the two forms cause disease of different severity, they are indistinguishable from one another. Smallpox was spread through respiratory transmission of virus found in the oropharyngeal secretions of infected individuals. Penetration was usually through the respiratory tract and local lymph nodes and then the virus entered the blood (primary viremia). Internal organs would be infected; later, the virus would reenter the blood (secondary viremia) and spread to the skin. The onset of smallpox was acute, with fever, malaise, headaches, and backaches. The initial toxemia phase lasted 4 to 5 days. On about the third or fourth day, the characteristic rash appeared. First, it appeared on the buccal and pharyngeal mucosa, face, and forearms. Within a day, it spread to the trunk and lower limbs. The lesions of the rash began first as macules, which soon became papules and then developed into pustular vesicles. The lesions usually protruded from the skin, and they were firm to touch. The lesions dried up and often became crusted by day 14. By the end of the third week, most crusts had fallen off, with the exception of those on the palms and the soles (67). This entire process took 3 to 4 weeks, and the areas affected by the rash could be permanently scarred. The rare hemorrhagic type smallpox that appeared in immunocompromised individuals was associated with bleeding from the conjunctiva and mucous membranes, very severe toxemia, and early death, usually before the lesions of the skin had developed. Modified-type smallpox was seen in persons who had been vaccinated, usually many years earlier. In these cases, the skin lesions evolved quickly and were more variable in size.

Histopathology. There is prominent ballooning and reticular degeneration. Under light microscopy, aggregations of variola virus particles, called *Guarnieri bodies*, may be found in the cytoplasm; occasional intranuclear inclusions can also be found. However, similar changes can be seen in vaccinia, monkeypox, or cowpox.

Vaccinia

Vaccinia virus was used for smallpox vaccination via inoculation into the superficial layers of the skin of the upper arm. However, with the eradication of smallpox, routine vaccination with vaccinia virus ceased for many years but may soon become more common because of security concerns. Four to 5 days following vaccination with vaccinia virus, a papule appears at the site of vaccination. Two or 3 days later, the papular lesion becomes vesicular, growing until it reaches its maximum diameter on the ninth or tenth day. The lesion dries from the center outward, and the brown scab falls off after about 3 weeks, leaving a scar—a mark by which previous vaccinees can be recognized (68). Complications of vaccination can occur but are very rare, including the following conditions: progressive vaccinia (vaccinia necrosum), which is a severe, potentially fatal illness characterized by progressive necrosis at the site of vaccination; eczema vaccinatum, which is similar to eczema herpeticum in patients with chronic eczema; generalized vaccinia, which is characterized by a vesicular rash that sometimes has covered the entire body; and postvaccinial encephalitis, the most serious neurologic complication, which has occurred from vaccination with vaccinia virus (69). Other localized lesions such as keloid, dermatofibrosarcoma protuberans, and malignant fibrous histiocytoma have been reported at the site of inoculation. These complications are extremely rare.

Histopathology. The histologic changes are similar to those of herpes simplex and zoster and varicella. However, intracytoplasmic inclusions are seen in vaccinia, unlike in herpes infection.

Human Cowpox Infection

Despite its name, the reservoir hosts of cowpox virus are rodents, from which it can occasionally spread to cats, cows, humans, and zoo animals, including large cats and elephants. Infection in these animals is usually manifested as a single, small, crusted ulcer. Transmission to humans has traditionally occurred via contact with the infected teats of milking cows. However, currently, infection is seen more commonly among domestic cats, from which it can be transmitted to humans. Patients present with painful, hemorrhagic pustules or black eschars, usually on the hand or face, accompanied by edema, erythema, lymphadenopathy, and systemic involvement (70). Crusted lesions resembling anthrax and sporotrichoid infection have been reported.

Histopathology. The pathology of the skin lesions caused by cowpox virus is similar to that of smallpox. However, there is greater epithelial thickening and less rapid cell necrosis. Early lesions of human cowpox infection show prominent reticular degeneration. Eosinophilic, intracytoplasmic inclusion bodies are present, a valuable feature in distinguishing poxvirus from herpesvirus infections. Under electron microscopic examination, it is rectangular and morphologically indistinguishable from the virus of variola.

Parapoxvirus Infections (Milkers' Nodules and Orf)

Milkers' nodules, orf, and bovine papular stomatitis pox are clinically identical in humans and are induced by indistinguishable paravaccinia viruses. *Milkers' nodules* are acquired from udders infected with pseudocowpox or paravaccinia (parapox). This disease is called *bovine papular stomatitis pox* when the source of the infection is calves with oral sores

contracted through sucking infected udders. *Orf* (ecthyma contagiosum) is acquired from infected sheep or goats with crusted lesions on the lips and in the mouth.

The most common presentation of orf is a circumscribed solitary nodule or papule on the fingers or hands (71). Milkers' nodules usually presents with multiple lesions. After an incubation period of 3 to 7 days, parapoxvirus infections produce one to three (rarely more) painful lesions measuring 1 to 2 cm in diameter on the fingers or occasionally elsewhere as a result of autoinoculation. During a period of approximately 6 weeks, they pass through six clinical stages, each lasting about 1 week: (a) the maculopapular stage; (b) the target stage, during which the lesions have red centers, white rings, and red halos; (c) the acute weeping stage; (d) the nodular stage, which shows hard, nontender nodules; (e) the papillomatous stage, in which the nodules have irregular surfaces; and (f) the regressive stage, during which the lesions involute without scarring.

Histopathology. During the maculopapular and target stages, there is vacuolization of cells in the upper third of the stratum malpighii, leading to multilocular vesicles. Eosinophilic inclusion bodies are in the cytoplasm of vacuolated epidermal cells, a distinguishing feature from herpesvirus infections (Fig. 25-9C). Intranuclear eosinophilic inclusion bodies are also present in some cases. During the target stage, vacuolated epidermal cells with inclusion bodies are only in the surrounding white ring. Ballooning degeneration occurs, the affected keratinocytes rupture, and the resulting defects have a tendency to coalesce and produce reticulated vesicles (Fig. 25-9A). The epidermis shows elongation of the rete ridges, and the dermis contains many newly formed, dilated capillaries and a mononuclear infiltrate (Fig. 25-9B).

In the acute weeping stage, the epidermis is necrotic throughout. A massive infiltrate of mononuclear cells extends throughout the dermis. In some lesions, the mononuclear cell infiltrates may be comprised mainly of large, transformed lymphoblasts. Such lesions might be misdiagnosed as a lymphoid neoplasm if careful attention is not given to the changes in the keratinocytes. A lichenoid reaction with a high percentage of histiocytes, a common response to viral infections of the skin, can also be seen. In the later stages, the epidermis shows acanthosis with finger-like downward projections, and the dermis shows vasodilatation and chronic inflammation, followed by resolution. The histology of orf and milkers' nodules is identical.

Histogenesis and Viral Identification. In lesions <2 weeks old, the virus can be grown in tissue cultures of various cell types, including bovine or rhesus monkey kidney cells and human amnion cells or fibroblasts. In older lesions, serologic changes or viral antigen demonstration in lesional material have to be relied on for identification. Electron microscopy reveals that the parapoxvirus is cylindrical in shape and has convex ends. It consists of a dense DNA core surrounded by a less dense, wide capsid and by two narrow, electron-dense outer layers. On average, the virion measures 140 by 310 nm.

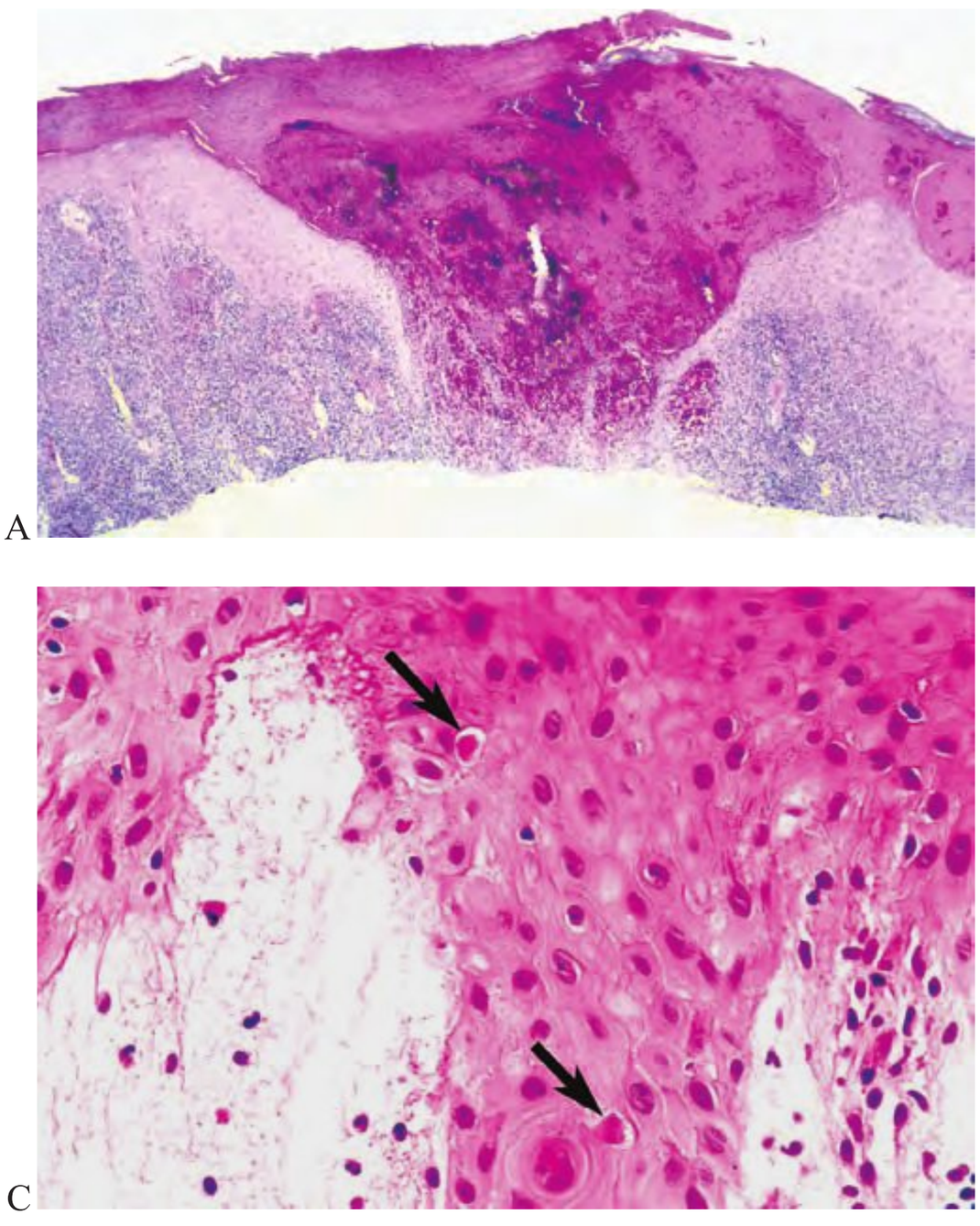


FIGURE 25-9. Orf. A: At scanning magnification, in the target stage, there is central hemorrhage and tissue necrosis with peripheral reticulated degeneration and dense inflammatory infiltrates. B: Reticulated vesicles (a characteristic feature of a viral infection affecting the epidermis), and the dermis contains many newly formed, dilated capillaries and a mononuclear infiltrate. C: Eosinophilic inclusion bodies in the cytoplasm of vacuolated epidermal cells (arrow points to the inclusions) distinguish orf from herpesvirus infections. Intranuclear eosinophilic inclusion bodies are also present in some cases.

Molluscum Contagiosum

Molluscum contagiosum occurs worldwide. It is seen most commonly in children, but it may be found in persons of all ages. The virus is transmitted by direct bodily contact, through minor abrasions, or indirectly via fomites. Among young adults, it is usually a sexually transmitted disease. The incubation period for this virus, as determined by human volunteers who underwent inoculation, ranges from 14 to 50 days.

Molluscum contagiosum may be found anywhere on the body but rarely occur on the palms or soles. It consists of a variable number of small, discrete, waxy, skin-colored, delled, dome-shaped papules, usually 2 to 5 mm in size (Fig. 25-10A). A papule of molluscum contagiosum may appear inflamed. In immunocompetent patients, the lesions involute spontaneously. During involution, there may be mild inflammation and tenderness.

Since 1980, there have been reports of greater severity of molluscum contagiosum in patients infected with HIV. In the setting of immunosuppression, molluscum contagiosum can attain considerable size and be widely disseminated. In immunocompromised patients, particularly those with AIDS, hundreds of lesions of molluscum contagiosum may be observed, showing little tendency toward involution. Furthermore, clinically normal skin in the vicinity of molluscum lesions in HIV-infected persons may be infected by molluscum virus (72). Infection with molluscum contagiosum produces little immunity, with reinfection being relatively common among immunocompromised individuals. In the context of AIDS, a variety of systemic fungal diseases, including cryptococcosis, histoplasmosis, and Penicillium marneffei, can disseminate and produce skin lesions that resemble molluscum contagiosum.

Histopathology. The epidermis is acanthotic in molluscum contagiosum. Many epidermal cells contain large, intracytoplasmic inclusion bodies—the so-called molluscum bodies (Fig. 25-10B). These bodies first appear as single, minute, ovoid eosinophilic structures in the lower cells of the stratum malpighii at a level one or two layers above the basal cell layer. The molluscum bodies increase in size as infected cells move toward the surface. The molluscum bodies in the upper layers of the epidermis displace and compress the nucleus so that it appears as a thin crescent at the periphery of the cell. At the level of the granular layer, the staining reaction of the molluscum bodies changes from eosinophilic to basophilic. In the horny layer, basophilic molluscum bodies measuring up to 35 μm in diameter lie enmeshed in a network of eosinophilic horny fibers. In the center of the lesion, the stratum corneum ultimately disintegrates, releasing the molluscum bodies. Thus, a central crater forms. Secondary infection and ulceration can occur.

The surrounding dermis usually shows little or no inflammatory reaction, except in instances in which the lesion of molluscum contagiosum ruptures and discharges molluscum bodies and horny material into the dermis. During the period of spontaneous involution, a mononuclear infiltrate may be observed in close apposition to the lesion infiltrating between the infected epidermal cells.

Electron microscopic examination reveals that the molluscum inclusion bodies contain—embedded in a protein matrix—large numbers of molluscum contagiosum viruses. The virus of molluscum contagiosum belongs to the poxvirus group. Like the viruses of variola, vaccinia, and cowpox, it is "brick-shaped" and measures approximately 300 by 240 nm. The virus of molluscum contagiosum has not been grown in tissue culture. Molluscum contagiosum virus can be detected directly in tissue specimens by using *in situ* hybridization (73).

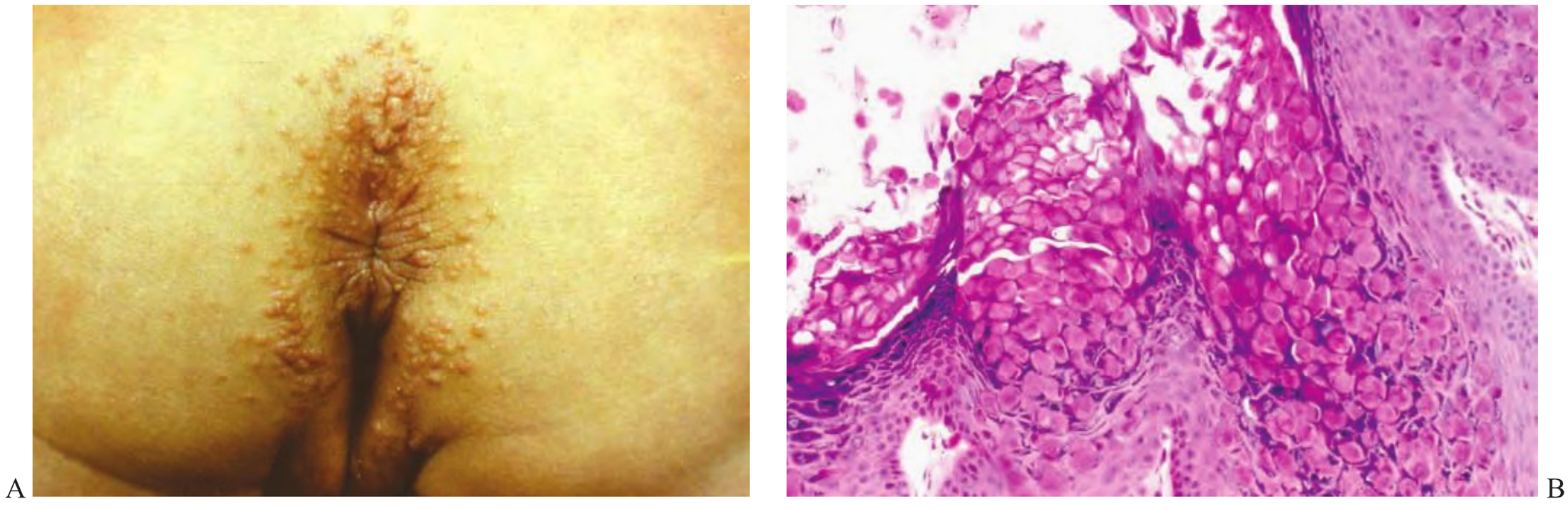


FIGURE 25-10. Molluscum contagiosum. A: Multiple lesions, some with characteristic central umbilication. B: Numerous intracytoplasmic inclusion bodies, so-called molluscum bodies, can be seen forming in the lower epidermis. They increase in size as they move toward the surface.

PAPILLOMAVIRIDAE

The human papillomavirus (HPV) belongs to the Papillomaviridae family. It consists of a group of nonenveloped

double-stranded DNA viruses. An infectious origin for skin warts was first recognized in 1891, and viral particles were isolated from human skin papillomatous lesions in 1949. Since that time, over 80 fully sequenced HPV genotypes have been identified, with another 70 additional genotypes suggested through PCR analysis (74). The genetic heterogeneity is reflected in the differing clinical presentations of HPV infection. The cutaneous and mucosal manifestations of HPV infection include the common wart verruca vulgaris, the genital wart condyloma acuminatum, and less common entities including epidermodysplasia verruciformis (EV) and oral focal epithelial hyperplasia (Heck's disease). HPV is regarded as an oncogenic virus and is well known to be associated with cervical and anogenital cancers (75). Recently, HPV has been implicated in oropharyngeal squamous cell carcinoma (76), lung cancer (77), esophageal cancer (78), and in nonmelanoma skin cancers (79), particularly in immunosuppressed patients (80). The specific viral genotypes show fairly good association with the different clinical presentations listed, although considerable overlap exists.

Verruca vulgaris: 1, 2, 4, 7, 49
Verruca plana: 3, 10, 28, 49
Palmoplantar wart: 1, 2, 3, 4, 27, 29, 57
Condyloma acuminatum (high cancer risk): 16, 18, 31, 33, 51
Focal epithelial hyperplasia: 13, 32
Bowenoid papulosis: 16, 18, 31, 33, 51
Butcher's warts: 7
EV: 3, 5, 8–10, 12, 14, 17, 19–29, 36, 38, 47, 50
Laryngeal carcinoma: 30
Head and neck (oropharyngeal) squamous cell carcinoma: 16
Giant condyloma of Bushke and Loewenstein: 6
Cervical and vulvar dysplasia: 16, 18, 31, 33, 51

The association of particular HPV types with specific groups of warts, however, is not absolute. The value of HPV typing in the clinical setting is not clear. Definitive HPV typing can be obtained through DNA hybridization or amplification of HPV genomic material by PCR. However, positive results cannot be considered definitive in predicting outcome. High-risk HPV types can be missed through sampling errors. In the end, close follow-up is important in the management of HPV infection, particularly when the patient has clinical exposure to potentially high-risk HPV types (81).

All HPV types target squamous epithelial cells. Entry of HPV into squamous epithelium results in three different type of infections: latent infection, in which there is no gross or microscopic evidence of disease; subclinical infection, in which colposcopy or microscopy reveals disease in the absence of clinical disease; and clinical disease. Early HPV genes are expressed in basal epithelial cells. Clinical and histologic evidence of HPV infection usually develops 1 to 8 months after initial exposure. Untreated, these lesions may regress spontaneously, persist as benign lesions, or progress to precancerous lesions and eventually cancer (82).

Verruca Vulgaris

Verruca vulgaris, the common wart, most commonly presents singly or in groups on the dorsal aspects of the fingers and hands as painless, circumscribed, firm, elevated papules with papillomatous ("verrucous") hyperkeratotic surfaces (Fig. 25-11A). The palms and soles are less common sites and present at these sites as mosaic warts. Verruca vulgaris is rarely identified on the oral mucosa. The face and scalp are the most common sites for filiform warts, variants of verruca vulgaris that show threadlike, keratinous projections arising from horny bases.

Verrucae vulgares are circumscribed, firm, elevated papules with papillomatous ("verrucous") hyperkeratotic surfaces. They occur singly or in groups. Generally, they are associated with little or no tenderness. Verrucae vulgares occur most commonly on the dorsal aspects of the fingers and hands. They are also found on the soles of the feet and less often on the palms as mosaic warts. Rarely, verrucae vulgares occur on the oral mucosa. Filiform warts, variants of verruca vulgaris, show threadlike, keratinous projections arising from horny bases. New warts may form at sites of trauma (Koebner phenomenon). Verrucae vulgares are often associated with HPV-2 but may be induced by HPV-1, -4, -7, and -49.

Histopathology. Verrucae vulgares show acanthosis, papillomatosis, and hyperkeratosis (Fig. 25-11B). The rete ridges are elongated and, at the periphery of the verruca, are often bent inward so that they appear to point radially toward the center (arborization). The characteristic features that distinguish verruca vulgaris from other papillomas are foci of vacuolated cells, referred to as *koilocytotic cells*; vertical tiers of parakeratotic cells; and foci of clumped keratohyaline granules (Fig. 25-11C). These three changes are quite pronounced in young verrucae vulgares. The foci of koilocytes are located in the upper stratum malpighii and in the granular layer. The koilocytes possess small, round, deeply basophilic nuclei surrounded by a clear halo and pale-staining cytoplasm. These cells contain few or no keratohyaline granules, even when they are located in the granular layer. The vertical tiers of parakeratotic cells are often located at the crests of papillomatous elevations of the rete malpighii overlying a focus of vacuolated cells. Compared with ordinary parakeratotic nuclei, the nuclei of the parakeratotic cells in verrucae vulgares are larger and more deeply basophilic, and many of them appear rounded rather than elongated. Although no granular cells are seen overlying the papillomatous crests, they are increased in number and size in the intervening valleys and contain heavy, irregular clumps of keratohyaline granules. Dilated capillaries and small areas of hemorrhage may be seen in the thickened horny layer at the tip of the vertical tiers of parakeratotic cells (Fig. 25-11C). In filiform warts, the papillae are more elongated than in verrucae vulgares (Fig. 25-11D).

Although warts are very common, especially in children and adolescents, defective cell-mediated immunity predisposes to the development of some types of warts. The frequency of warts in persons with renal transplants receiving immunosup-

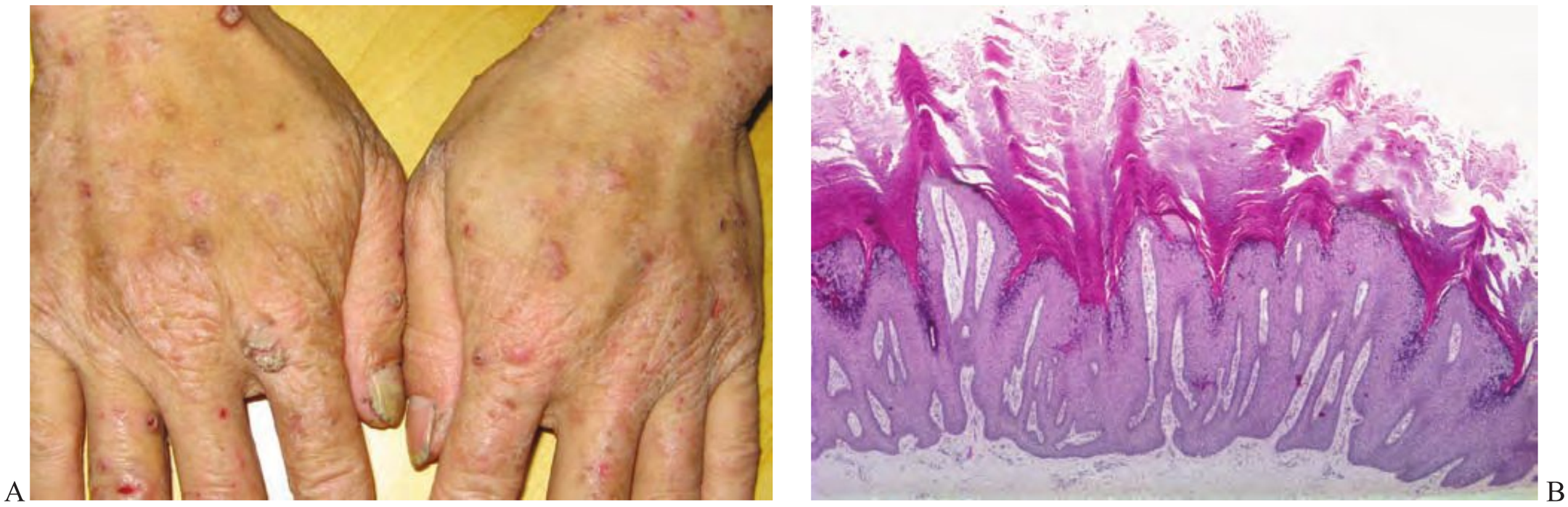


FIGURE 25-11. Verruca vulgaris. A: Multiple lesions most commonly seen on the hands and fingers. B: Low magnification. Hyperkeratosis, acanthosis, and papillomatosis are seen. The rete ridges are elongated and bent inward at both margins and thus appear to point radially to the center. C: High magnification. Groups of large, vacuolated cells lie in the upper stratum malpighii and granular layer. D: Verruca vulgaris of filiform type. There is marked papillomatosis.

pressive therapy is greater than that of the general population (83). In the context of HIV infection, a variety of papillomavirus infections have been reported. Eradication of cutaneous infection becomes increasingly difficult as the degree of immunosuppression becomes more profound.

Histogenesis and Viral Identification. No difference has been noted in electron microscopic appearance among the virus particles in the various types of HPV. However, the quantity varies with the different types. Frequently, virus particles are absent in verrucae vulgares on electron microscopic examination. Negative results of electron microscopic examination do not exclude the presence of HPV. Viral antigens, such as papillomavirus common antigen, can be detected by using immunohistochemistry, and HPV DNA can be amplified from lesions by using PCR with appropriate primers. Viral genomic material can also be identified by *in situ* hybridization. Viral DNA replication occurs in proliferating basal cells, but structural capsid protein forms in the mid-epidermis; thus, mature HPV viral structures, if present, are observed only in the upper epidermis.

The virus particles are spherical bodies with a diameter of about 50 nm. Each particle consists of an electron-dense nucleoid with a stippled appearance surrounded by a less dense capsid. The wart virus replicates in the nucleus, where the viral

particles are located as dense aggregates in a crystalloid arrangement. Eosinophilic intranuclear bodies are very rare in verrucae vulgares. The wart virus does not grow in tissue cultures and is not pathogenic for any animals.

Deep Palmoplantar Warts

Deep palmoplantar warts can be tender and occasionally swollen and red. Although they may be multiple, they do not coalesce as do mosaic warts, which are verrucae vulgares. Deep palmoplantar warts occur not only on the palms and soles but also on the lateral aspects and tips of the fingers and toes. Unlike superficial, mosaic-type palmoplantar warts, deep palmoplantar warts usually are covered with a thick callus (Fig. 25-12A). When the callus is removed with a scalpel, the wart becomes apparent.

A plantar wart associated with HPV-60 may appear as a nodule on the weight-bearing surface of the sole. The nodule usually is smooth with visible rete ridges but may become hyperkeratotic. If the lesion is incised, cheesy material may be expressed. A pigmented verrucous variant associated with HPV-65 and a whitish keratotic wart associated with HPV-63 have been reported.

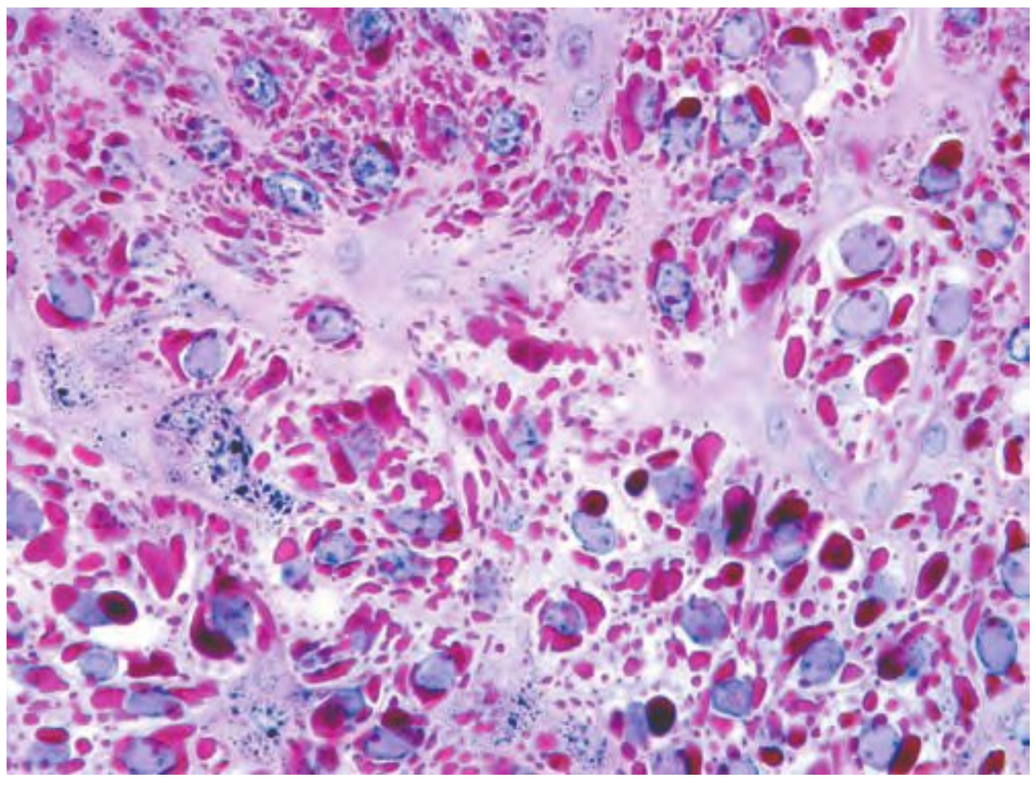
Histopathology. Whereas superficial, mosaic-type palmoplantar warts have a histologic appearance analogous to that of verruca vulgaris and represent HPV-2 or HPV-4 infection, deep palmoplantar warts are commonly associated with HPV-1 infection but can also be seen with HPV-60, -63, and -65. These lesions, also known as *myrmecia* ("anthill") or *inclusion warts*, are characterized by abundant keratohyalin, which differs from normal keratohyalin by being eosinophilic. There is prominent hyperkeratosis. Starting in the lower epidermis, the cytoplasm of many cells contains numerous eosinophilic granules, which enlarge in the upper stratum malpighii and coalesce to form large, irregularly shaped, homogeneous "inclusion bodies." They either encase the vacuolated nucleus or are separated from it by perinuclear vacuolization. The nuclei in the stratum corneum persist, appearing as deeply basophilic round bodies surrounded by a wide, clear zone (Fig. 25-12B). In addition to the large intracytoplasmic eosinophilic inclusion bodies, some of the cells in the upper stratum malpighii with vacuolated nuclei contain a small intranuclear eosinophilic "inclusion body." It is round and of about the same size as the nucleolus, which, however, is basophilic (Fig. 25-12C). Regression of plantar warts is often



A



B



C

FIGURE 25-12. Palmoplantar wart (myrmecia). A: The lesions are flat with prominent hyperkeratosis. Vascular thromboses can be seen in some lesions. B: Virally induced proliferation of keratinocytes results in the lesion. The elongated retia are displaced laterally while their tips point to the center in the deep portion. The lesion is covered by thickened keratin, resulting in a tendency to grow inward rather than outward from the surface. C: The epidermal squamous cells contain polygonal, refractile-appearing, eosinophilic, cytoplasmic inclusions. Nuclei also contain round eosinophilic bodies.

associated with thrombosis of superficial vessels, hemorrhage, and necrosis of the epidermis.

Histogenesis and Viral Identification. Under electron microscopic examination, viral particles are first observed in the upper portion of the stratum malpighii within and around the nucleolus. Their number increases, and in cells just beneath the stratum corneum, nucleoli are no longer detected. In many instances, the material of the nucleus appears to be entirely replaced by virus particles except for a thin rim of chromatin closely applied to the nuclear membrane. The particles tend to be arranged in regular or crystalline formations. In the stratum corneum, no normal cell structures are recognizable, but there remain large, compact aggregates of virus particles surrounded by keratinous matter.

Verruca Plana

Verrucae planae are slightly elevated, flat, smooth papules. They may be hyperpigmented. The face and the dorsa of the hands are affected most commonly (Fig. 25-13A). In rare instances, there is extensive involvement, with lesions also on the extremities and trunk. If starting in childhood and occurring in several members of the family, such disseminate cases of verruca plana have been mistakenly held to be instances of EV, from which they differ by the absence of red, "tinea versicolor–like" patches and lack of malignant transformation of some of the exposed lesions.

Histopathology. Verrucae planae show hyperkeratosis and acanthosis but, unlike verrucae vulgares, have no papillomatosis, only slight elongation of the rete ridges, and no areas of parakeratosis. In the upper stratum malpighii, including the granular layer, there is diffuse vacuolization of the cells (Fig. 25-13B). Some of the vacuolated cells are enlarged to about twice their normal size. The nuclei of the vacuolated cells lie at the centers of the cells, and some of them appear deeply basophilic. The granular layer is uniformly thickened, and the stratum corneum has a pronounced basket-weave appearance resulting from vacuolization of the horny cells. The dermis appears normal. In spontaneously regressing warts, there is often a superficial lymphocytic infiltrate in the dermis with exocytosis and apoptosis of cells in the epidermis.

Histogenesis. Verrucae planae are induced by HPV-3 and HPV-10. Electron microscopic examination reveals marked cytoplasmic edema. The tonofilaments are dislodged to the periphery of the cell. The keratohyaline granules appear normal. Viral particles are numerous in the nuclei of vacuolated cells.

Epidermodysplasia Verruciformis

EV is a genetic disease characterized by HPV infection with types not seen in otherwise healthy individuals. It usually begins in childhood and is characterized by a generalized infection by HPV, frequent association with cutaneous carcinomas, and abnormalities of cell-mediated immunity (84). Two forms of EV are recognized. One form is induced by HPV-3 and HPV-10 and characterized by a persistent widespread eruption resembling verrucae planae with a tendency toward confluence into plaques. Some of the cases are familial. There is no tendency to malignant transformation in this form. The other form is primarily related to HPV-5. There is often a familial history with an autosomal recessive or X-linked recessive inheritance. In addition to the plane warts, irregularly outlined, slightly scaling macules of various shades of brown, red, and white, tinea versicolor–like lesions, and seborrheic keratosis–like lesions have been noted (85). The eruption usually begins in childhood. Development of Bowen's disease (squamous cell carcinoma *in situ*) within lesions in exposed areas is a common occurrence, and invasive lesions of squamous cell

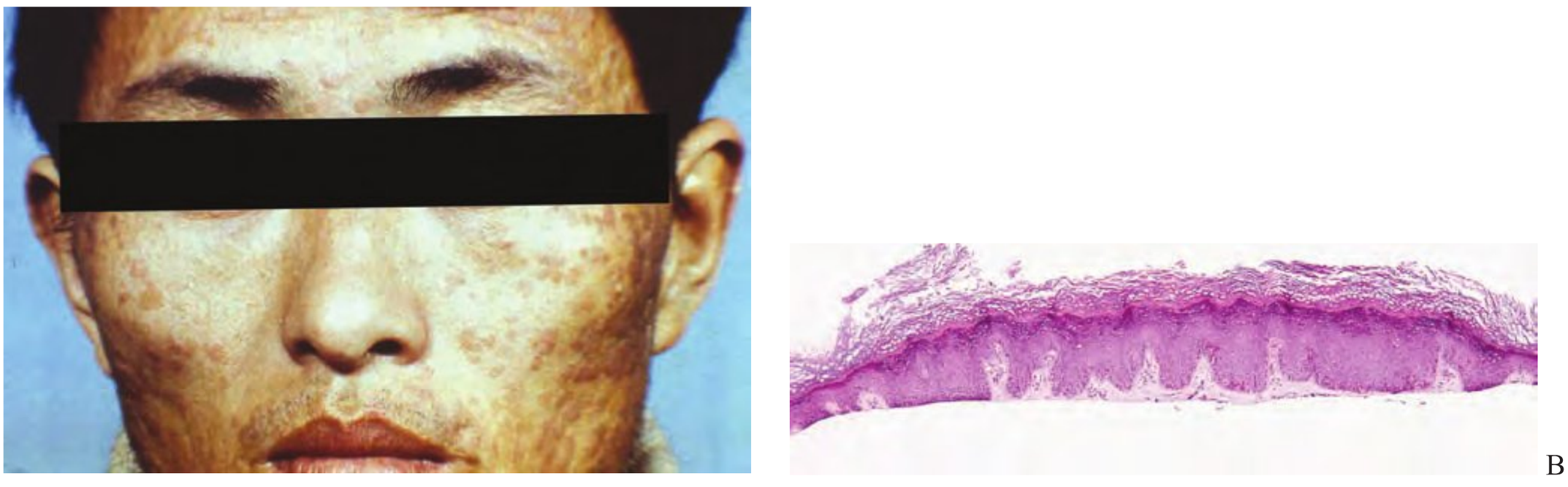


FIGURE 25-13. Verruca plana. A: Flat, smooth, flesh-colored papules, often on the face or hand. B: Hyperkeratosis and acanthosis are observed, but no papillomatosis or parakeratosis. Numerous vacuolated cells lie in the upper stratum malpighii, including the granular layer. The horny layer has a pronounced basket-weave appearance resulting from the vacuolization of the horny cells.

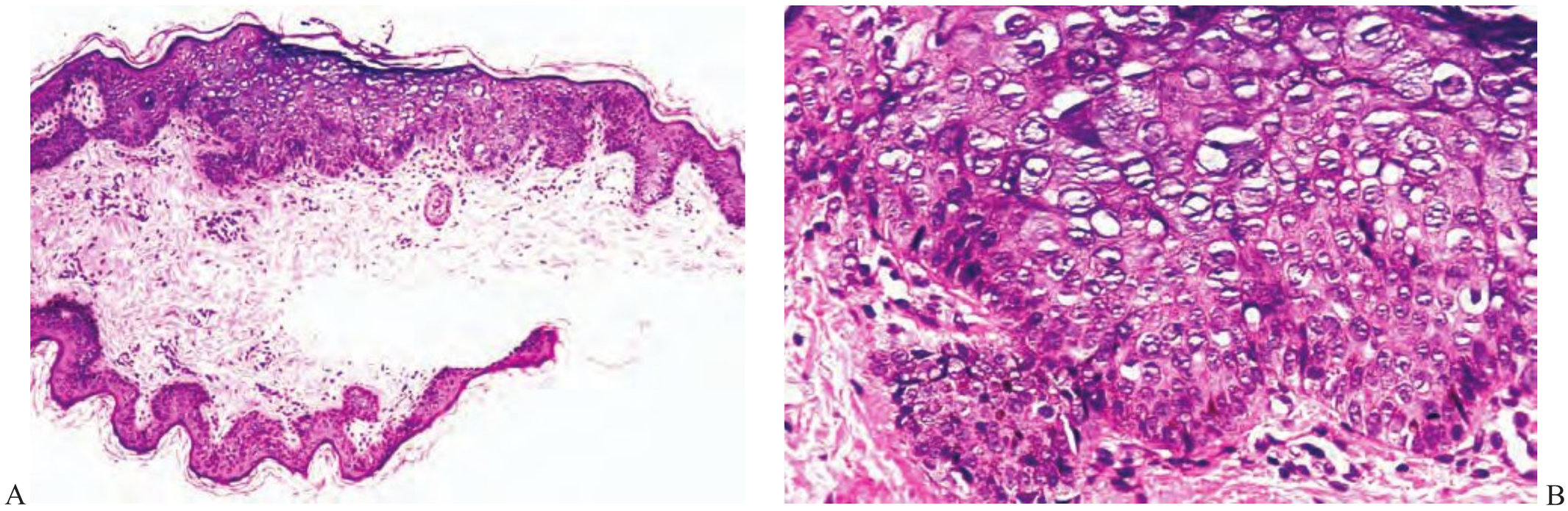


FIGURE 25-14. Epidermodysplasia verruciformis. A: The epidermis is hyperkeratotic and slightly acanthotic. Vacuolated cells are present in the upper stratum malpighii and granular layer. B: Affected keratinocytes have abundant, slightly basophilic cytoplasm. Keratohyalin granules may be prominent, although not in this example. Although some nuclei may appear pyknotic, others appear large, round, and empty.

carcinoma are occasionally found. Malignant transformation occurs in about 25% of patients with EV. The oncogenic potential is highest for HPV-5, followed by HPV-8. EV-like lesions can develop in renal transplant patients (86) and HIV-infected persons (87).

Histopathology. The epidermal changes, although similar to those observed in verruca plana, often differ by being more pronounced and more extensive. Affected keratinocytes are swollen and irregularly shaped. They show abundant, slightly basophilic cytoplasm and contain numerous round, basophilic keratohyalin granules. A few dyskeratotic cells may be seen in the lower part of the epidermis. Although some nuclei appear pyknotic, others appear large, round, and empty owing to marginal distribution of the chromatin (Fig. 25-14). In immunocompromised patients, EV often lacks the histologic features of verruca planae, a focally thickened granular layer is a marker for viral detection, and the risk for dysplasia in such lesions is much higher than in EV not associated with acquired immunosuppression (88).

Histogenesis. In EV skin lesions, many HPV types have been found, and in some individual patients, several types have been identified (89). Electron microscopic examination shows viral particles, often in a semicrystalline pattern within nuclei located in the stratum granulosum. In contrast, the swollen cells in the stratum malpighii show virions in their nuclei in small aggregates only in some cases but none at all in others.

Viral particles are absent in lesions of Bowen's disease or squamous cell carcinoma arising from EV, but rarely these can be observed in the upper layers of the epidermis overlying malignant lesions. However, HPV-5–specific DNA or HPV-8–specific DNA has been demonstrated on several occasions in squamous cell carcinomas arising in lesions of EV. The underlying defect in EV is not clear but may involve oncogene or immunologic dysfunction.

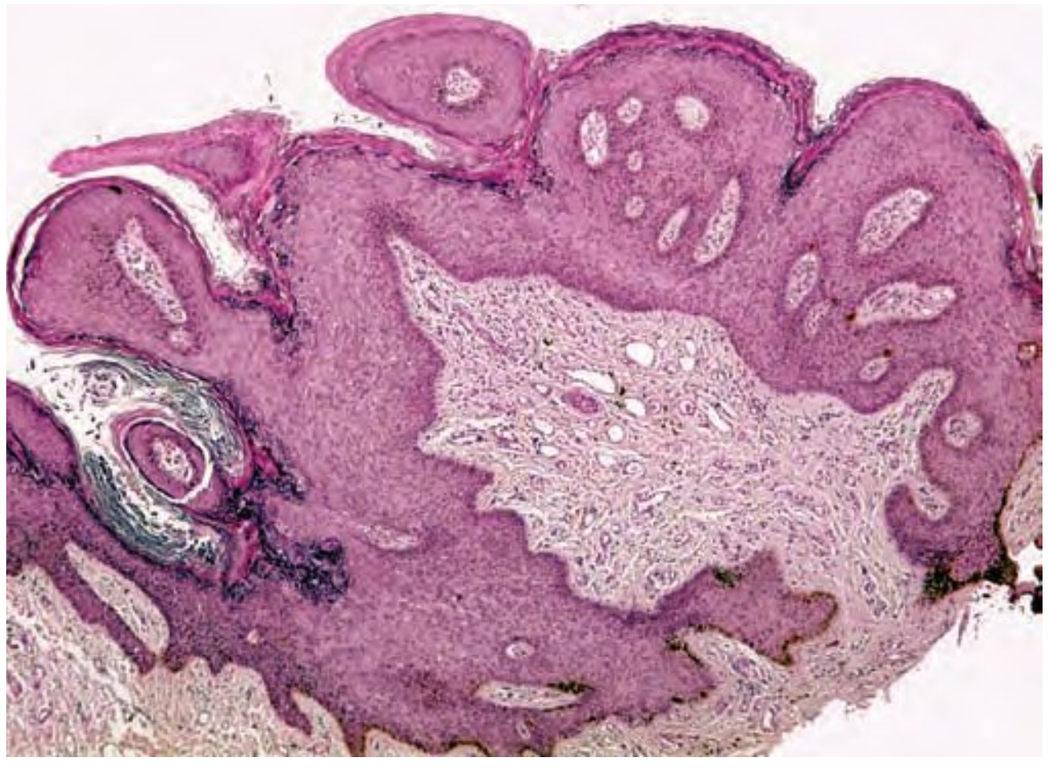
Condyloma Acuminatum

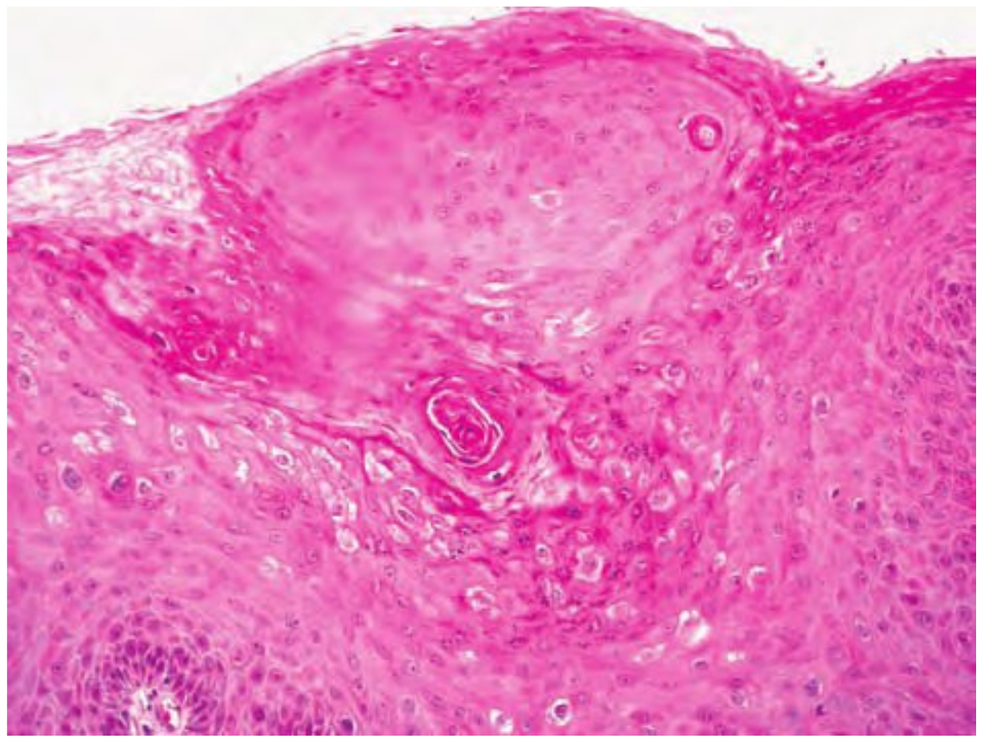
Condylomata acuminata, or anogenital warts, can occur on the penis, female genitals, and in the anal region. Condylomata acuminate are transmitted sexually, and HPV infection is one of the most common viral sexually transmitted diseases in the world, with an estimated 1% prevalence in the sexually active population in the United States. The estimated prevalence of HPV DNA or HPV antigens in young women may be as high as 10% to 11%. Recent studies show that HPV DNA is detectable by PCR in more than 99.7% of cervical cancers, making HPV infection the most important risk factor in the development of this disease (90). Malignant progression is associated with infection by certain HPV types. Anogenital HPV types 6 and 11 rarely progress to invasive disease and are considered low risk. HPV types 16, 18, 31, 33, and 51 have been associated with both *in situ* and invasive processes of the male and female genital regions as well as the vagina and cervix in women. Additional types associated with malignancy include 35, 39, 42–45, 52 and 56. However, even with infection by high-risk types, these lesions most often spontaneously regress with no long-term adverse effects (91). Progression includes a spectrum from Bowen's disease to squamous cell carcinoma, potentially with extension to metastasis.

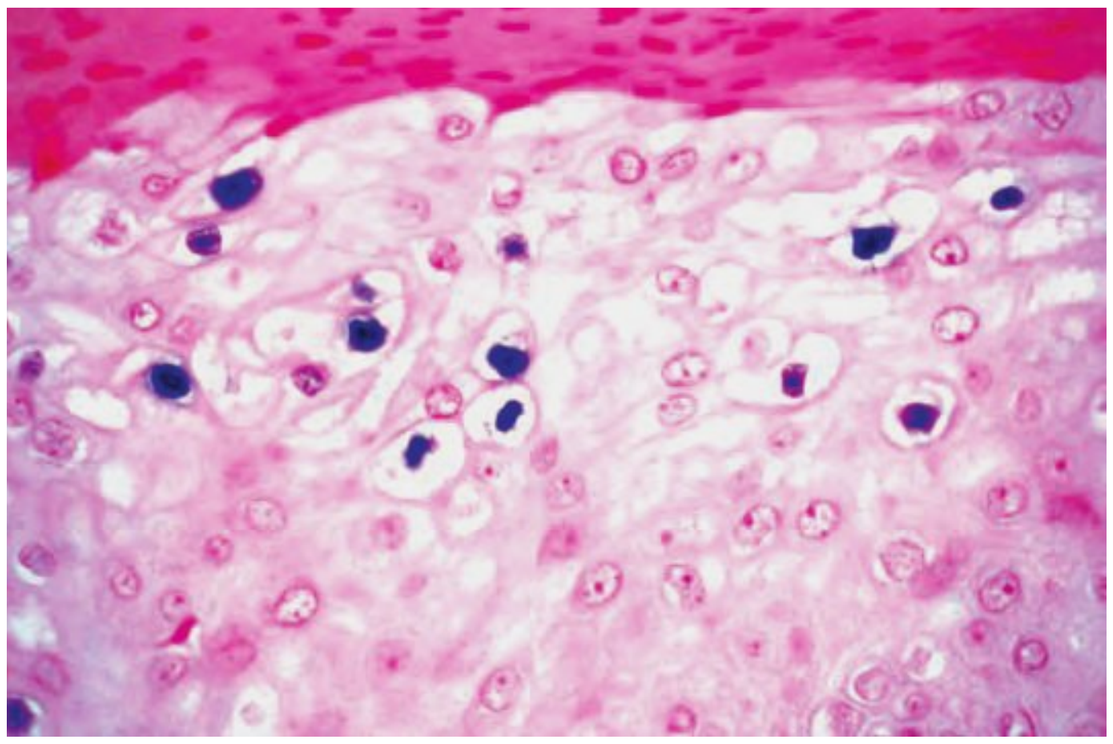
Condylomata acuminata usually are found on the penis and around the anus in men. In women, frequent areas of infection include the vulva, vaginal introitus, perineal area, perianal area, and cervix. Lesions of the skin consist of fairly soft, verrucous papules that occasionally coalesce into cauliflower-like masses (Fig. 25-15A). Condylomas are flatter on mucosal surfaces.

Histopathology. In condyloma acuminatum, the stratum corneum is only slightly thickened. Lesions located on mucosal surfaces show parakeratosis. The stratum malpighii shows papillomatosis and considerable acanthosis, with thickening


A


B


C


D

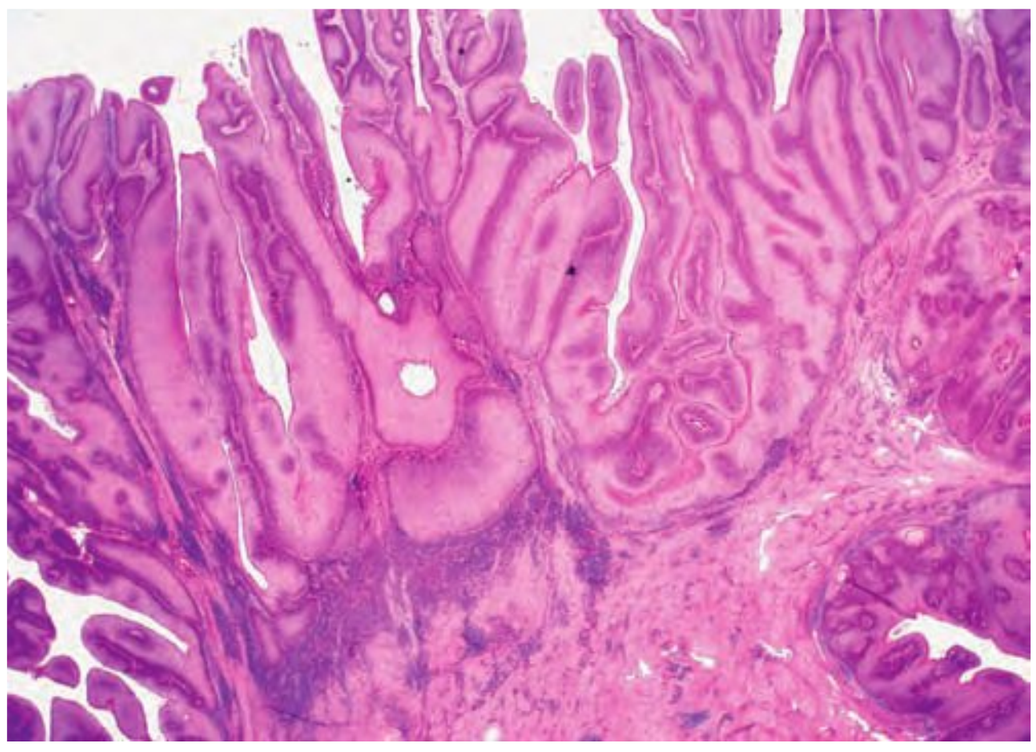

E

FIGURE 25-15. Condyloma acuminatum. A: Cauliflower-like or filiform lesions in the anogenital region. B: There is papillomatosis and acanthosis (low power). C: Many cells of the stratum malpighii appear vacuolated and have round, hyperchromatic nuclei (high power). D: In situ hybridization shows HPV in the squamous cells. E: Giant condyloma acuminatum with marked acanthosis and more endophytic growth.

and elongation of the rete ridges. Mitotic figures may be present. Usually, invasive squamous cell carcinoma can be ruled out because the epithelial cells show an orderly arrangement and the border between the epithelial proliferations and the dermis is sharp (Fig. 25-15B). The most characteristic feature, important for the diagnosis, is the presence of areas in which the epithelial cells show distinct perinuclear vacuolization. These vacuolated epithelial cells are relatively large and possess hyperchromatic, round nuclei resembling the nuclei seen in the upper portion of the epidermis in verrucae vulgares (Fig. 25-15C). It must be kept in mind, however, that vacuolization is a normal occurrence in the upper portions of all mucosal surfaces; thus, vacuolization in condylomata acuminata can be regarded as being possibly of viral genesis only if it extends into the

deeper portions of the stratum malpighii. Koilocytotic ("raisin") nuclei, double nuclei, and apoptotic keratinocytes may be present but are often less prominent than in uterine cervical lesions.

The diagnosis of HPV infections of the vulva can be complicated by the frequent absence of koilocytosis. HPV detection in lesions that depart from the typical morphology of condyloma can be achieved by *in situ* hybridization (Fig. 25-15D) or molecular tests. In one study, HPV DNA—principally HPV-6—was detected in 18 of 25 vulvar seborrheic keratoses (72%), while 15% of nongenital seborrheic keratoses were positive for this virus. Therefore, a majority of vulva seborrheic keratoses may represent senescent condylomas (92).

Giant Condylomata Acuminata of Buschke and Loewenstein

The Buschke-Loewenstein tumor, also called *giant condyloma acuminatum*, is generally observed in males. The most frequent location is the glans penis and foreskin (where urethral fistulas may result), but they may occur also on the vulva and in the anal region. Clinically, it is a cauliflower-like tumor with resemblance to a large aggregate of condylomata acuminata, especially in the early stage. It is characterized by its large size with the propensity to ulcerate and infiltrate into deeper tissues, contrasting with a microscopically benign pattern. The hallmark of the disease is the high rate of recurrence (66%) and of malignant transformation (56%). Distant metastases are extremely rare. The overall mortality is 20%, all occurring in patients with recurrences (93).

Histopathology. The lesion shows a papillomatous growth characterized predominantly by epithelial hyperplasia, hyperacanthosis, and hyperkeratosis (Fig. 25-15E). Generally, vacuolization of keratinocytes is mild or absent, in contrast to condyloma acuminatum. There is tremendous proliferation of the epidermis with displacement of the underlying tissue, but the ratio of nucleus to cytoplasm is low. The invasive strands of tumor usually possess a well-developed basal cell layer. (See verrucous carcinoma for further discussion.)

Histogenesis. Papillomaviruses induce a variety of proliferative lesions in humans. Of the many types of HPV that have been identified, a subset that includes types 16, 18, 31, 33, and 51 is associated with anogenital cancers (94). These cancers develop from precursor lesions such as condylomata acuminata on the external genitalia, vaginal intraepithelial neoplasia (VIN), and cervical intraepithelial neoplasia (CIN). Viral production occurs in low-grade lesions that are only slightly altered in their pattern of differentiation from normal cells, but the concentration of mature virions in condylomata acuminata is low. The production of viral particles, genome amplification, capsid protein synthesis, and virion assembly is dependent on differentiation and is restricted to suprabasal cells. In more atypical lesions, viral DNA is usually found integrated into host chromosomes and no viral production is noted. The viral DNA encodes nine overlapping genes, early (E1-7) and late (L1-2). Early genes are involved in oncogenic transformation in high-risk HPV types, especially E6 and E7, which enable HPV to use cellular proteins for continued viral replication by arresting the process of keratinocyte differentiation and inactivation of cell cycle regulators such as p53 and retinoblastoma protein (Rb), thus providing the initial step in progression to malignancy (95).

BOWENOID PAPULOSIS OF THE GENITALIA

Bowenoid papuloses are small, red papules of the genitalia. Some lesions are distinctly verrucous in appearance. The lesions are located in men on the glans and shaft of the penis and in women in the perineal and vulvar areas. Generally, the lesions are diagnosed clinically as genital warts, and the histologic finding of "Bowen's disease" appears incongruous.

The lesions have a definite tendency toward spontaneous resolution; some lesions regress, but others may appear and in turn also regress. Still, in some patients, lesions have persisted for prolonged periods. In rare cases, invasive squamous cell carcinoma has been described as arising in a Bowenoid papule.

Some authors regard the disorder as benign and, in particular, as different from Bowen's disease (57), but others have found that Bowenoid papulosis presents a premalignant lesion with a high risk for cervical neoplasia both for female patients and for sexual partners of male patients (96). Invasive squamous cell carcinoma develops in a small number of cases, and it seems that women over 40 years of age have the greatest risk.

Histopathology. Bowenoid papulosis shows the typical features of Bowen's disease. These features consist of full-thickness epidermal atypia with crowding and an irregular, "windblown" arrangement of the nuclei, many of which are large, hyperchromatic, and pleomorphic (Fig. 25-16). Dyskeratotic and multinucleated keratinocytes are also present, as are atypical mitoses. The basement membrane is intact. True koilocytes are uncommon. Bowenoid papulosis may be histologically indistinguishable from *vulvar intraepithelial neoplasia* (VIN III), a term that is synonymous with squamous cell carcinoma *in situ* or Bowen's disease. Some researchers believe that bowenoid papulosis differs from Bowen's disease by virtue of a lesser degree of cytologic atypia. In a few instances, bowenoid papulosis and condylomata acuminata have been found coexisting in the same patient.

Histogenesis. Bowenoid papulosis represents infection by HPV types associated with high risk of malignancy evolution, such as types 16, 18, 31, 33, and 51. As noted previously, these types elaborate oncoproteins that interfere with normal cellular homeostasis.

Differential Diagnosis. Bowenoid papulosis of the genitalia in most instances is differentiated from Bowen's disease on the basis of clinical data, such as onset at an earlier average age, multiplicity of lesions, smaller size of lesions, verrucoid appearance of

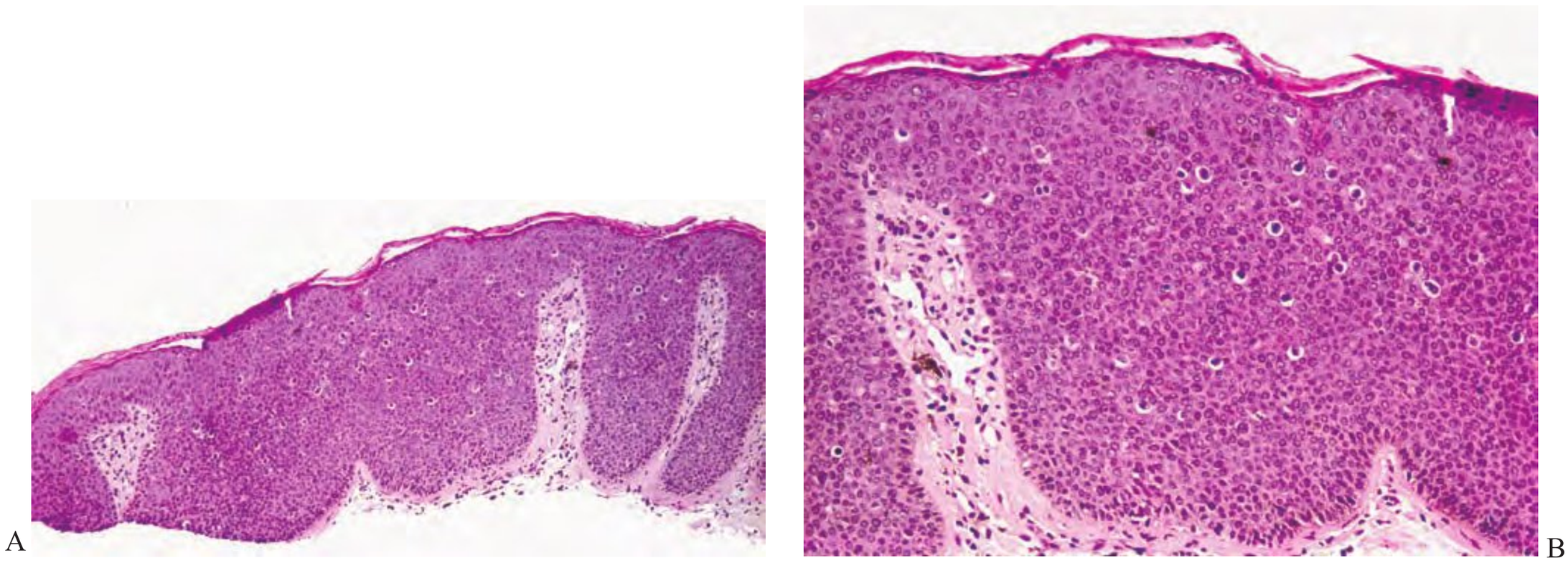


FIGURE 25-16. Bowenoid papulosis. A: The epithelium is irregularly thickened with disorderly maturation, which may impart a "windblown" look at scanning or intermediate magnification. B: The keratinocytic nuclei are crowded, and there is partial arrest of maturation. Mitoses are present above the basal layers, and the nuclei tend to be hyperchromatic and irregular, sometimes with nucleoli.

some lesions, and tendency toward spontaneous regression. Thus, Bowen's disease or squamous cell carcinoma *in situ* (VIN III) cannot be ruled out by biopsy alone in most cases.

Changes induced by recent application of podophyllum resin need to be considered. The changes induced by podophyllum resin consist of necrotic keratinocytes and bizarre mitotic figures and are most pronounced during the first 72 hours after application.

ORAL FOCAL EPITHELIAL HYPERPLASIA

A rare condition described in Native Americans, oral focal epithelial hyperplasia (Heck's disease) has since been found to occur in many countries and races but most commonly among the Eskimos of Greenland (97). It primarily occurs in children, often in small endemic foci, but lesions may occur in young and middle-aged adults. There is no gender predilection. Sites of greatest involvement include the labial, buccal, and lingual mucosa, but gingival and tonsillar lesions have also been reported.

There are numerous soft, white papules 2 to 10 mm in diameter. Individual lesions are broad based or slightly elevated as well as demarcated plaques. Papules and plaques are usually the color of normal mucosa but may be pale or, rarely, white. Most are discrete, but some are confluent. The lesions are asymptomatic. Although the disease is chronic, spontaneous remissions occur. Oral focal hyperplasia has been described in the context of HIV infection (98).

Histopathology. The oral epithelium shows acanthosis with thickening and elongation of the rete ridges. The thickened mucosa extends upward, not down into underlying connective tissues, hence the lesional rete ridges are at the same depth as the adjacent normal rete ridges. The ridges themselves are widened, often confluent, and sometimes club shaped; they are not long and thin as in *psoriasis* and other diseases. Throughout the epithelium, there are areas where the cells show marked vacuolization and stain only faintly. Vacuolization is most pronounced in the upper portion of the epithelium, but it may extend into the broadened rete ridges (Fig. 25-17).

Histogenesis. Electron microscopic examination reveals viral particles with the size of HPV arranged in a crystalline pattern. HPV types 13 and 32 are typical for oral focal epithelial hyperplasia (99).

Differential Diagnosis. The histologic appearance of the affected oral epithelium in focal epithelial hyperplasia is identical to that of oral epithelial nevus, or white sponge nevus.

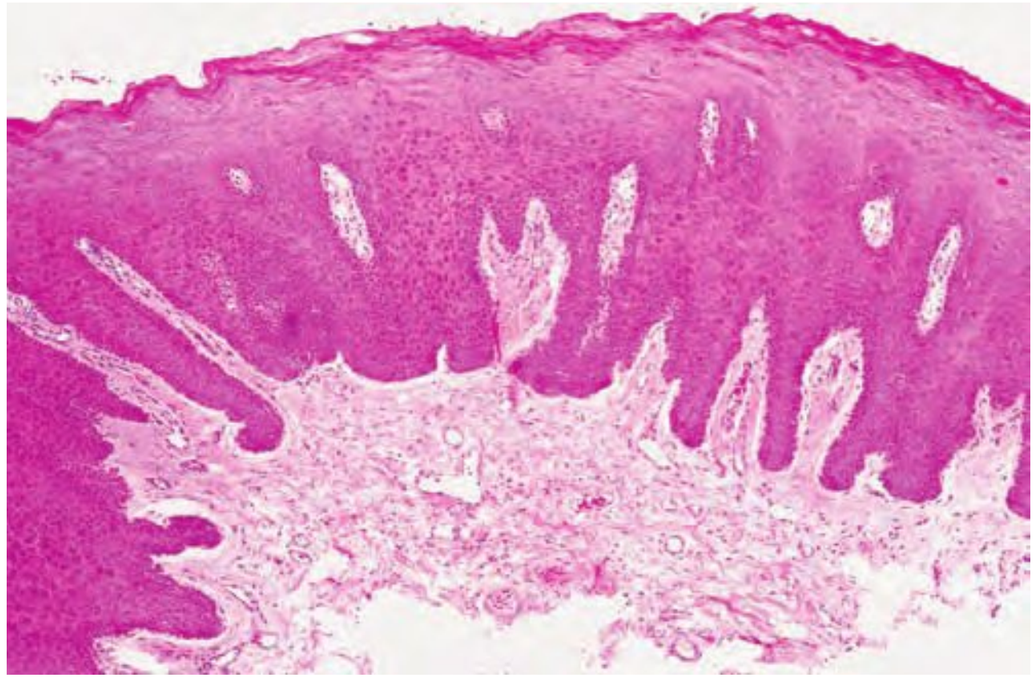


FIGURE 25-17. Oral focal epithelial hyperplasia (Heck's disease). The oral epithelium shows acanthosis with thickening and elongation of the rete ridges. The ridges are widened, often confluent, and sometimes club shaped. Vacuolization is most pronounced in the upper portion of the epithelium.

PICORNAVIRIDAE

Picornaviridae consists of single-stranded RNA viruses that are 10 to 30 nm, naked, icosahedral, and contain only four to six genes. They are the smallest of the RNA viruses and are very important in human disease. Picornaviridae infections of humans have been classified into five genera: Enterovirus (polio), Hepadnavirus (hepatitis A), Cardiovirus (encephalomyocarditis), Rhinovirus (common cold), and Apthovirus (foot and mouth diseases). Picornaviridae infection is one of the most common causes of viral exanthem. In addition to nonspecific findings, enterovirus infection also causes distinct syndromes such as hand-foot-and-mouth disease, herpangina, and hemorrhagic conjunctivitis (100).

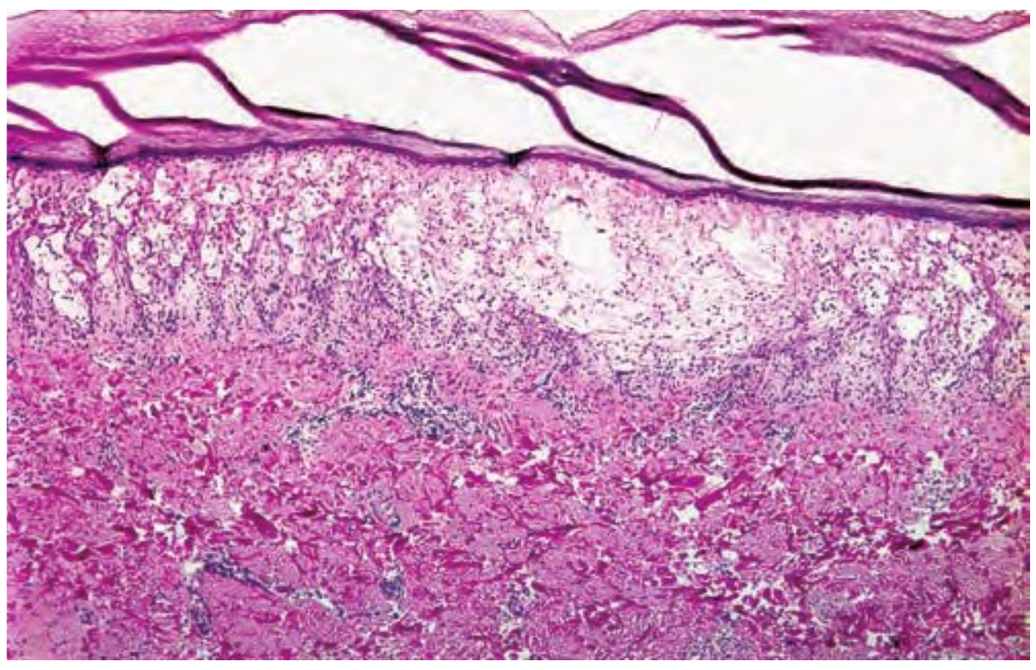
Hand-foot-and-mouth Disease

Hand-foot-and-mouth disease is caused by a coxsackie virus, which is an enterovirus. In most instances, coxsackie virus type A16 has been isolated; only rarely has another type, such as A5 or A9, been found (101). Hand-foot-and-mouth disease occurs in small epidemics, affecting mainly children and having a mild course that usually lasts less than a week. Transmission is mainly via fecal–oral contact and less commonly by respiratory droplets (102). Symptoms usually appear 3 to 5 days after exposure. After a 1- to 2-day mild prodrome of low-grade fever, sore throat, and malaise, small red macules present on the oral mucosa and progress to 1- to 3-mm small vesicles, where they evolve into small ulcers. Between 25% and 65% of patients may have the classic vesicular lesions on the hands and feet, which present as scattered small vesicles surrounded by an erythematous halo on the palms of the hands (Fig. 25-18A), soles of the feet, and ventral surfaces and sides of the fingers and toes (103). Similar lesions may develop on the rest of the skin.

Histopathology. Early vesicles are intraepidermal, whereas old vesicles may be subepidermal in location. There is pronounced reticular degeneration of the epidermis, resulting in multilocular vesiculation. In the deep layers of the epidermis, some ballooning degeneration may be found. Neither inclusion bodies nor multinucleated giant cells are present (Fig. 25-18B, C).

Histogenesis and Diagnosis. Viral culture has been the gold standard until recently; PCR has become the diagnostic test for rapid and accurate enterovirus infection. The sensitivity of PCR is almost double that of viral culture (104). Electron microscopic examination reveals that within their cytoplasm, some keratinocytes contain aggregates of virus particles exhibiting a crystalloid pattern (105). The coxsackie virus can be cultured from stool and occasionally from skin vesicles. The virus grows well on human epithelial cell and monkey kidney cell cultures.


A


B

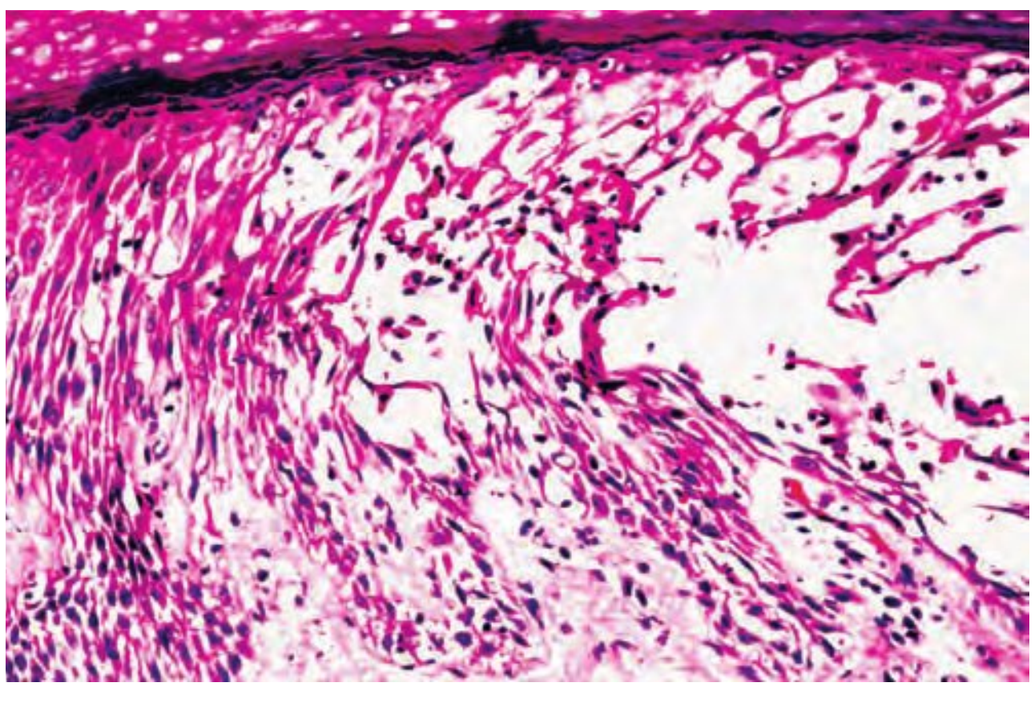

C

FIGURE 25-18. Hand-foot-and-mouth disease. A: Small vesicles on the palm of the hand with surrounding erythema. B: Scanning magnification shows intraepidermal vesicles with pronounced reticular degeneration. C: Pronounced reticular degeneration and balloon degeneration. Neither inclusion bodies nor multinucleated cells are present.

Hepatitis A Virus

The hepatitis A virus is a common cause of hepatitis worldwide. Spread of infection is through the fecal–oral route. Hepatitis A is endemic in developing countries, and most residents are exposed in childhood. In contrast, the adult population in developed countries demonstrates falling rates of exposure with improvements in hygiene and sanitation. Hepatitis A usually presents as fever, jaundice, and hepatomegaly. Extrahepatic manifestations are rarely found in hepatitis A viral infection. Urticaria and scarlatiniform eruption and rare cases of cutaneous vasculitis and cryoglobulinemia have been reported (106).

RETROVIRIDAE

Retroviridae are RNA retroviruses that currently are classified into seven genera, including HIV, the cause of AIDS, and human T-lymphotropic virus.

Acquired Immunodeficiency Syndrome

HIV infects predominantly $CD4^+$ cells, most notably T helper cells, and leads to a profound alteration of immune system function that predisposes patients to numerous opportunistic infections, malignancies, and neurologic diseases. The virus is spread almost exclusively through blood and semen.

Cutaneous findings in HIV disease are frequent and include viral, bacterial, fungal, and noninfectious etiologies (107). Some infections occur in clinically obscure forms because they do not have recognizable morphologic features. In addition, systemic infectious diseases can produce skin lesions, even though the classic organs of involvement for that agent may not include the skin. Dermatologic diseases common to the general population, such as *seborrheic dermatitis*, often have an increased prevalence or severity in these individuals (108). Several skin diseases occur nearly exclusively in HIV-infected individuals, such as oral hairy leukoplakia, bacillary angiomatosis, and KS.

HIV itself produces cutaneous findings shortly after exposure. In addition, gradual deterioration of the immune system renders HIV-infected patients susceptible to numerous cutaneous viral diseases, including herpesviruses, HPV, and molluscum contagiosum (109). Approximately 2 to 6 weeks following HIV exposure, patients may present with a transient illness related to HIV replication and host response. More than 50% of patients report symptoms of acute HIV infection: a macular or morbilliform rash usually involving the trunk is present in 40% to 80% of patients with acute HIV infection (110). Because the standard immunoassay and Western blot are often negative with acute infection, additional tests may be needed when there is a high index of suspicion. P24 antigen assay has fewer false positives and may be a more cost-effective way to diagnose primary HIV infection (111).

Pruritic papular eruption is the most common cutaneous manifestation in HIV-infected patients. Opportunistic viral infections affecting the skin and mucous membranes are also common (40). *Herpetic infections* are one of the most important causes of opportunistic infections in patients with HIV and frequently include cutaneous manifestations. Unlike in the healthy individual, in which case the lesions are often self-limited, herpetic infections cause significant chronic morbidity in immunocompromised patients. As immune function declines, the herpetic lesions may become chronic and progress to painful ulceration. *Herpes zoster* may be complicated by repeated bouts, involvement of multiple dermatomes, chronic verrucous zoster; rarely, herpes zoster may disseminate. *CMV* infection is associated with $CD4^+$ cell counts <100 and has a spectrum of presentations including pulmonary, ocular, gastrointestinal, and neurologic involvement, although CMV skin lesions are uncommon (112). While a majority of adults harbor EBV in latent phase, *oral hairy leukoplakia* is a rare disorder found almost exclusively in HIV-infected individuals. Approximately 25% of HIV-infected individuals may be affected. White, verrucous, confluent plaques that are most commonly located on the lateral aspects of the tongue characterize oral hairy leukoplakia, which do not scrape off with a tongue depressor (113). EBV appears to be necessary for production of this lesion, although HPV and *Candida* are also frequently present. The condition is a result of EBV infection of epithelial cells that leads to hyperkeratotic thickening. *Molluscum contagiosum* generally presents as $CD4^+$ counts fall below $100/mm^3$. While the lesions spontaneously resolve in immunocompetent hosts, they are often extensive and progressive in HIV-infected individuals, who are also subject to so-called giant molluscum contagiosum with lesions ranging from 1 to 6 cm in diameter (114).

Bacterial infections are also common in AIDS. *Staphylococcus aureus* is the most common cutaneous bacterial pathogen in HIV-seropositive patients. HIV-infected patients are also prone to streptococcal impetigo and axillary lymphadenitis. Another unique infectious disease first recognized in the context of HIV infection is *bacillary angiomatosis*. Bacillary angiomatosis is a systemic infectious disease caused by gram-negative *Bartonella henselae* or *Bartonella quintana* (115). Patients may have palpable subcutaneous nodules, which may resemble KS or hemangioma but resolve with appropriate antibiotic therapy. The lesions often are painful, unlike those of KS. HIV-infected patients are susceptible to mycobacterial infections that can sometimes produce unusual skin manifestations. *Syphilis* is common in these individuals and often the presenting infection of HIV disease (116). *Secondary syphilis* assumes a variety of manifestations in HIV-infected patients, including oral erosions, nodules, papules, vesicles, hyperkeratotic plaques, and papulosquamous or maculopapular eruptions.

Patients with HIV are subject to fungal, protozoa, and arthropod infections that produce mucocutaneous findings. Oral candidiasis is often an early clinical manifestation of AIDS and in progressing may cause painful esophagitis. Other infections such as *Cryptococcus*, *Histoplasma*, *Coccidioidomycosis*, *tinea versicolor*, *phaeohyphomycosis*, *nocardiosis*, and *mucormycosis* are not uncommonly seen in these patients (117). *Scabies* mite is the most common parasitic infestation of

HIV-infected individuals (118). Scabies is highly contagious in HIV-infected patients via direct contact. *Demodicidosis* involves the proliferation of *Demodex* mites within the pilosebaceous unit and is reported in association with HIV infection (119). *Disseminated acanthamebiasis* has been reported in these patients and often presents skin manifestations such as pustules, subcutaneous and deep dermal nodules, and ulcers, most often seen on the extremities and face.

Noninfectious cutaneous disorders are also common in HIV infection and can occur at all stages of disease. An explosive episode of *psoriasis* or severe *seborrheic dermatitis* can be the presenting symptom of HIV disease. Seborrheic dermatitis is a common disease affecting 2% to 4% of the general population, but up to 85% of HIV-positive individuals experience seborrheic dermatitis at some time during their diseases. It can be quite severe, with the severity correlating with the patient's clinical status and CD4 count (120). Less common areas such as the chest, back, axilla, and groin are often involved in HIV-seropositive patients. The histology of this eruption is similar to that of idiopathic seborrheic dermatitis, although some feel that distinctive histologic patterns are present (121). While the incidence of psoriasis in HIV disease is similar to the general population, it is often more severe, refractory to treatment, and has a higher prevalence of psoriatic arthritis. *Reiter's syndrome*, characterized by arthritis, urethritis, and conjunctivitis, may be associated with psoriasis in HIV-infected individuals (122). As many as 30% of HIV-infected individuals experience *xerosis* or *acquired ichthyosis* with fine white scales and cracking skin without erythema, which may be diffuse or preferentially affect the anterior tibia, dorsal hand, and forearm (123). Whereas xerosis reveals minimal inflammation microscopically, acquired ichthyosis is histologically similar to ichthyosis vulgaris, often with hyperkeratosis and diminished or absence of the granular cell layer. A nonspecific follicular eruption, named *eosinophilic pustular folliculitis*, is present in a significant number of patients with HIV infection (124). The eruption is chronic and pruritic. An interface dermatitis associated with HIV, observed in a series of 25 patients with AIDS, presents as a more or less widespread eruption of pink or red macules, papules, or plaques. It resembles and may represent a form of drug eruption or erythema multiforme (125).

Adverse cutaneous drug reactions are common in HIV-positive individuals, and they are prone to side effects associated with antimicrobial and antiviral medications (126). For example, after 1 to 2 weeks of trimethoprim-sulfamethoxazole treatment for *Pneumocystis carinii* infection, up to 50% to 60% of HIV-infected patients may develop a morbilliform rash. HIV-infected individuals also have an increased incidence of photosensitivity reactions. *Chronic actinic dermatitis*, a rare photosensitivity reaction, is sometimes the presenting manifestation of HIV seropositivity (127). *Porphyria cutanea tarda* (PCT) is reported more frequently in HIV-infected individuals when compared with the general population. Other lesions, such as pityriasis rubra pilaris, porokeratosis, yellow nail syndrome, alopecia, asteatosis, vasculitis, acrodermatitis enteropathica, and neutrophilic eccrine hidradenitis have been reported.

KS is the most common AIDS-associated cancer in the United States. Over 95% of all KS lesions have been associated with HHV-8 (128). Skin lesions of KS typically present with asymptomatic reddish-purple patches that sometimes progress to raised plaques or nodules. One third of patients experience oral cavity lesions characterized by red-to-purple plaques or nodules. Other tumors such as melanoma (129) and squamous and basal cell carcinoma have been reported in these patients.

Histopathology. The histology of the acute exanthema of HIV infection is rather nonspecific, with a tight perivascular infiltrate of lymphocytes in the dermis. Epidermal changes are usually mild but may include spongiosis, vacuolar change, and/or keratinocyte apoptosis (130,131), or there may be nonspecific lymphocytic infiltrates with mild epidermal changes, primarily spongiosis (110).

The lesions of oral hairy leukoplakia show irregular keratin projections, parakeratosis, and acanthosis. A characteristic finding within the epithelium is vacuolar change of superficial keratinocytes (Fig. 25-8). *Candida* organisms may be demonstrable. Seborrheic dermatitis in patients with AIDS may show nonspecific changes, including spotty keratinocytic necrosis, leukocytoclasia, and plasma cells in a superficial perivascular infiltrate (121). The papular eruption of AIDS may exhibit nonspecific perivascular eosinophils with mild folliculitis, although epithelioid cell granulomas have also been reported (132). The interface dermatitis shows, as the name implies, vacuolar alteration of the basal cell layer, scattered necrotic keratinocytes, and a superficial perivascular lymphohistiocytic infiltrate. The vacuolar alteration and number of necrotic keratinocytes tend to be more pronounced than in drug eruptions (125). The changes found are nonspecific but suggestive of features described in graft-versus-host disease and become more prominent in late-stage disease. *Eosinophilic pustular folliculitis* shows folliculitis with transmigration of eosinophils into the follicular epithelium, mimicking the changes observed in Ofuji's disease. However, in many cases, the histologic picture is less specific, showing only a polymorphous inflammatory response and mild folliculitis (131,133). *Cutaneous acanthamebiasis* shows both pustular and vasculitis changes; the microscopic identification of organisms is difficult because of the macrophage-like appearance of the microbes in routine sections (134). A periodic acid-Schiff (PAS) stain can be used to highlight the organisms.

DISEASES CAUSED BY OTHER VIRUSES

Hepatitis B virus

The hepatitis B virus (HBV) is a double-stranded DNA virus belonging to the Hepadnaviridae family. Transmission of the virus is frequently through intravenous drug use, sexual activity, and maternal–fetal transmission (135). During the acute phase, 15% of the patients will develop urticaria, fever, and malaise (136). Polyarteritis nodosum (PAN) is one of the more serious and common complications of HBV infection (137).

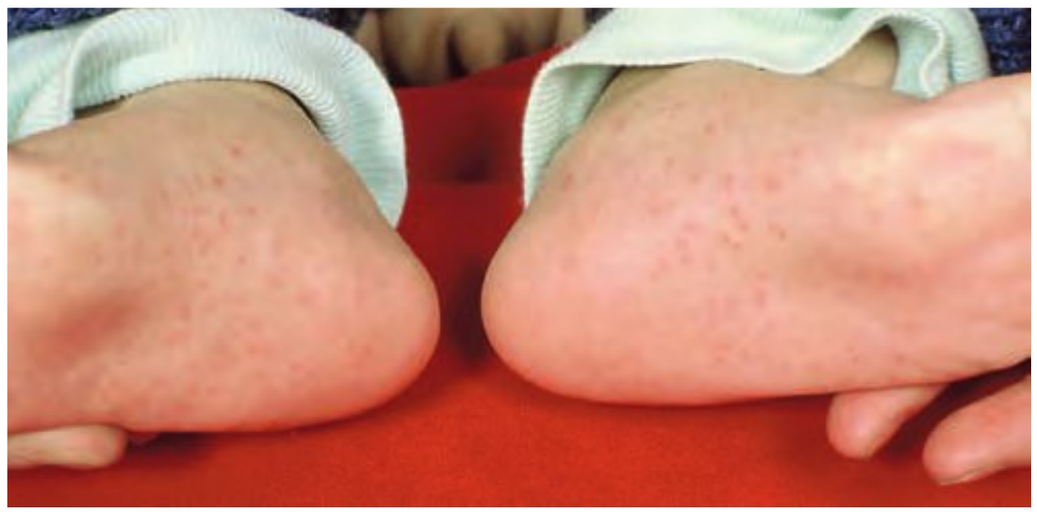


FIGURE 25-19. Papular acrodermatitis of childhood. Numerous erythematous papules are present on the feet of this boy.

About 2 in 500 people with HBV develop PAN, but up to 50% of people with PAN test positive for hepatitis B surface antigen (HBsAg). Cutaneous involvement occurs in 10% to 20% of the persons with PAN, which presents as palpable purpura that progress to large ulcers. Tender, purple, subcutaneous nodules can occur as well as livedo vasculitis (138). There is fibrinoid necrosis of the medium-size vessel wall with a cellular infiltrate composed mainly of $CD8^+$ T cells and macrophages. Depositions of immune complex, IgM, C3, and HBsAg in the vessel walls are observed.

Papular acrodermatitis of childhood (Gianotti-Crosti syndrome) occurs in children infected with HBV but is not common in adults (139). The clinical presentation includes a nonrelapsing erythematous papular eruption localized to the face and limbs (Fig. 25-19), with lymphadenopathy and acute hepatitis (mostly anicteric). The lesions do not affect mucosal surfaces. Papular acrodermatitis of childhood is common in southern Europe and Japan but rare in the United States. This condition can also be associated with CMV, EBV, respiratory syncytial virus, and enterovirus infection (140). The histology is characterized by a mixture of spongiotic and lichenoid dermatitis with a dense perivascular infiltrate.

Serum sickness–like syndrome is considered the most common dermatologic manifestation associated with HBV, which occurs in 20% to 30% of patients during the prodromal phase of the HBV infection. The skin manifestation includes urticaria, angioedema, and rashes. The urticaria lesions show erythrocyte extravasation, endothelial cell swelling, and various degrees of fibrinoid change of postcapillary venules (141). The pathology is induced by deposition of immune complexes, which are composed of HBsAg, IgG, IgM, and C3.

HBV has also been associated with mixed cryoglobulinemia (MC) (142); however, it is much less common than that associated with hepatitis C virus (HCV) infection. A recurrent papular rash on the trunk and extremities (143) and lichen planus (LP) have been reported as complications of hepatitis B vaccination in both adults and children (144).

Hepatitis C Virus

HCV is a single-stranded RNA virus that belongs to Hepacivirus, the third genus of the Flaviviridae family. Individuals with exposure to blood or blood products are at risk of infection with HCV. The prevalence in the United States ranges from 0.5% to 2.0%. *MC* is the most documented extrahepatic manifestation of HCV infection (145). It presents cutaneously as inflammatory, palpable purpura, which is usually confined to the lower extremities, progressing to ulceration. It is established that the majority (80%) of what was previously known as *essential MC* is now known to be related to chronic HCV infection (146). Despite a high prevalence of HCV markers in patients with MC, only an estimated 13% to 54% of patients with chronic HCV will develop MC. It is believed that HCV-IgG and HCV-lipoprotein complexes may act as B-cell superantigens inducing the synthesis of non-HCV reactive IgM with rheumatoid factor–like activity, leading to immune complex formation. Because of the high prevalence of liver abnormalities seen in patients with MC, hepatotropic viruses should be ruled out as causative agents. Histologic features for MC are those of an acute vasculitis involving small- and/or medium-sized dermal vessels. Intravascular hyaline deposits are generally not seen except in the areas beneath the ulcer.

LP is common in patients with HCV, with the prevalence of HCV ranging from 16% to 55% and 0.17% to 4.80% in LP patients and control groups, respectively (147). The lesions of HCV-related LP are similar to those of classic LP. However, a majority of reported HCV-related LP cases have oral involvement. Histologically, LP is characterized by a subepidermal, bandlike lymphohistiocytic infiltrate with interface change, sawtooth rete ridges, and pigmentary continence.

Recent reports have documented a high but variable prevalence of HCV infection in patients with porphyria cutanea tarda (PCT). The prevalence is higher in southern Europe (67% to 91%) and lower in northern Europe (8% to 10%). The prevalence in the United States is reported to be between 50% and 75% (148). In most cases, the HCV exposure and associated liver dysfunction precede the onset of PCT, suggesting that a viral infection can reveal a porphyrin metabolism defect in susceptible patients. Histologically, PCT is characterized by a cell poor subepidermal bulla with increased PAS-positive diastase-resistant hyaline material in the vessel walls and basement membrane.

Other lesions associated with HCV infection include erythema multiforme and erythema nodosum (149), Henoch-Schönlein purpura (150), Behçet's syndrome (151), necrolytic acral erythema (152), PAN (153), prurigo nodularis (154), pyoderma gangrenosum (155), and urticarial vasculitis (156).

Parvovirus B19

Parvovirus is a single-stranded DNA virus belonging to the Parvoviridae family. Parvovirus B19 is the only Parvovirus that clearly causes human disease (157). The virus is highly tropic for erythroid progenitor cells and thus is classified as an erythrovirus. The cellular receptor for B19 is a globoside, also known as *blood group P antigen* (40). Parvovirus infection is ubiquitous and occurs worldwide. Transmission of the virus occurs through the respiratory route in most cases. Two dermatologic conditions have been linked to Parvovirus B19



FIGURE 25-20. Erythema infectiosum (fifth disease). The lesion has the classic slapped-cheek appearance. The bright red erythema appears abruptly over the cheeks and is marked by nasal, perioral, and periorbital sparing.

infection, *erythema infectiosum*, and *papular purpuric "gloves-and-socks" syndrome* (157,158). Infection may also result in nonspecific findings, such as reticular erythema, maculopapular eruptions, purpuric eruptions, palpable purpura, and angioedema. Other dermatologic entities, such as erythema multiforme (159) and papular acrodermatitis of childhood (Gianotti-Crosti syndrome) (160), as well as recently various vasculitic syndromes, including Henoch-Schönlein purpura (HSP), Wegener's granulomatosis, and microscopic polyarteritis, have been linked to B19 infection (161).

The most well-known dermatologic manifestation of Parvovirus B19 is *erythema infectiosum*. This well-recognized exanthema also is called *fifth disease*, with a distinctive "slapped cheek" appearance (Fig. 25-20). Less widely recognized and described only a decade ago, papular purpuric "gloves-and-socks" syndrome is also associated with Parvovirus B19. Clinically, the rash consists of symmetric erythema and edema of the hands and feet, with gradual progression to petechiae and purpura. One of the clinical hallmarks of the rash is the sharp demarcation on the wrists and ankles. Resolution occurs within 1 to 2 weeks, with no permanent sequelae. However, in immunocompromised patients, papular purpuric "gloves-and-socks" syndrome may lead to more serious complications, such as persistent anemia. The histology is not entirely specific. Most cases have revealed interstitial histiocytic infiltrates with piecemeal fragmentation of collagen and a mononuclear cell-predominant vascular injury pattern, showing dilated and irregular-shaped dermal vessels with swelling of endothelial cells. Mild to moderate perivascular infiltrates of mononuclear cells have been noted (162).

Measles

Measles virus is a single-stranded RNA virus that belongs to the Paramyxoviridae family. Measles is an epidemic disease with a worldwide distribution. Measles virus is transmitted via respiratory secretions, predominantly as aerosols but also by direct contact. The symptoms usually last for 10 days and resolve without consequence. However, there is an increased risk of more severe diseases, such as severe pneumonitis or encephalitis, in immunocompromised individuals (163). A biopsy of the rash shows nonspecific histologic change with epidermal spongiosis and mild vesiculation with scattered degenerated keratinocytes (164). Biopsies from AIDS patients with measles show necrosis of clusters of keratinocytes in the upper spinous layer and granular layer of the epidermis. Unlike in erythema multiforme, the necrosis occurs in the basal layer keratinocytes. Multinucleated keratinocytes may or may not be prominent in the measles biopsy. Cytoplasmic swelling of the keratinocytes in the granular layer may be present even when multinucleated cells are sparse (165).

Rubella

Rubella is an enveloped, single-stranded RNA virus that belongs to the Togaviridae family. Rubella, also known as *German measles*, is a viral exanthema of childhood that is generally subclinical and inconsequential. Viremia occurs approximately 1 week before the rash; the rash is seen when circulating antibodies appear. The rash is maculopapular, erythematous, discrete, and pruritic. The face is usually the first area of devolvement, then spreads to extremities. The entire body may be involved within 1 day. The second day, there is clearing of the face and the rash is commonly cleared by the third day. Histologically, the change is not specific with a mild, perivascular lymphocytic infiltrate (166,167).

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CHAPTER 26

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The Histiocytoses

The histiocytic disorders cover a wide range of primary and secondary, solitary and multiple, benign and malignant disorders unified only by being for the most part uncommon and poorly understood. The "X" in histiocytosis X as originally proposed by Lichtenstein (1) was designed to reflect the unknown; even though we have drifted away from the designation, it to some degree still reflects the state of our knowledge. The word "histiocyte" itself is not particularly helpful. Loosely translated, it means a "cell of the tissue." Medical dictionaries tend to define the histiocyte as a "macrophage" or a "tissue macrophage," but many of the diseases known as histiocytoses are not disorders of macrophages but instead involve dendritic cells. Despite these misgivings, we retain the term histiocytosis, as have major textbooks (2,3) and reviews (4–8).

Recent research has clarified some aspects of the terminology but made others more confusing. There are two major cell lines responsible for the spectrum of diseases considered as histiocytoses. The following markers are useful in identifying these cells (Table 26-1):

1. The bone marrow–derived monocytes, which migrate to tissue, where they differentiate into macrophages or professional phagocytes, known by many names based on their site, such as Kupffer cells in the liver. There are a number of monoclonal antibodies available to identify macrophages; most are directed against CD68. Stains for CD14 and CD163 are also used.
2. The dendritic cells are for the most part bone marrow derived and reside in the skin, lymph nodes, or other organs. Two are relevant for here (9):
   a. The Langerhans cell (LC) is an antigen-processing cell characterized by Birbeck granules, S100 protein, CD1a, and langerin (CD207) positivity. LC initially take up antigens in the epidermis, migrate through the dermis to lymphatics and then lymph nodes, and there present processed antigens in association with major histocompatibility complex molecules to T cells. The more mature form is the interdigitating dendritic cell (IDC), which lacks Birbeck granules, CD1a, and langerin.
   b. The dermal/interstitial dendritic cell is a perivascular cell positive for factor XIIIa (FXIIIa) and fascin that fails to stain for S100 protein or CD1a. FXIIIa can also be expressed by activated macrophages. FXIIIa is the rate-limiting enzyme in the formation of fibrin thrombi and is most prominent in the superficial dermis. It is more likely to be positive in acute and early lesions. The number of different dermal dendritic cells and their precursors has expanded rapidly in recent years, but clinicopathologic correlation is lacking.
3. A source of confusion is the indeterminate cell, whose vague name accurately reflects the current situation. No single definition is agreed on; possibilities cited in the recent literature include the following:
   - A veiled cell, that is, a LC migrating to the dermis
   - A LC precursor (exactly the opposite of a veiled cell)
   - A cell with features of both a macrophage and LC. There is marked overlap between the dermal/interstitial dendritic cells and macrophages. with potential for shifting markers even relatively late in development.

A number of cautions are required. A diagnosis is rarely if ever based on the presence or absence of a single antigen, but instead is based on the clinicopathologic picture. Both macrophages and dendritic cells go through a maturation process, and so their profiles may change. In addition, because monocytes and most dendritic cells arise from a similar bone marrow–derived stem cell, there are overlaps with macrophages expressing S100 protein or even CD1a, but not langerin; similarly, dermal dendritic cells may express macrophage markers. We do not find FXIIIa specific enough to agree that its presence unequivocally identifies dermal cells as of dendritic cell origin. Dermatofibromas that meet all other morphologic criteria for a fibrocytic origin in early lesions regularly stain with FXIIIa.

Histiocytic lesions can usually be diagnosed based on their light microscopic pattern using a much more limited number of stains (Table 26-2). Our detailed classification is presented in Table 26-3. The classification of the Histiocyte Society is designed primarily for childhood disorders (10), whereas that of the World Health Organization concentrates on malignant neoplasms in adults and ignores cutaneous xanthogranulomas (11).

In addition to the diseases to be discussed in this chapter, a wide array of disorders can display similar histologic patterns. Most are discussed elsewhere in this book.

1. Metabolic disorders: In addition to hyperlipoproteinemias and other disorders of fat metabolism, many lysosomal disorders and other storage diseases may feature cutaneous xanthomas or other infiltrates. The diagnosis of these disorders

TABLE 26-1 Markers for "Histiocytes"

Cell type	Useful marker
Monocyte (source of all the rest)	CD14
Macrophage	CD14, CD68, CD163
Sinus histiocytosis macrophage	CD14, CD68, CD163, S100 protein, fascin
Dermal/interstitial dendritic cell	CD14, CD163, FXIIIa, fascin
Langerhans cell	CD1a, langerin, S100 protein

is not a practical question for the dermatopathologist, and they will not be further considered.

2. Infectious diseases. Tuberculosis, lepromatous leprosy, other mycobacterial infections, and leishmaniasis may produce granulomas. Malakoplakia is a chronic granulomatous reaction, presumably to an infectious agent, that occurs occasionally in the skin. The key histologic finding is the presence of intracellular Michaelis-Gutmann bodies.
3. Proliferations. Some lymphomas present with cutaneous granulomatous infiltrates; included in this group are Hodgkin's lymphoma and some forms of T-cell lymphoma. Most diseases diagnosed in the past as histiocytic malignancies are lymphomas. Malignant fibrous histiocytoma and its more superficial cutaneous variant atypical fibroxanthoma are established diagnoses, but their line of differentiation remains controversial. Melanocytic tumors can be confused with macrophage disorders, both clinically and histologically. The red-brown color of xanthogranulomas is similar to that of Spitz nevi. Balloon cell nevi and melanoma are occasionally mistaken histologically for xanthomatous lesions (12). Touton giant cells can sometimes be confused with multinucleated rosette cells in melanocytic nevi (13). Fortunately, immunohistochemical studies readily resolve these potential difficulties (14).
4. Trauma. Most dermatofibromas and some verruciform xanthomas are the result of trauma, be it an insect bite, folliculitis, or another insult. Some xanthomas arise secondary to cutaneous damage from light or after marked inflammation. External objects, such as glass fragments, silica, and many others, may produce cutaneous granulomas, often of the sarcoidal type. A ruptured follicular cyst is also accompanied by a macrophage response.
5. Idiopathic. Unfortunately, most "histiocytic" diseases fit here, and there is little logic to what has been considered a macrophage disorder and what has been cubby holed elsewhere. For example, granuloma annulare has a macrophage infiltrate but is considered a necrobiotic disorder. Both rheumatoid arthritis and sarcoidosis may feature infiltrates of macrophages in the skin and other organs; nonetheless, they are not considered "histiocytoses."

TABLE 26-2 Simplified Approach to Histiocytic Lesions

	S100 protein	CD1a or langerin	CD68
Langerhans cell disease	+	+	−
Rosai-Dorfman disease	+	−	+
Juvenile xanthogranuloma	−	−	+

TABLE 26-3 Detailed Classification of Histiocytoses

Langerhans cell disease	
Xanthogranuloma family	Juvenile xanthogranuloma
	Papular xanthoma
	Scalloped cell xanthogranuloma
	Xanthoma disseminatum
	Reticulohistiocytoma
	Multicentric reticulohistiocytosis
	Spindle cell xanthogranuloma
	Progressive nodular histiocytosis
	Benign cephalic histiocytosis
	Generalized eruptive histiocytosis
Other histiocytic disorders	Indeterminate cell histiocytosis
	Dermal dendrocytoma
	Rosai-Dorfman disease
	Histiocytic sarcoma
Xanthomas associated with lipid abnormalities	Eruptive
	Tuberous
	Tendon
	Plane
	Xanthelasma
Normolipemic xanthomas	Necrobiotic xanthogranuloma
	Diffuse normolipemic plane xanthoma
	Verruciform xanthoma
	Miscellaneous

LANGERHANS CELL DISEASE

Langerhans cell disease (LCD) is characterized by a proliferation of Langerhans cells. The clinical spectrum of LCD is broad, with skin involvement a common finding. Whereas LCD has been subdivided into several clinical types, overlaps are the rule, not the exception, and lumping appears more appropriate than splitting. Acute disseminated LCD (Abt-Letterer-Siwe disease) usually occurs in infants (15) but can be seen in older children or adults. The most common manifestations are fever, anemia, thrombocytopenia, enlargement of the liver and spleen, lymphadenopathy, and pulmonary infiltrates. Osteolytic lesions are uncommon except in the mastoid region

of the temporal bone, resulting in a clinical picture of otitis media (16–18).

Cutaneous lesions are found in about 80% of cases, often as a presenting sign. Numerous closely set, red-brown papules covered with scales or crusts may be accompanied by petechiae. This type of eruption may be extensive, involving particularly the scalp, face, and trunk, with a striking resemblance to seborrheic dermatitis or Darier's disease. Cutaneous LCD is very pleomorphic; lesions may be vesicular (19), ulcerated, urticarial (20), or, rarely, xanthomatous (21). If there is a diffuse cutaneous eruption, one must anticipate multiorgan involvement. In rare instances, a widespread cutaneous eruption is the only clinical manifestation in infants and even in the elderly, in whom anogenital involvement is common (22,23). The prognosis in such cases is good. Other adults may have similar cutaneous findings but also multisystem disease and do poorly.

Congenital self-healing reticulohistiocytosis (CSHRH) (Hashimoto-Pritzker disease) (24) is another variant of LCD, not a distinct disorder. It is usually present at birth but may not appear until several days or weeks after delivery. Affected infants have scattered papules and nodules. Large nodules tend to become eroded or ulcerated. Usually, the number of lesions varies from several to a dozen; on rare occasions, numerous lesions are widely scattered over the entire skin. In about 25% of cases, a solitary nodule is present. The lesions begin to involute within 2 to 3 months and usually have completely regressed within 12 months (25,26). But the patients should be carefully followed; relapses may occur, including bone involvement, and the occasional case may advance to acute disseminated disease (27). Although acute disseminated LCD may also be present at birth, it is rarely nodular.

In chronic multifocal LCD, diabetes insipidus, exophthalmos, and multiple defects of the bones, especially of the cranium, represent the classic triad of Hand-Schüller-Christian disease. Any one or even all three of the cardinal symptoms may be absent, and entirely different organs may be involved. For example, enlargement of the liver, spleen, lungs, or lymph nodes may be found. Osteolytic lesions of the long bones may result in spontaneous fractures. Cutaneous lesions occur in about one third of the cases. Three types of skin lesions may be found. Most common are infiltrated nodules and plaques undergoing ulceration, especially in the axillae, the anogenital region, and the mouth. Next in frequency is an extensive eruption identical to that in infants but usually less severe. Finally, in rare instances yellow xanthomas are seen. Patients with LCD also tend to develop more juvenile xanthogranulomas than expected (28,29).

Chronic focal LCD or eosinophilic granuloma represents the fourth and least severe variant. The lesions are either solitary or few. Most common are lesions of the bones, but the skin or the oral mucosa is occasionally involved, either with or without osseous lesions. Involvement of the jaw leading to a loose or floating tooth is a fairly typical occurrence. Although the lesions are usually chronic, some heal spontaneously, and simple surgery is generally curative. In rare instances, cases originally diagnosed as chronic focal disease may progress into multifocal or even disseminated disease.

The clinical course and the prognosis of LCD are difficult to predict. The most important parameters in prognosis are those recommended for staging: the age of the patient, the number of organs involved, and the degree of organ dysfunction. Abnormalities of the bone marrow, spleen, liver, or lungs suggest a poor prognosis. Skin involvement alone suggests a favorable outcome. Paradoxically, the presence of skin disease at birth (the nodules of CSHRH) is a good sign, but involvement before the age of 2 years (Letterer-Siwe disease) is a bad one. Histologic features correlate poorly with outcome (30). Patients with disseminated LCD seem to be at risk for a variety of systemic neoplasms, including lymphomas, leukemias, and lung tumors (31). In addition, they may experience secondary macrophage activation syndrome, also known as reactive hemophagocytic lymphohistiocytosis, which is usually fatal. In general, about 10% of patients with multifocal disease die, 30% undergo complete remission, and the remaining 60% embark upon a chronic, shifting course (16,32).

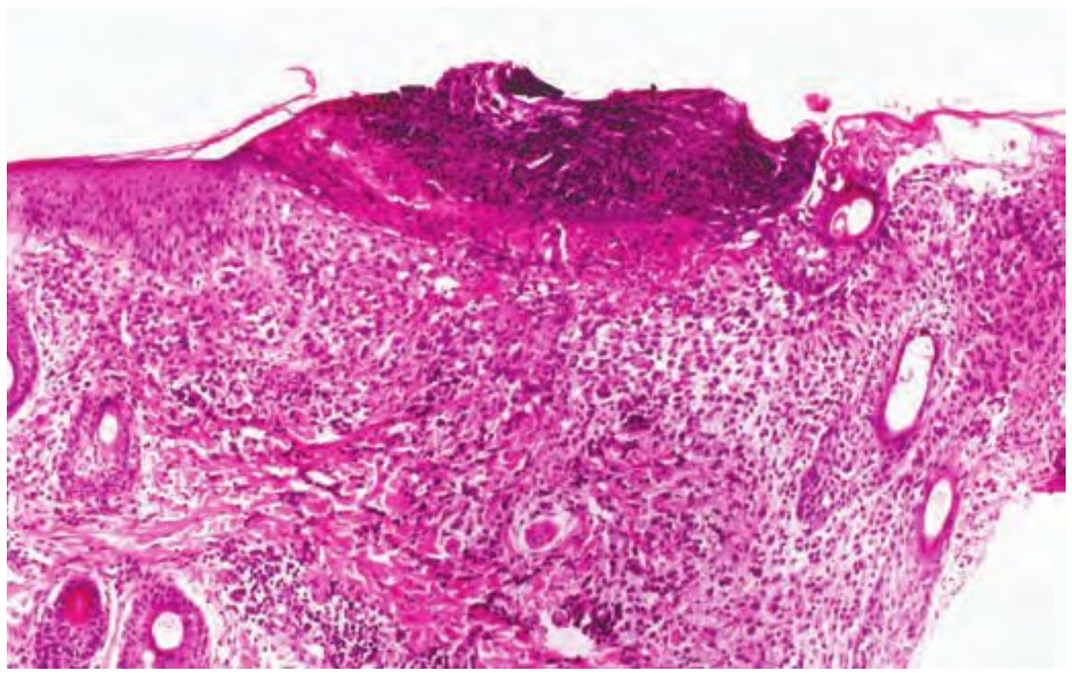
Histopathology. The histologic picture unites the many varied forms of LCD. The key to diagnosis is identifying the typical LCD cell in the appropriate surroundings. The cell has a distinct folded or lobulated, often kidney-shaped, nucleus. Nucleoli are not prominent, and the slightly eosinophilic cytoplasm is unremarkable. A variety of methods can be used to confirm the identity of such cells. For years the gold standard has been to use electron microscopy to search for the typical Birbeck or Langerhans cell granules. Today, S100 protein, CD1a, and langerin can all be identified using paraffin-fixed tissue. Langerin is every bit as specific as Birbeck granules.

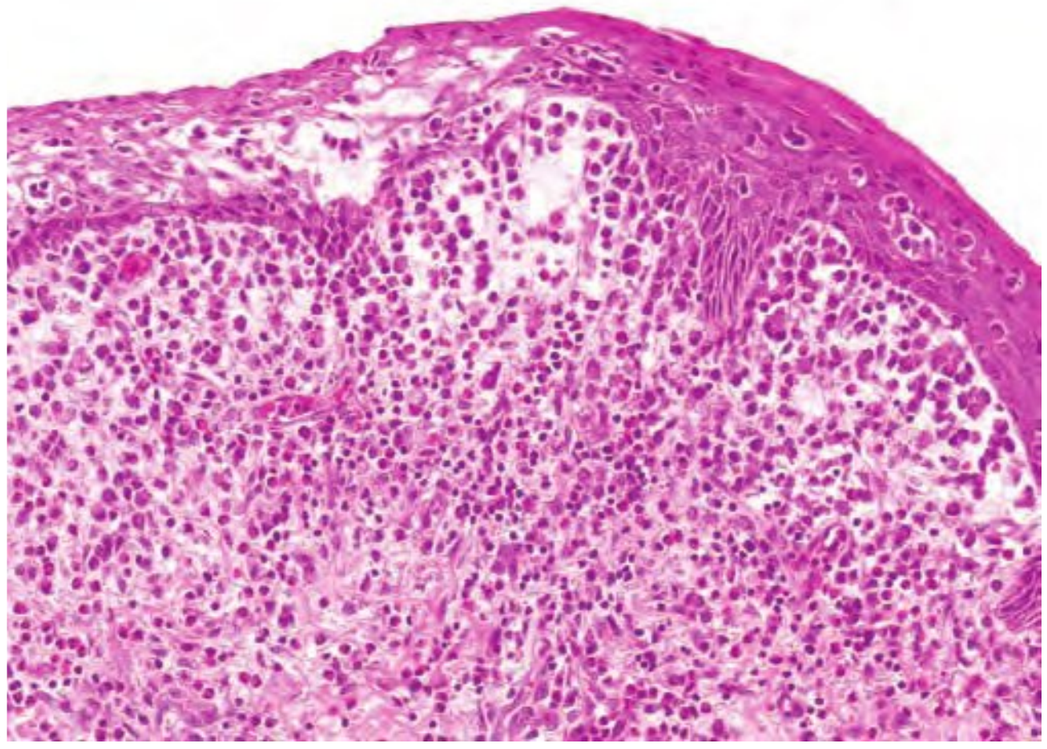
Although Lever emphasized three kinds of histologic reactions in LCD —proliferative, granulomatous, and xanthomatous— only the first two are commonly seen. A relationship exists between the type of histologic reaction and the clinical type of disease. In general, the proliferative reaction with its almost pure LC infiltrate is typical of acute disseminated LCD and the granulomatous reaction of chronic focal or multifocal LCD, as the name eosinophilic granuloma suggests. The xanthomatous reaction is seen in Hand-Schüller-Christian disease but primarily in other organs, especially the meninges and bones. Xanthomatous lesions in the skin are decidedly rare (21).

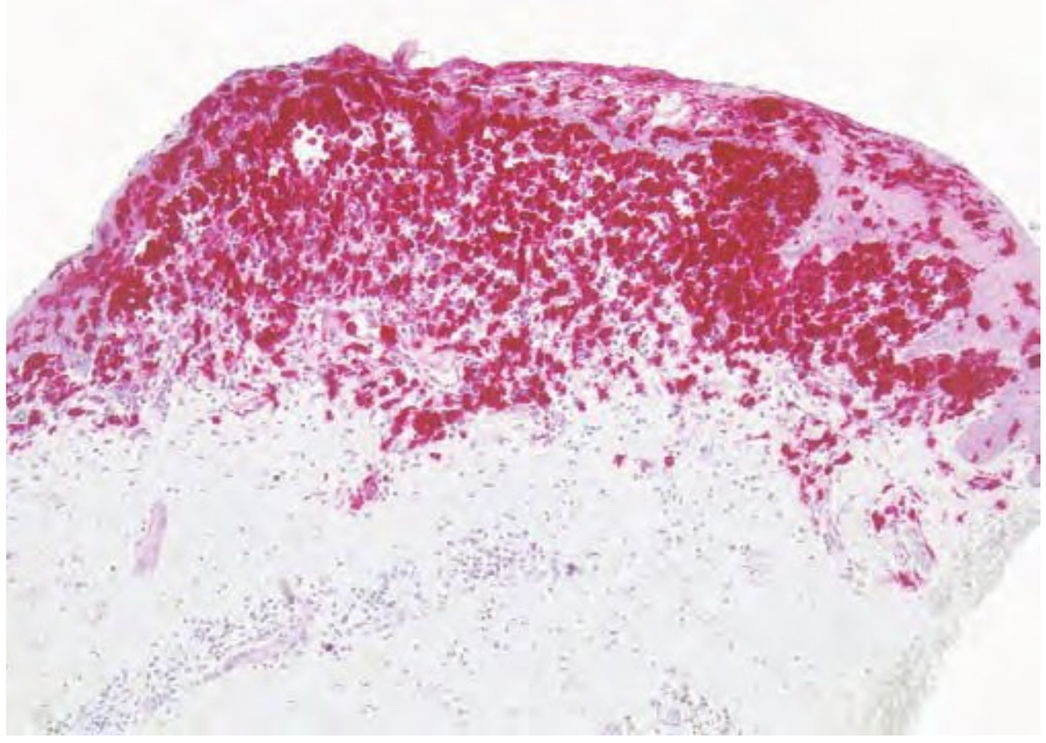
The proliferative reaction is encountered in the skin in petechiae, as well as in almost translucent, hemorrhagic, or crusted papules. It is characterized by the presence of an extensive infiltrate of LC. The infiltrate usually lies close to or involves the epidermis, resulting in ulceration and crusting (Fig. 26-1A). Large, kidney-shaped tumor cells can be seen just below or even impinging on the epidermis (Fig. 26-1B). Staining with S100 protein, CD1a, or langerin shows both the normal and abnormal LC (Fig. 26-1C).

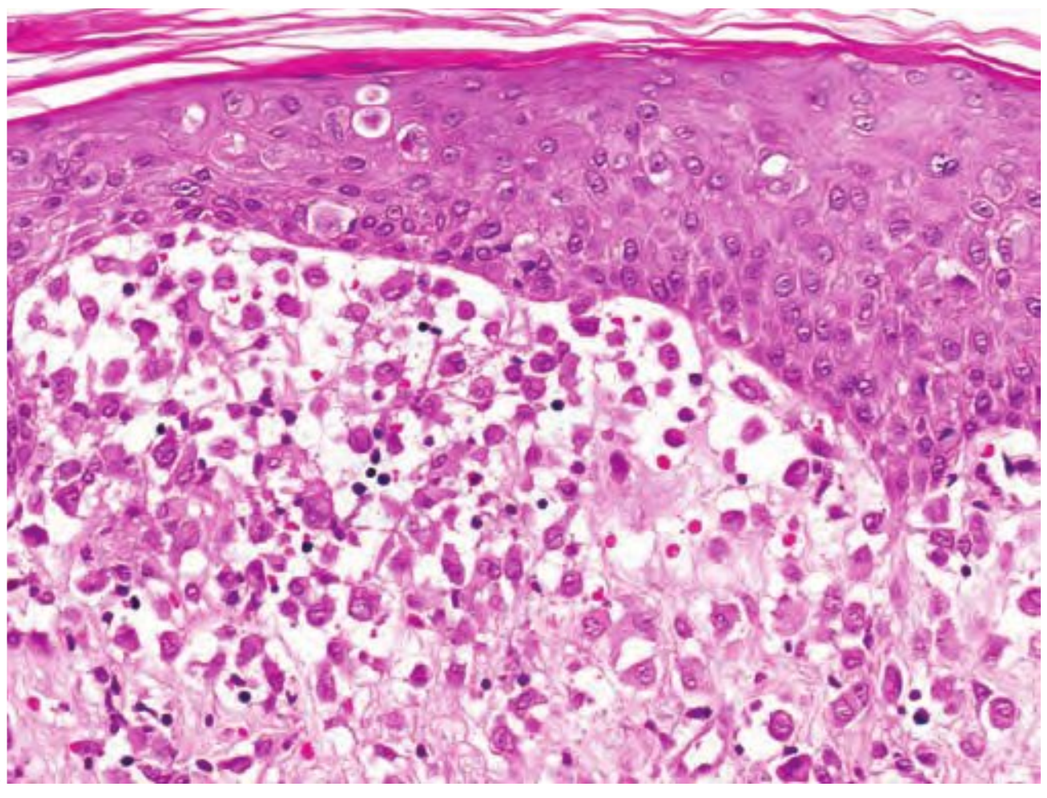
The nodules of CSHRH show densely aggregated LC with abundant eosinophilic cytoplasm (Fig. 26-1D). Some of the LC are large and form giant cells, with diameters up to 50 μm. In some cells, the cytoplasm has a "ground glass" appearance


A


B


C


D


E

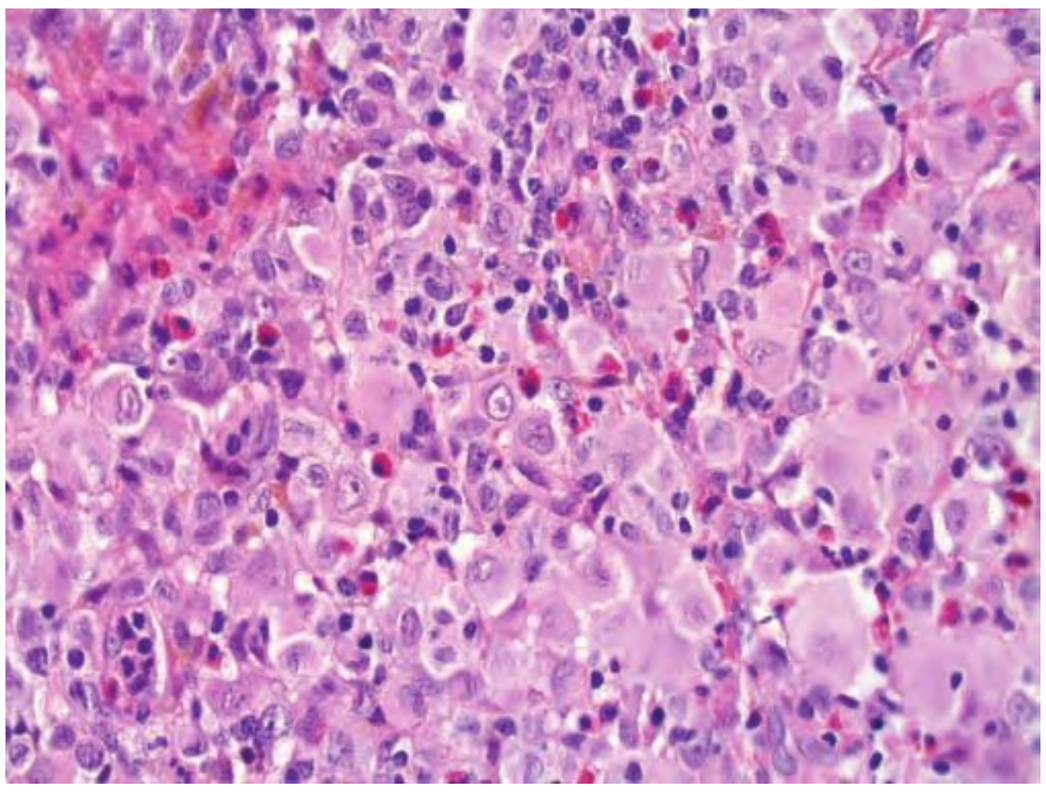

F

FIGURE 26-1. Langerhans cell (LD) disease. A: Widespread hemorrhagic papules with scale in an infant. B: Crusted papular lesion in a young infant. A dense cellular infiltrate is seen beneath the crust. C: Higher magnification showing accumulations of LCs along the epidermal–dermal junction. D: Staining with anti-CD1a identifies both normal epidermal LCs and the tumoral LCs in the papillary dermis. E: The dermal papillae are filled by large, kidney-shaped cells. F: A deep, nodular cutaneous infiltrate rich in eosinophils with clusters of typical large LCs. (A: Courtesy of Wilfried Neuse, Düsseldorf, Germany. C, D: Courtesy of Markus Hantschke, Friedrichshafen, Germany. E: Courtesy of Werner Kempf, Zürich, Switzerland.)

responsible for the term "reticulohistiocyte," a morphologic pattern seen occasionally in LCD and commonly in macrophage disorders. CHRSH cannot be histologically separated from other lesions of LCD.

The granulomatous reaction is found most commonly in infiltrated plaques and nodules in the genital area, in the axillary region, or on the scalp, as well as in the soft tissue and bone lesions. Extensive aggregates of LC often extend deep into the dermis. Eosinophils are present in various quantities (Fig. 26-1E). Generally, they lie in clusters instead of being diffusely scattered and may develop into microabscesses. Irregularly shaped, multinucleated giant cells are occasionally seen. In addition, some neutrophils, lymphocytes, and plasma cells may be present. Frequently, extravasation of erythrocytes is found.

The uncommon xanthomatous reaction reveals in the dermis numerous foamy cells, as well as varying numbers of LC and some eosinophils. Multinucleated giant cells are frequently present. They are mainly of the foreign-body type but occasionally have the appearance of Touton giant cells. The S100 protein and CD1a staining is likely to be weak or even negative in the foamy cells.

A final question is that of malignant LCD ("malignant histiocytosis X;" not to be confused with malignant histiocytosis). The International Lymphoma Study group identified several examples of Langerhans cell sarcoma (33). In such instances, there may be nodal, extranodal, or systemic involvement by highly atypical LC with frequently mitoses and marked pleomorphism (34). Acute disseminated LCD can reasonably be argued to be a malignancy because it is progressive, destructive, and potentially fatal and shows clonality. Some cases have been identified with marked cytological atypia, including mitoses, and a poor clinical outcome (35–37). Unfortunately, most often the diagnosis has been made retrospectively; cellular morphology is a poor way to predict the course of LCD, except in the case of nodular, frankly anaplastic sarcomas or lymphomas, both of which are rare.

Visceral Lesions. The visceral lesions seen in LCD show the same three types of reactions just described for the skin. The organs most commonly affected are the spleen, liver, lungs, lymph nodes, and bones. In Hand-Schüller-Christian disease, the diabetes insipidus is caused by granulomatous infiltration of the hypothalamus-pituitary axis; the exophthalmos, by retroorbital accumulations of granulomatous tissue; and the multiple defects in the skull, by the osteolytic effect of granulomatous infiltrates. Pulmonary LCD typically occurs in adult smokers, but lung involvement can be seen in children with widespread disease, in whom it is a poor sign.

Pathogenesis. Although the key cell of LCD is very similar to a normal Langerhans cell, there may be subtle differences. The cell of LCD is immature and may express CD68 and HLA-DR in a paranuclear pattern. Birbeck granules are convincing proof of the relationship, but they are present in varying amounts in LCD. Particularly when dealing with a sparsely infiltrated dermatitic picture, the search can be frustrating. In denser infiltrates, one can usually readily find the characteristic organelles.

LCD is most often a clonal process. Different groups have studied female patients with the disease and used a variety of X-linked polymorphisms to demonstrate clonality (38,39). A loss of heterozygosity may also be detected; it appears more likely in high-risk lesions and in those from patients with multisystem disease (40). Despite these studies, many view LCD as a reactive process because of its tendency toward spontaneous remissions and its good response to mild, nontoxic therapeutic regimens. In a fascinating historical review, Nezelof and Basset, who identified the cell of then "histiocytosis X" as a LC, lamented that fact that discovering this association has provided few clues to what causes the disease (41).

Differential Diagnosis. The differential diagnosis for LCD varies with the histologic pattern. The most difficult situation is an early proliferative dermatitic lesion with little epidermotropism and few characteristic cells. Without adequate clinical background, it is easy to make the mistaken diagnosis of superficial perivascular dermatitis. One should keep LCD in mind in all biopsies of dermatitis from infants and freely employ the S100 protein stain for screening. When a nodule or tumor is present, the presence of eosinophils and the sheets of characteristic cells usually lead to the diagnosis. The cutaneous xanthomas are not distinctive, and whereas the foamy cells may stain weakly with S100 protein or CD1a, usually the surrounding infiltrate has enough positive cells to allow a diagnosis. Some cases of CSHRH may be clinically confused with the blueberry muffin syndrome, congenital leukemic infiltrates, or mast cell disease, but the microscopic picture brings clarity.

XANTHOGRANULOMA FAMILY

The xanthogranuloma family is the largest group of cutaneous histiocytic disorders. The source of xanthogranuloma cells is unclear; the two most often proffered candidates are macrophages and dermal/interstitial dendritic cells (42,43). Macrophages seem likely based on CD68 staining and the propensity for xanthomatous transformation (44). The main evidence for dermal/interstitial dendritic cells is FXIIIa positivity, but we question its specificity. Another explanation is alternate activation of macrophages leading to the expression of stabilin-1, a receptor that links exogenous signals to a variety of intracellular vesicular functions. Stabilin-1 can be identified by anti–MS-1 antibodies and seems to be a marker for cutaneous macrophage disorders, as compared to systemic ones (45). Finally, some have suggested that xanthogranuloma cells may arise from plasmacytoid dendritic cells/monocytes (46). We use the term macrophages for the rest of this chapter, fully recognizing that it may be incorrect in some instances.

Xanthogranulomas contain cells with a wide variety of morphologic characteristics, including vacuolated, xanthomatized, spindle-shaped, scalloped, and oncocytic cells (Fig. 26-2 and Table 26-4). A classic xanthogranuloma contains a mixture of these different cell types, but there are some disorders in which one cell type predominates; these disorders may

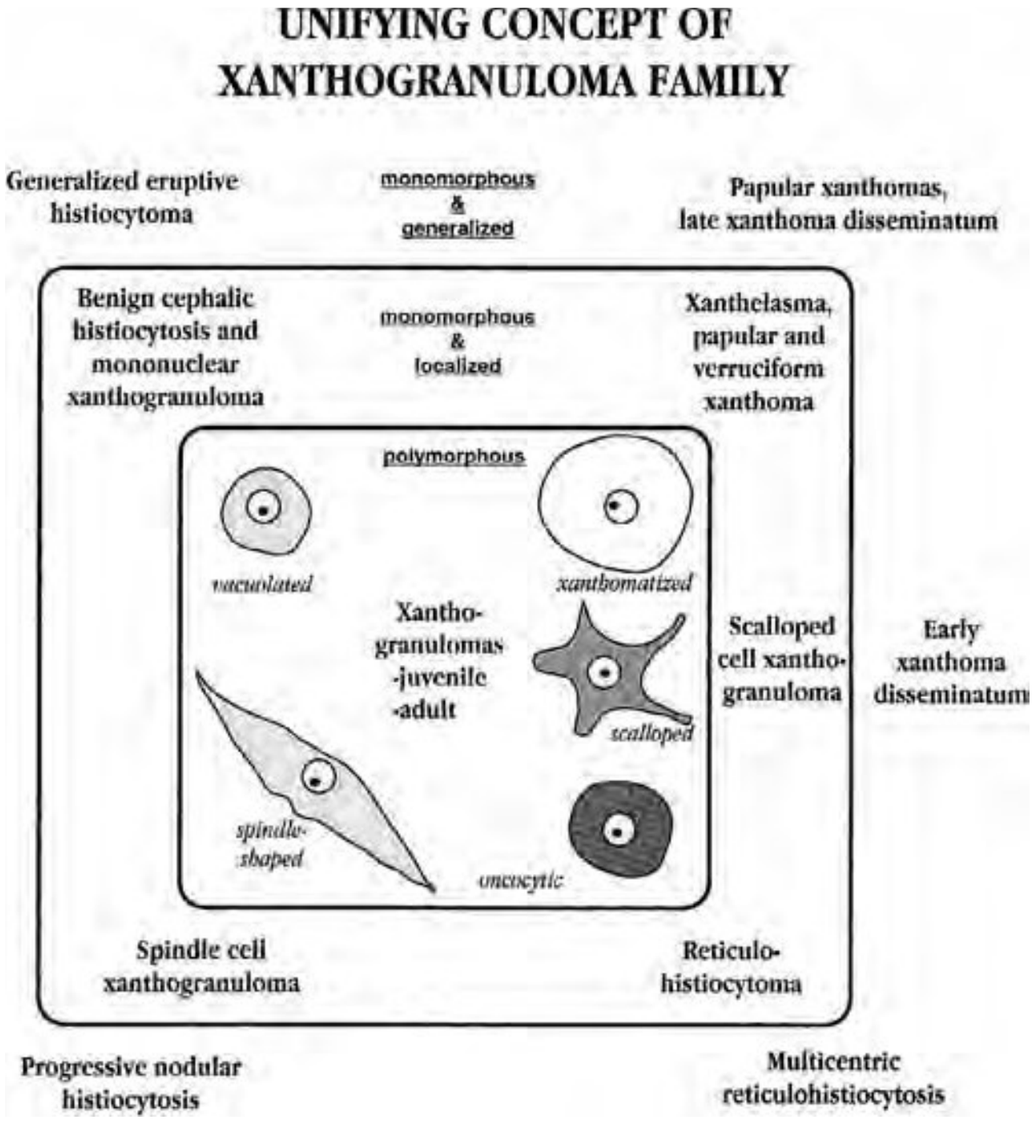


FIGURE 26-2. Unifying concept of the xanthogranuloma family.

be further divided into solitary and multiple forms, as the diagram shows (47).

Juvenile Xanthogranuloma

Juvenile xanthogranuloma (JXG) is a benign disorder in which one, several, or occasionally numerous red-to-yellow nodules are present. Because the lesions are also seen in adults, JXG is admittedly an imperfect term. Because we have used xanthogranuloma to describe a type of lesion and family of disorders, we prefer to retain the designation JXG for these specific lesions.

The papules and nodules are usually 0.5 to 1.0 cm in diameter. Most lesions appear during the first year of life; 20% are present at birth. In children the lesions may grow rapidly but almost always regress within a year. Lesions in adults are not uncommon but are usually solitary and persistent (48–50). JXG may be clinically subdivided into several forms. The micronodular variant is most common; patients are infants with many small nodules. Occasionally a macronodular form is seen with only a few lesions, but these are often several centimeters in diameter. The solitary giant xanthogranuloma may be larger than 5 cm (51). Plaques may also be seen, as well as prominent nasal involvement (the Cyrano sign) (52). There are also subcutaneous or deep JXG (53–55). On occasion JXG develops in patients with LCD; this probably reflects the similarities between the responsible cells.

A number of systemic complications are associated with JXG (56). Ocular involvement including glaucoma and bleeding into the anterior chamber is the most common; it occurs in less than 10% of young patients (57). Oral lesions may occur. An association between JXG, café-au-lait macules, neurofibromatosis I, and juvenile chronic myelogenous leukemia has been reported but must be rare (58,59). JXG has also been identified in many other organ systems, including the central nervous system, kidney, lungs, liver, testes, and pericardium.

In two large series, involving more than 300 patients in pediatric pathology referral centers, 5% of the patients had widespread systemic disease (48,49). These patients are at risk for infections and macrophage activation syndrome, and some may die. Although some of these children present with cutaneous disease, most do not. It is neither necessary nor wise to raise the specter of systemic involvement each time an infant or a child is seen with a solitary cutaneous JXG.

Bone involvement with JXG can be confusing. Erdheim-Chester disease is a rare macrophage disorder almost always seen in adults (mean age greater than 50 years) featuring symmetric lesions of the long bones associated with extraskeletal disease in 50% of cases (60–62). Skin is the third-most-common such site, after kidney and retroperitoneum. Typical findings include xanthelasmas (63) and occasionally red-brown papules or nodules suggesting JXG. The cells in Erdheim-Chester disease mark just as do any other JXG cells. The outlook for patients with extraskeletal diseases is poor, with most dying within 3 to 5 years from renal, cardiac, or pulmonary disease. Thus, when adults have apparent skeletal xanthogranulomas, one must be suspicious of this diagnosis. Rarely, children have been reported with the disease.

TABLE 26-4 Patterns of Cutaneous Macrophages

Type of macrophage	Associated giant cells
Foamy	Touton
Scalloped	Foreign body
Oncocytic	Ground glass
Spindle	Rarely seen
Vacuolated	Few

Histopathology: The typical JXG contains macrophages with a variety of cellular features (64). On low power, a well-circumscribed nodule, often exophytic and with an epidermal collarette, is found (Fig. 26-3A). Typically many of the stylized morphologic variants of macrophages can be seen. There is usually a characteristic progression as the lesions mature (65). Early lesions may show large accumulations of vacuolated cells without significant lipid infiltration intermingled with only a few lymphocytes and eosinophils (Fig. 26-3B). When no foamy cells or giant cells are seen, the possibility of JXG is often overlooked (66,67). This mononuclear variant of JXG is identical to lesions found in benign cephalic histiocytosis and generalized eruptive histiocytosis. Usually some degree of lipidization is present, even in very early lesions, manifested by pale cells. In mature lesions, a granulomatous infiltrate is usually present containing foamy cells, foreign-body giant cells, and Touton giant cells, as well as macrophages, lymphocytes,

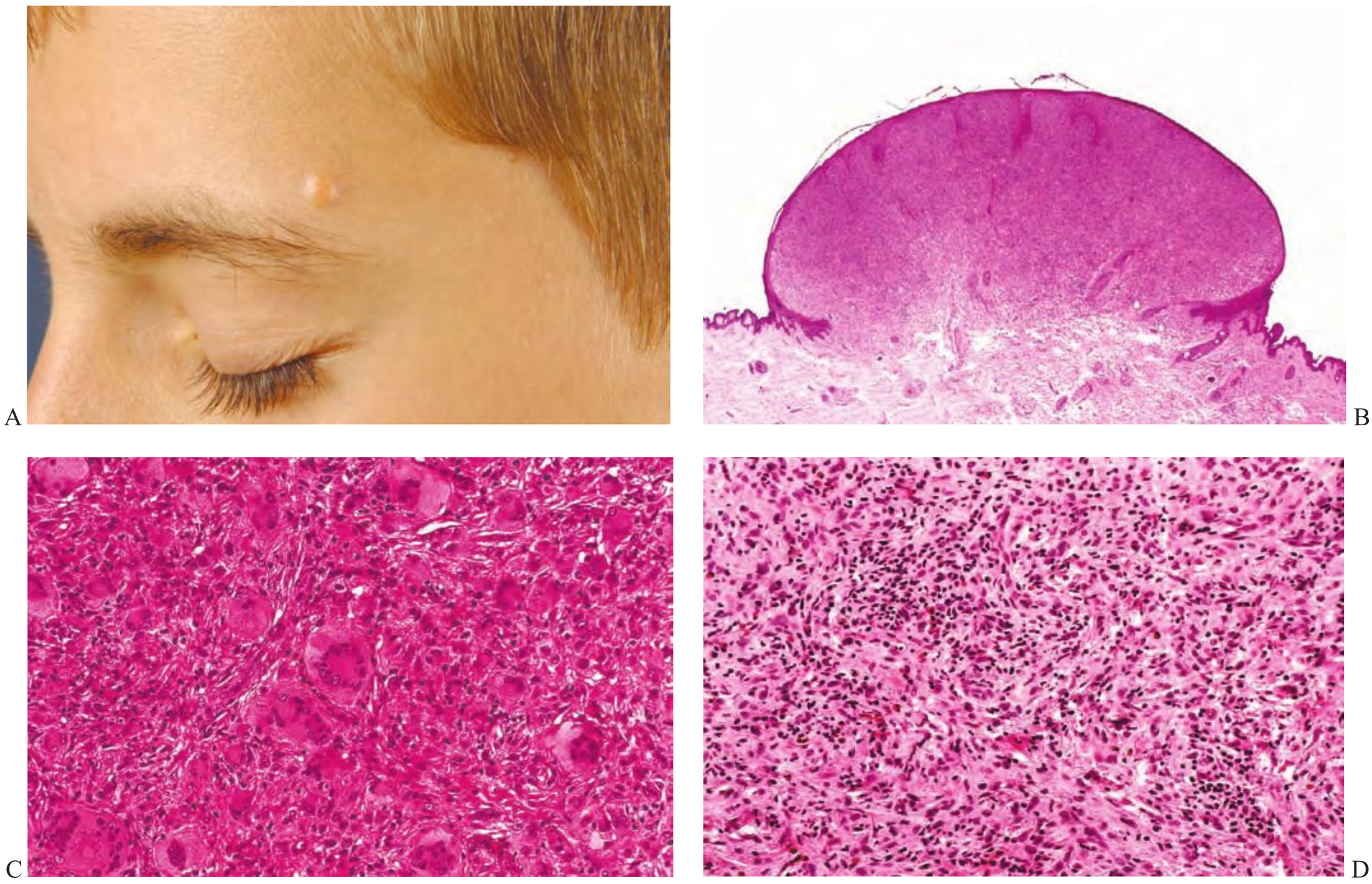


FIGURE 26-3. Juvenile xanthogranuloma. A: Yellow-brown nodule in a typical facial location in a child. B: Elevated nodule with epidermal collarette. At scanning magnification, a pale pink color and a few giant cells can be identified. C: Numerous Touton giant cells; cytoplasm within the wreath of macrophages is slightly more eosinophilic than that at the periphery. D: Numerous mononuclear macrophages admixed with eosinophils without Touton giant cells. (A: Courtesy of Wilfried Neuse, Düsseldorf, Germany.)

and eosinophils (68). The presence of giant cells, most of them Touton giant cells, showing a wreath of nuclei surrounded by foamy cytoplasm is quite typical for JXG (Fig. 26-3C) but not diagnostic because wreath-shaped giant cells can be seen in other disorders, including some melanocytic nevi. Occasionally, Touton giant cells are absent even in mature lesions. Older, regressing lesions show fibrosis replacing part of the infiltrate. Two types of spindle/dendritic cells may be identified; the spindle-cell or fusiform macrophages are dispersed throughout the lesion and are S100 protein negative. LC may be found as bystanders, generally at the periphery of the lesion.

Pathogenesis. The cause of JXG is unknown. The cell of origin is controversial, as discussed previously.

Differential Diagnosis. The clinical differential diagnosis includes Spitz nevi, mastocytomas, and dermatofibromas. The typical histologic picture of JXG is unmistakable. The many variants lead to a baffling array of diagnostic possibilities, which are considered under the individual variants.

Papular Xanthoma

Papular xanthomas (PX) are small red-brown papules often with a yellowish hue. Patients present with one, several, or many papules (69,70). Although the lesions may be generalized, they have neither the distribution pattern of xanthoma disseminatum nor the confluence of diffuse normolipemic plane xanthoma. Plaques are not seen. The patients show no abnormalities of lipid metabolism. Most patients are adults, but occasional cases have been seen in children (71,72). The oral mucosa may be involved.

Histopathology. Nodules containing foamy cells with numerous Touton giant cells are seen in the dermis. Extracellular lipids are not seen. Even when early lesions are biopsied, xanthomatized cells predominate, with only a small component of mononuclear vacuolated macrophages or other cell types (Fig. 26-4A, B).

Pathogenesis. Why some macrophages become xanthomatized in the presence of normal serum lipid levels is not known. Despite the early definition of papular xanthoma as a macrophage disorder without a macrophage precursor phase,

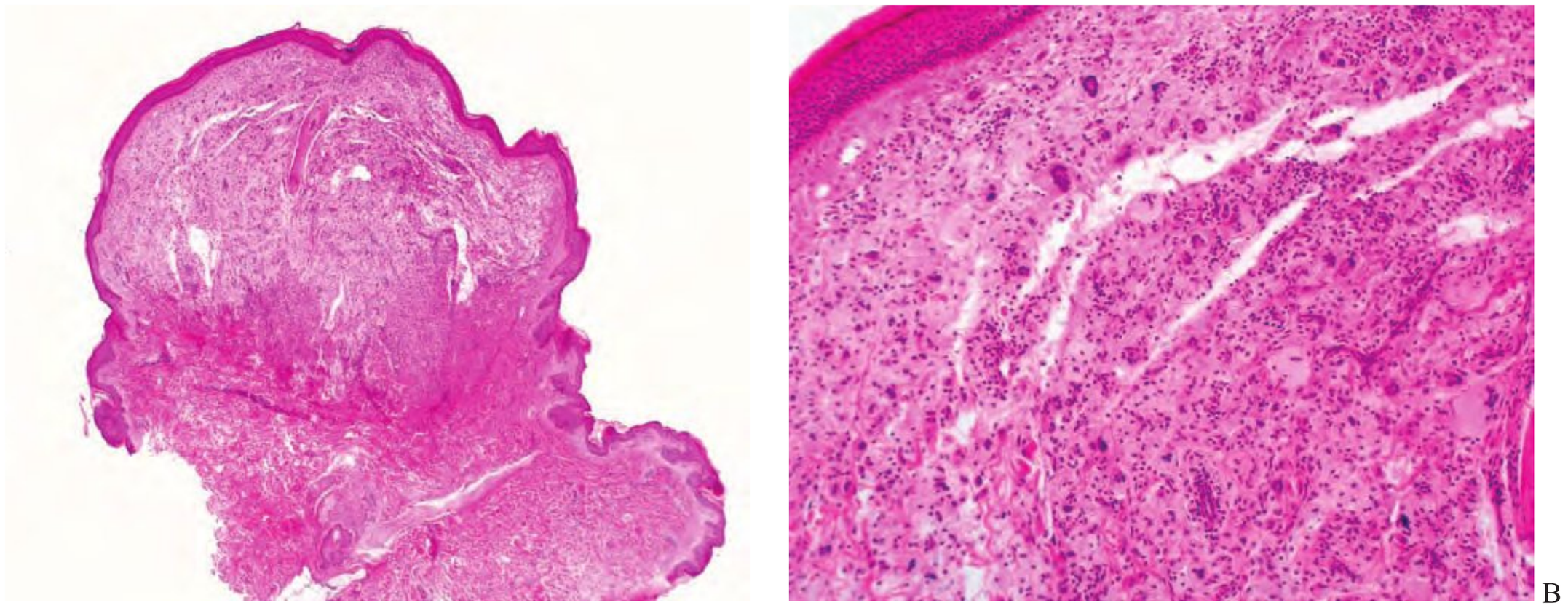


FIGURE 26-4. Papular xanthoma. A: Pale papule without epidermal reaction or clefting. B: Numerous foamy macrophages and Touton giant cells. Extracellular lipids are not present.

there must be macrophages present initially that rapidly become xanthomatized. Neutrophilic papular xanthomas have been described in normolipemic patients with HIV/AIDS. They may develop following similar pathways to the paraneoplastic xanthomas secondary to the massive changes in lymphocyte proliferation. These xanthomas contain neutrophils and nuclear dust in addition to foamy cells.

Differential Diagnosis. Papules made up of predominately foamy cells may also be associated with elevated lipid levels or be a paraneoplastic marker, as in diffuse normolipemic plane xanthoma. Solitary lesions may be mistaken clinically for dermatofibroma, Spitz nevus, and a variety of other benign proliferations.

Scalloped Cell Xanthogranuloma

Scalloped cell xanthogranuloma is not clinically distinct. We identified a number of lesions in which the predominant macrophage is scalloped once we had become aware of this morphologic variant in xanthoma disseminatum and began searching for solitary lesions to fill in our unifying concept scheme (73). The lesions are typically on the head, neck, or back of young men and may be diagnosed as juvenile xanthogranuloma or, less often, melanocytic nevus or basal cell carcinoma. Histologically, scalloped macrophages predominate, although a mélange of other macrophage types may be found (Fig 26-5A, B).

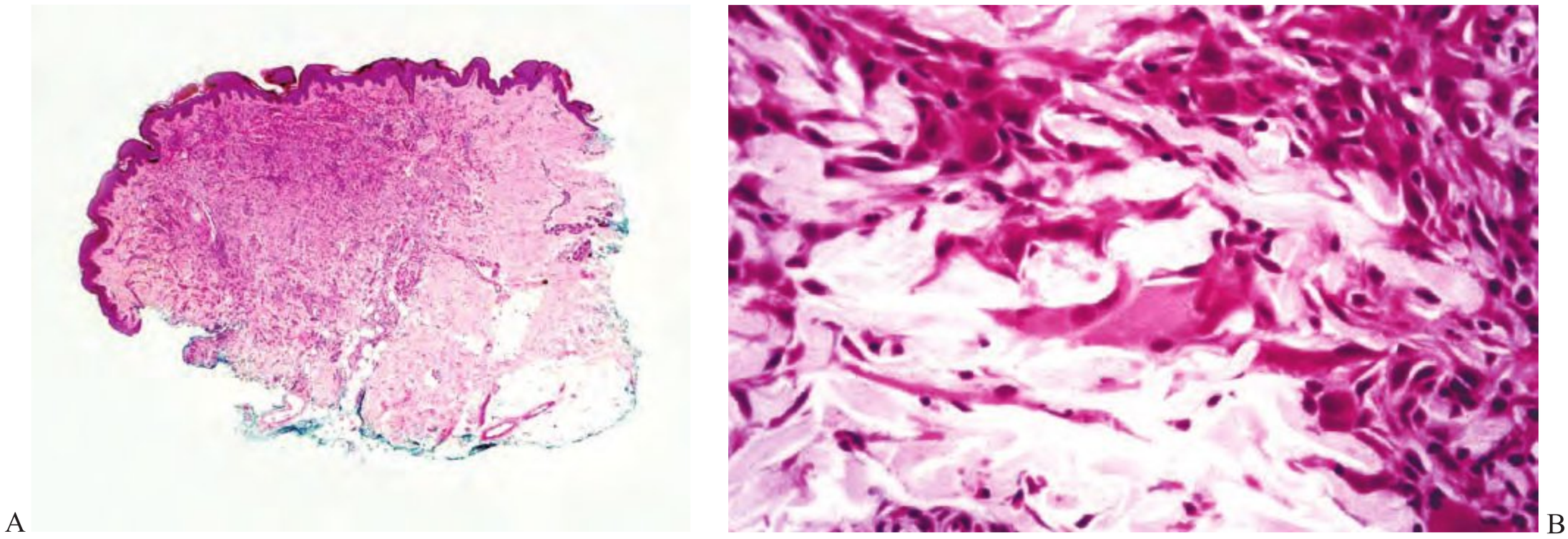


FIGURE 26-5. Scalloped cell xanthogranuloma. A: Small, well-circumscribed dermal nodule without obvious giant cells or pale areas. B: Pale scalloped macrophages seen at the base of the infiltrate. Such cells can also be found in the early lesions of xanthoma disseminatum.

Xanthoma Disseminatum

Xanthoma disseminatum (XD) is a rare but distinctive disorder featuring numerous widely disseminated but often closely set and even coalescing, round to oval, orange or yellow-brown papules and nodules. Lesions are found mainly on the flexor surfaces, such as the neck, axillae, antecubital fossae, groin, and perianal region. Peculiar target lesions may be seen. Often there are lesions around the eyes. The mucous membranes are affected in 40% to 60% of cases. In addition to oral lesions, there may be pharyngeal and laryngeal involvement. Three patterns have been identified; the most typical is the persistent form. Rarely, lesions may regress spontaneously, and even more infrequently in the progressive form there may be significant internal organ involvement. The largest review (74) suggests that most cases begin in childhood, where the diagnosis can be problematic, as, for example, in an infant with mucosal and pituitary lesions. We have only seen the disease in adults.

Diabetes insipidus is encountered in about 40% of cases but usually is less severe than that associated with LCD. Characteristically, internal lesions other than diabetes insipidus are absent. In a few instances multiple osteolytic lesions have been found, especially in the long bones, as well as lung and central nervous system infiltrates.

Histopathology. In early lesions, scalloped macrophages dominate the histologic picture, with few foamy cells. More-developed lesions may still show scalloped cells, but xanthomatization occurs in most cases. Most well-developed lesions contain a mixture of scalloped cells, foamy cells, and inflammatory cells, as well as Touton and foreign-body giant cells (Fig. 26-6) (75).

Pathogenesis. In the past, some authors assumed a relationship between XD and LCD. Although in both conditions xanthomatous lesions and diabetes insipidus may occur, XD occurs in older patients, often has mucosal involvement, and only rarely involves bone. Finally, xanthomatous lesions are expected in XD and rare in LCD.

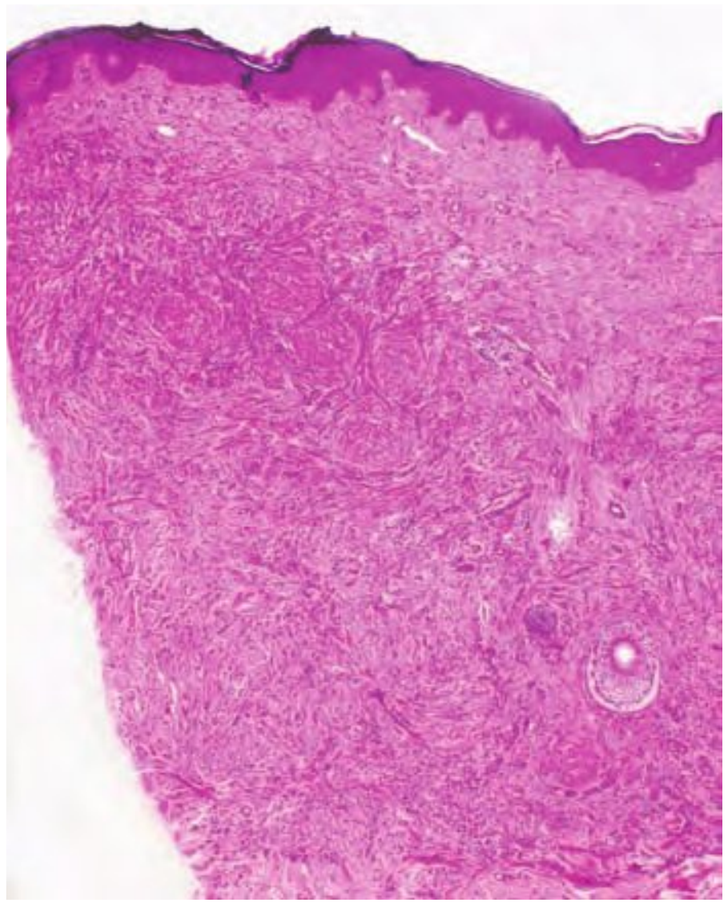


FIGURE 26-6. Xanthoma disseminatum. Combination of spindle cells in the upper dermis and foam cells deeper.

Reticulohistiocytosis and Multicentric Reticulohistiocytosis

We divide what has traditionally been called reticulohistiocytosis into giant cell reticulohistiocytoma (GCRH) and multicentric reticulohistiocytosis (MRH). Both disorders occur almost exclusively in adults. The histologic picture is very similar in the two types, but everything else is different.

GCRH is simply a xanthogranuloma in which the oncocytic macrophages and "ground glass" giant cells predominate. It is never clinically unique but diagnosed as a JXG or dermatofibroma. The clinical features, distribution, and course are identical to those of JXG (76). In greater than 90% of cases, the lesion is single, but occasionally multiple lesions are seen (77). Even patients with multiple lesions show no sign of systemic involvement. The newly suggested term of solitary epithelioid histiocytoma (78) may cause confusion with dermatofibroma/histiocytoma, and so we prefer not to use it.

In multicentric reticulohistiocytosis, a name first coined by Goltz and Laymon (79), the patients tend to be females, usually in the fifth or sixth decade of life, with widespread cutaneous involvement and a destructive arthritis (80–82). Nodules ranging in size from a few millimeters to several centimeters are most common on the extremities. Multiple papules on the face may coalesce, producing a leonine facies. Many small papules along the nail fold create the "coral bead sign." In about half of the patients, nodules are present also on the oral or nasal mucosa. Finally, about 25% also have xanthelasmas.

The polyarthritis may be mild or severe but is almost always present. It may be mutilating, especially on the hands, through destruction of articular cartilage and subarticular bone. In addition, there is an association with hyperlipidemia (30% to 50%), a variety of internal malignancies (15% to 30%) (83,84), and autoimmune diseases (5% to 15%). The disease tends to wax and wane over many years (85).

Histopathology. The characteristic histologic feature in both GCRH and MRH is the presence of numerous multinucleate giant cells and oncocytic macrophages showing abundant eosinophilic, finely granular cytoplasm, often with a "ground glass" appearance (Fig. 26-7A, B). There may be subtle microscopic differences between solitary and multiple lesions (86). In older lesions giant cells and fibrosis are more common. Staining for vimentin and CD45 also appears common, whereas FXIIIa is usually negative (87). Some lesions have been described sharing features with dendritic cells (88).

The polyarthritis present in nearly all instances of MRH is caused by the same type of infiltrate as found in the cutaneous lesions. In early or mild cases, the granulomatous infiltrate is confined to the synovial membrane. Although similar infiltrates have been described in other organs, their clinical significance is unclear.

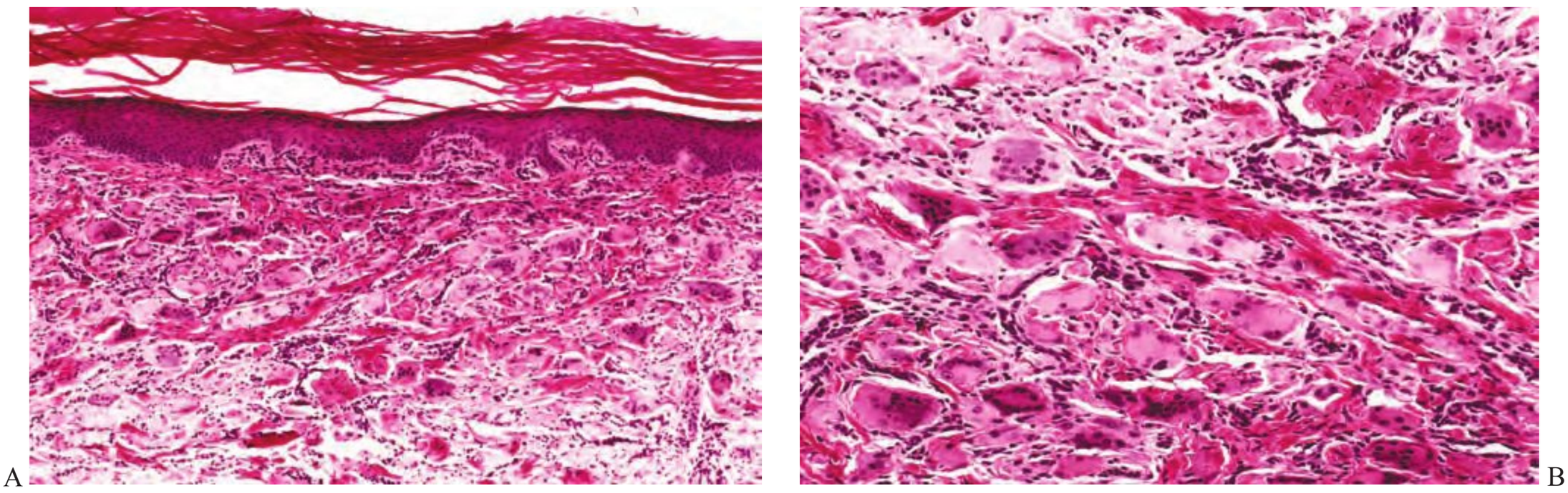


FIGURE 26-7. Multicentric reticulohistiocytosis. A: A diffuse dermal giant cell infiltrate with sparse inflammation and a thinned epidermis. B: Relatively clear giant cells with finely granular cytoplasm ("milk glass" appearance) replacing the upper dermis. The giant cells are large and irregular, containing many haphazardly arranged nuclei.

Pathogenesis. Ultrastructural examination shows abundant mitochondria and lysosomes, which correlate with the ground glass appearance. Similar changes are found in oncocytic thyroid and renal tumors. The cause of the solitary lesions is unknown, just as with JXG.

Differential Diagnosis. It is futile to try and distinguish between a solitary GCRH and JXG. The two lesions are part of a spectrum, and overlaps occur. A single macrophage lesion with ground glass cytoplasm does not make the diagnosis of MRH but instead should simply be viewed as having the same clinical significance as JXG. The clinical differential diagnosis of MRH is lengthy, but a skin biopsy is quite helpful in pointing one in the right direction. Gout, rheumatoid arthritis, sarcoidosis, dermatomyositis, and even lepromatous leprosy may be considered (89).

Spindle Cell Xanthogranuloma

Spindle cell xanthogranulomas are not clinically distinct. They are usually on the head or neck of young adults and identified as JXG or dermatofibromas (90). Deep spindle cell xanthogranulomas may cause puzzlement; in one case, a woman presented with cutaneous JXG and later developed spindle cell xanthogranuloma of the breast (91). Histologically they are even more likely to be misdiagnosed, usually as dermatofibromas or blue nevi. Microscopically they lack melanin and do not have reactive changes in the overlying epidermis or lateral entrapment of collagen so typical of dermatofibromas (Fig. 26-8A, B). They stain with the typical macrophage stains, but also for FXIIIa and smooth muscle actin.

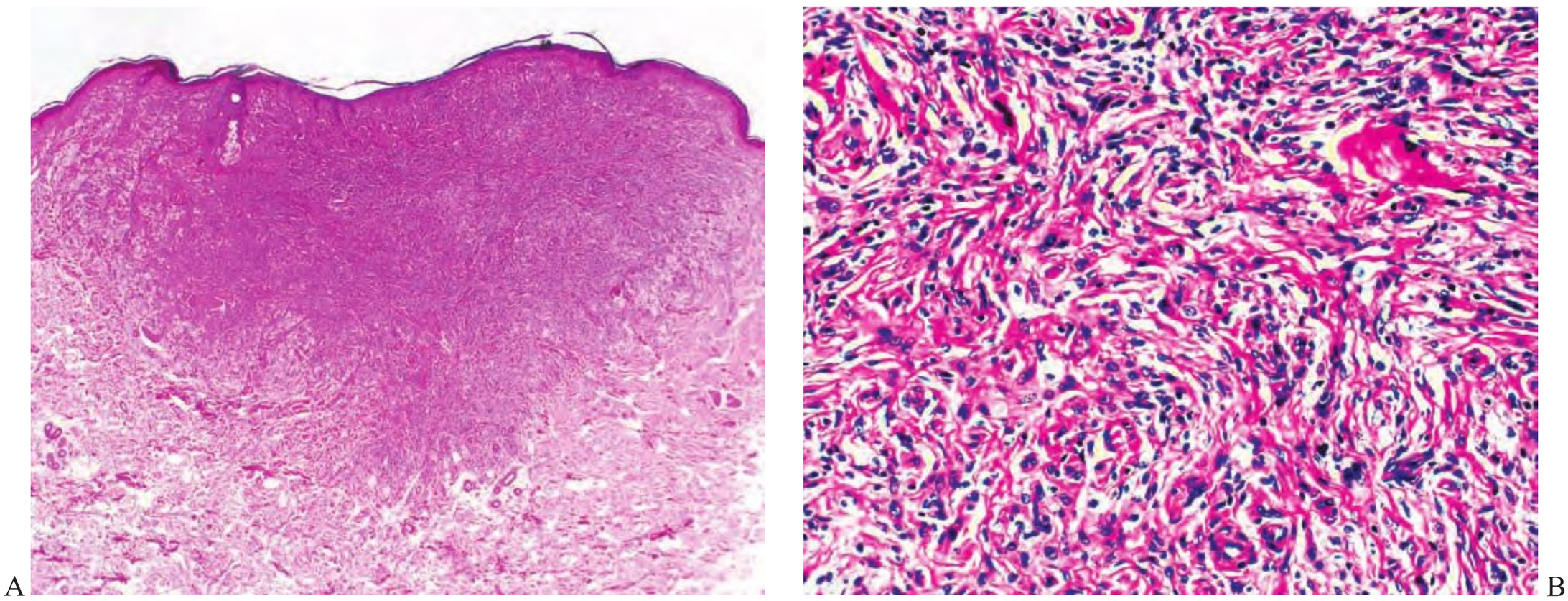


FIGURE 26-8. Spindle cell xanthogranuloma/progressive nodular histiocytosis. A: Dermal nodule with storiform pattern. No evidence of epidermal reaction or peripheral entrapment of collagen. B: Spindled macrophages admixed with a few foamy cells. The lesion was from a patient with progressive nodular histiocytosis.

Progressive Nodular Histiocytosis

Progressive nodular histiocytosis is a rare, clinically distinct disorder. Patients typically have hundreds of lesions of two types: superficial xanthomatous papules 2 to 10 mm in diameter and deep fibrous nodules 1 to 3 cm in diameter. The key to diagnosis lies in these two distinct lesions (92,93). Conjunctival, oral, or laryngeal lesions may occur, as well as rare systemic lesions (94,95). Lesions rarely if ever regress. Familial or congenital cases have not been reported.

Histopathology. Two patterns can be recognized that correlate with the clinical lesions. The smaller papules are xanthomatous with foamy cells and occasional Touton giant cells; they are papular xanthomas. The larger nodules are spindle cell xanthogranulomas (Fig. 26-8A, B).

Differential Diagnosis. When the distinctive clinical picture is present, the diagnosis of progressive nodular histiocytosis should be considered, but no harm is done if the patient is diagnosed with multiple JXG.

Benign Cephalic Histiocytosis

Benign cephalic histiocytosis is a self-healing eruption usually limited to the skin (96). The eruption usually starts during the first 3 years of life and is almost always on the face, although it may become generalized (Fig. 26-9A). The lesions consist of red-to-yellow papules, which after a few years become flat and pigmented and finally resolve. There are overlaps with multiple JXG (97,98). Systemic involvement is rare (99,100).

Histopathology. The infiltrate tends to be sparse and consists of macrophages with regularly shaped nuclei and sparse cytoplasm. Three patterns have been observed: papillary dermal, lichenoid, and diffuse (101). The papillary dermal pattern is most common; there is a cohesive infiltrate of macrophages in the upper

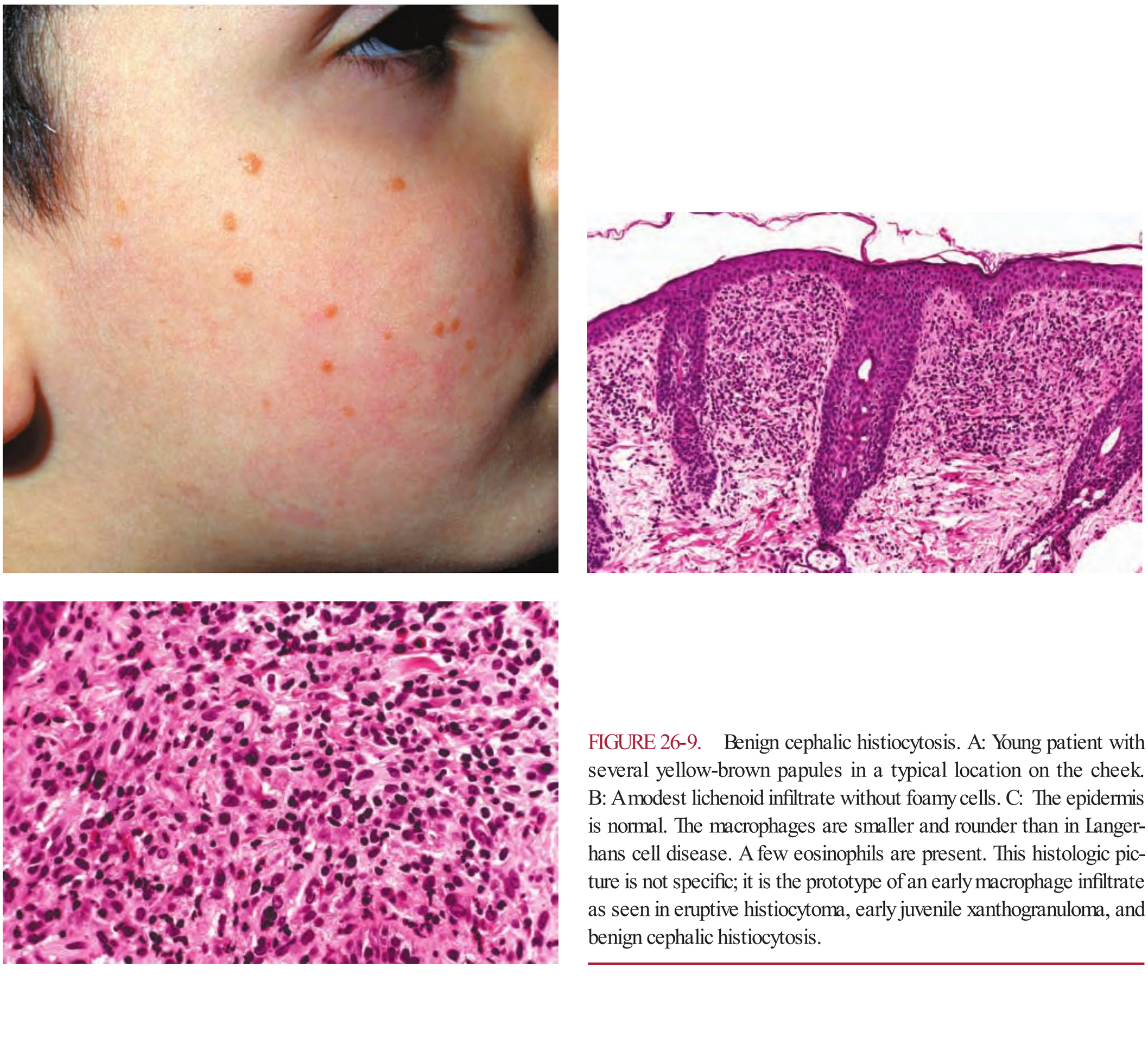


FIGURE 26-9. Benign cephalic histiocytosis. A: Young patient with several yellow-brown papules in a typical location on the cheek. B: A modest lichenoid infiltrate without foamy cells. C: The epidermis is normal. The macrophages are smaller and rounder than in Langerhans cell disease. A few eosinophils are present. This histologic picture is not specific; it is the prototype of an early macrophage infiltrate as seen in eruptive histiocytoma, early juvenile xanthogranuloma, and benign cephalic histiocytosis.

dermis. The cells tend to be large and have an eosinophilic cytoplasm. Foamy cells and epidermotropism are rare; eosinophils are often seen. The diffuse pattern is a minor variant in which the macrophages are sparser and spread throughout the dermis. The lichenoid pattern is easily confused with LCD, but the nuclear changes seen in the latter are not present; crusting and ulceration are also uncommon (Fig. 26-9B, C).

Pathogenesis. The cause of BCH is unknown.

Differential Diagnosis. It is most important to exclude LCD because clinical distinction can on occasion be difficult. Benign cephalic histiocytosis overlaps with generalized eruptive histiocytosis, progressive nodular histiocytosis, papular xanthomas, and multiple JXG. In an instructive case, a child with BCH developed more typical JXG after varicella infection with facial involvement. If the lesions are clinically typical, the diagnosis can be made with some confidence.

Generalized Eruptive Histiocytosis

Generalized eruptive histiocytosis may represent the initial stage of a variety of macrophage disorders, including JXG, xanthoma disseminatum, multicentric reticulohistiocytosis, and progressive nodular histiocytosis (47). Clinically it is characterized by the presence of innumerable flesh-colored to red macules and papules that develop in crops and may involute spontaneously (102). The disease takes a variable course; it may persist, remit, or relapse. As the infiltrates regress, the lesions may evolve into hyperpigmented macules. Although most patients are adults, the condition may arise in infancy (103,104). In rare instances, oral lesions have been observed. There may be an associated underlying disorder, such as a malignancy (105); the eruption may improve when the malignancy is treated (106).

Histopathology. Histologic examination reveals an infiltrate composed of various types of macrophages; most often small vacuolated cells are seen in a perivascular arrangement, but other morphologic variants may be represented or even dominate. Multinucleated giant cells are usually absent (107).

Pathogenesis. The etiology is unknown. These cells appear so rapidly that it is not surprising that they are often undifferentiated. Older lesions may show fibrosis or giant cells. The macrophages may in some cases appear in response to cytokines released by neoplasms, but in general their appearance remains unexplained.

Differential Diagnosis. The sudden onset and the lack of foamy cells or giant cells should suggest the diagnosis.

OTHER HISTIOCYTIC DISORDERS

Indeterminate Cell Histiocytosis

The diagnosis of indeterminate cell histiocytosis (ICH) was first proposed by Wood et al. when they reassessed a previously reported case (108). Clinically, most patients show numerous persistent red-brown papules or nodules that may coalesce.

Histopathology. The histologic picture is quite variable. Most commonly a monomorphous infiltrate of mononuclear cells intermingled with some giant cells and foamy cells is found. In our hands, these cases are positive for S100 protein and CD68, as well as showing focal CD1a reactivity (109). Other lesions more closely resemble LCD but lack the appropriate markers.

Pathogenesis. We do not consider ICH as a single specific entity. In addition, most cases described as ICH have little to do with the several different cells described as indeterminate cells. We suspect that most cases are macrophage disorders—variants of xanthogranuloma in which the predominant cell is derived from an earlier or aberrant lineage (110,111). Other cases, such as those resembling CSHRH, are clearly variants on LCD. Some examples of ICH may be reactive; such infiltrates have been described in nodular scabies (112) and after pityriasis rosea (113). A spindle cell variant has also been described (114).

Dermal Dendrocytoma

Both congenital (115,116) and acquired (117) lesions have been described that feature dermal dendrocytes. Because the available markers have changed greatly over the two decades during which the handful of cases have been described, there is no unifying pattern. In general, there have been dermal spindle cells staining for FXIIIA, fascin, vimentin, and CD34. We suspect that most of these cases represent dermatofibromas or spindle-cell xanthogranulomas.

Rosai-Dorfman Disease

The term "sinus histiocytosis with massive lymphadenopathy" was first used by Rosai and Dorfman in 1969 (118), although Destombes had previously described the disorder in Africa. Massive cervical lymphadenopathy, usually bilateral and painless, is the most common manifestation. Rosai-Dorfman disease (RDD) is generally a benign disorder in spite of its propensity to form large masses and to disseminate to both nodal and extranodal sites. In most patients the disease resolves spontaneously, others have persistent problems, and very few die (119). About 10% of patients with nodal disease have cutaneous involvement. The lesions are typically papules or nodules. The skin and subcutaneous soft tissue are also the most common sites of involvement when patients present with extranodal disease. Such individuals may represent a separate but closely related disorder because very few advance to nodal or systemic disease (120–125). Occasionally the soft tissue lesion may present as a breast mass or panniculitis (126).

Histopathology. The skin lesions contain a polymorphous infiltrate in which lymphocytes and macrophages with clear cytoplasm are most prominent. The low-power view has been compared to that of a "lymph node in the skin" (Fig. 26-10A, B). Occasionally they may be multinucleated or have a foamy

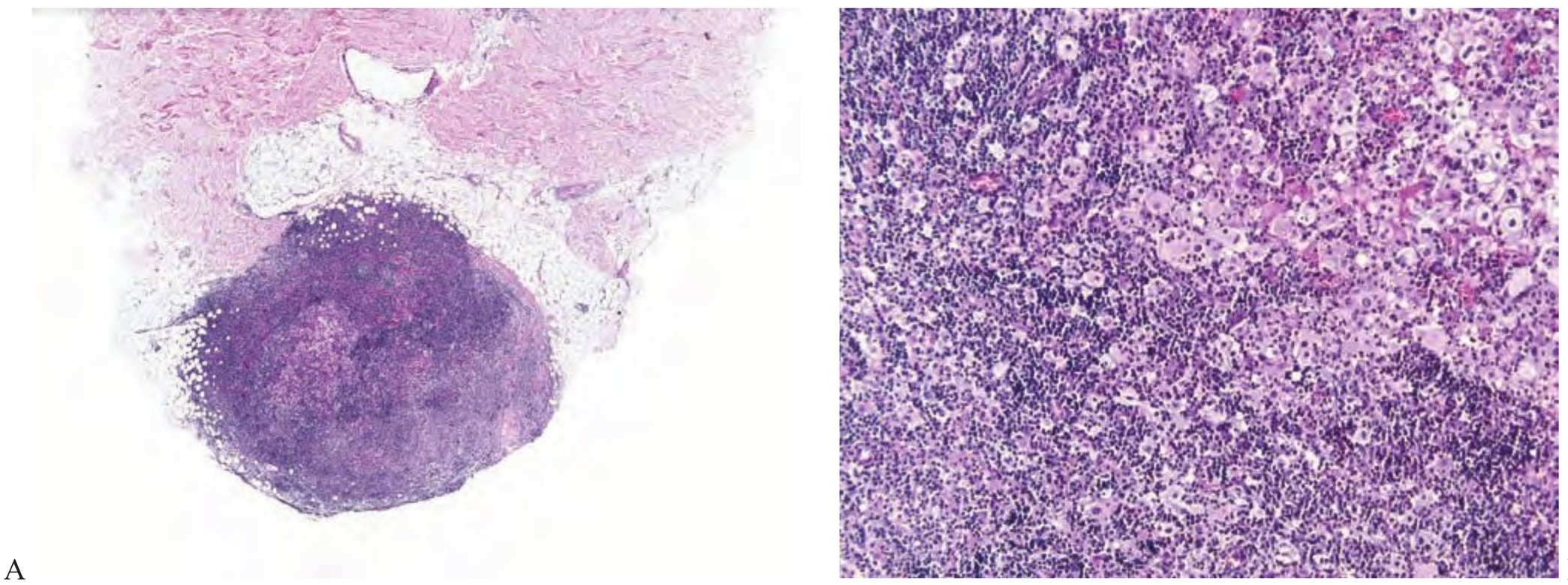


FIGURE 26-10. Sinus histiocytosis with massive lymphadenopathy. A: Subcutaneous nodular infiltrate rich in pale-staining cells centrally. B: Typical pattern of pale sinusoidal macrophages admixed with darker-staining lymphocytes. C: Numerous large macrophages, several of which have ingested lymphocytes, demonstrating emperipolesis. (All courtesy of Michael Flaig, Munich, Germany.)

cytoplasm. The hallmark histologic feature is emperipolesis of lymphocytes (Fig. 26-10C, inset). Emperipolesis differs slightly from phagocytosis in that the lymphocytes are taken up but seem not to be attacked and digested by enzymes. Thus they appear intact. On occasion, red cells can also be taken up. There are also often plasma cells, sometimes leading to deposits of crystalline immunoglobulins. In the lymph nodes, the sinuses are greatly dilated and crowded with inflammatory cells, particularly macrophages. Here they tend to have an abundant foamy cytoplasm and also display emperipolesis. The lymph node changes in autoimmune lymphoproliferative syndrome with defects in Fas-mediated apoptosis are very similar to those of RDD.

Pathogenesis. The cells are unusual activated macrophages that are positive for CD68, other macrophage markers, and fascin but are also S100 protein positive. They are CD1a and langerin negative. Over the years a variety of viruses have been implicated as triggers, including most recently parvovirus B19 (127). The lymph node changes resemble those in patients with autoimmune lymphoproliferative syndrome (128).

HISTIOCYTIC SARCOMA

Even though malignant tumors of macrophage lineage are rare, they are occasionally encountered in the skin. The large International Lymphoma Study Group identified 18 such cases, with 3 involving the skin, both with solitary and multiple lesions (33). There were also 3 cases of widespread systemic disease, corresponding to the old term of malignant histiocytosis. The tumors consist of large cells with frequent mitoses and varying degrees of pleomorphism. Multinucleate giant cells, foamy cells, and spindle-shaped cells may be encountered. Erythrophagocytosis is absent or inconspicuous, whereas emperipolesis is even rarer. The diagnosis must be supported by CD68 positivity, which is also accompanied by positive lysozyme staining in 90% of cases. Other macrophage markers

may also be positive, as well as S100 protein. Markers for dendritic cells, T cells, and B cells must be negative. Rare cases with overlap phenotypes have been reported (129). On electron microscopy, lysosomes are found but Birbeck granules and desmosomes are absent. Histiocytic sarcoma is an aggressive disease; only patients with solitary extranodal disease such as a single skin lesion are occasionally cured.

XANTHOMAS ASSOCIATED WITH LIPID ABNORMALITIES

Even though we place xanthomas among the macrophage disorders, we have left those associated with lipid abnormalities as a separate category because they are generally viewed as such by both clinicians and pathologists. Xanthomas are a cutaneous clue to the possible presence of hyperlipidemia, defined as an elevated fasting cholesterol level of greater than 200 mg/dL or a triglyceride level of greater than180 mg/dL. Today the high-density-lipoprotein (HDL)-cholesterol is also measured and used to calculate the low-density-lipoprotein (LDL)-cholesterol level. The desirable LDL-cholesterol level is less than 130 mg/dL. If abnormalities are detected, lipoprotein analysis is also usually performed. Hyperlipidemia may be unexpectedly identified during routine evaluations or searched for because of a family history of lipid abnormalities, cardiovascular disease, or the presence of one of its many secondary causes.

Once hyperlipidemia is identified, one must first exclude these secondary causes, which include diabetes mellitus, hypothyroidism, nephrotic syndrome, biliary disease, alcohol abuse, and a variety of medications, including estrogens, corticosteroids, and retinoids. In the 1960s Frederickson classified the primary hyperlipidemias on the basis of their electrophoretic lipoprotein phenotype. He considered not just cholesterol and triglycerides, but also the main lipoprotein classes in which they were transported throughout the body—chylomicrons, very low-density lipoproteins (VLDLs), LDLs, and HDLs. This traditional scheme is still used for a first diagnostic orientation but does not allow pathophysiologic classification of the lipoprotein disorder for two reasons:

1. The protein component of lipoproteins, known as apoproteins, has been extensively characterized and subdivided. The different apoproteins bind lipids, regulate enzymes, and identify cell receptors. For example, a patient may have normal amounts of cholesterol but decreased levels of HDL, which is essential for the removal of intracellular cholesterol.
2. The specific genetic defect has been identified for most disorders; the best known of which is familial hypercholesterolemia in which there is an absent or functionally defective LDL receptor.

Most patients with lipoprotein abnormalities do not have xanthomas, but the presence of xanthomas and especially the identification of extracellular lipids on histologic examination of the lesion should alert the clinician to the need for an internal evaluation. The type of xanthoma is primarily a clinical diagnosis and correlates poorly with the exact lipid abnormality. With these limitations in mind, Table 26-5 gives a brief overview of the relationship between xanthomas and hyperlipidemias (130).

TABLE 26-5 Algorithm for Cutaneous Xanthomas

When an infiltrate with foamy cells is found:
1. Is extracellular lipid present?
   If YES, marker for underlying hyperlipidemia
2. Check serum lipid levels
   a. If abnormal, diagnosis confirmed
   b. If normal, consider
      (i) Xanthogranulomas (papular xanthoma, xanthoma disseminatum)
      (ii) Noncholesterol lipid disorders (sitosterolemia, cholestanolemia)
      (iii) Paraneoplastic disorders
      (iv) Postinflammatory, posttraumatic lesions
      (v) Storage disorders and other rare syndromes

The xanthomas may clinically be divided into eruptive xanthomas, tuberous xanthomas, tendon xanthomas, and plane xanthomas. We view xanthelasmas as a morphologic variant of plane xanthoma more closely related to the macrophage disorders but discuss it here for the sake of continuity. Eruptive xanthomas are almost always associated with chylomicronemia and are most commonly seen in secondary forms of hyperlipoproteinemia. Eruptive xanthomas consist of small, soft, yellow papules with a predilection for the buttocks and the posterior aspects of the thighs (Fig. 26-11A). They come and go with fluctuations in the chylomicron level in the plasma. The lipid in these lesions is primarily triglycerides. Triglycerides are more rapidly metabolized than cholesterol. This may explain the more transient nature of eruptive xanthomas than other xanthomas.

Tuberous and tuberoeruptive xanthomas are found predominantly in cases with an increase in LDL and VLDL remnants. They are large nodes or plaques located most commonly on the elbows, knees, fingers, and buttocks. Most of the lipid in these xanthomas is in the form of cholesterol.

Tendon xanthomas occur in patients with excessive plasma LDL levels, such as familial hypercholesterolemia and familial apolipoprotein B-100 protein defect, as well as in phytosterolemia and cholestanolemia (cerebrotendinous xanthomatosis). The Achilles tendons and the extensor tendons of the fingers are most frequently affected.

Plane xanthomas typically develop in skin folds and especially in the palmar creases, where they are diagnostic for dysbetalipoproteinemia. Diffuse plane xanthomas are typically seen as multiple grouped papules and poorly defined yellowish plaques in normolipemic patients, often with paraproteinemia, lymphoma, or leukemia. On the other hand, intertriginous plane xanthomas suggest homozygous familial hypercholesterolemia. The palmar xanthomas associated with cholestasis (primary biliary cirrhosis and biliary atresia) are plaquelike and tend to extend past the creases.

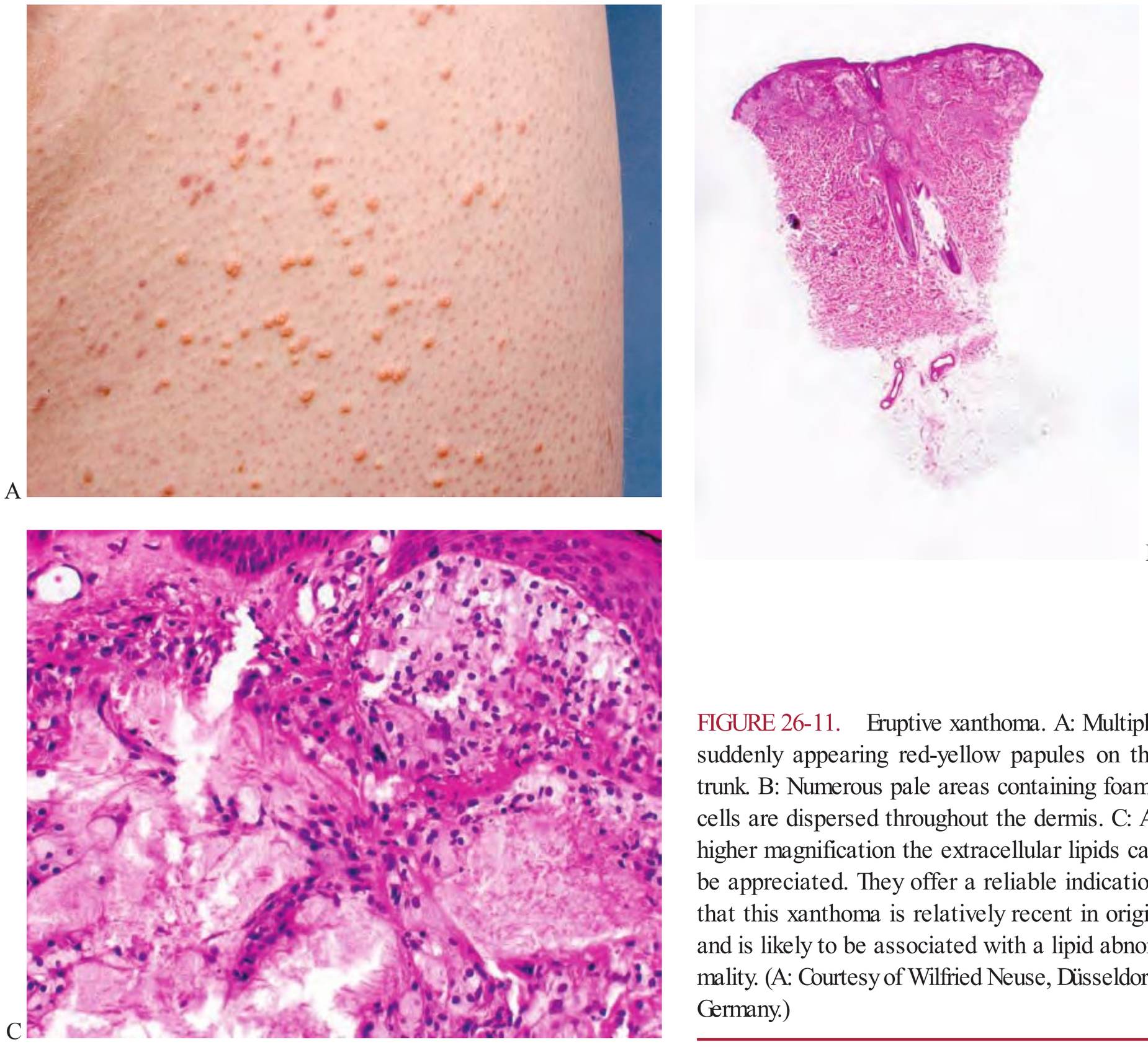


FIGURE 26-11. Eruptive xanthoma. A: Multiple suddenly appearing red-yellow papules on the trunk. B: Numerous pale areas containing foamy cells are dispersed throughout the dermis. C: At higher magnification the extracellular lipids can be appreciated. They offer a reliable indication that this xanthoma is relatively recent in origin and is likely to be associated with a lipid abnormality. (A: Courtesy of Wilfried Neuse, Düsseldorf, Germany.)

Xanthelasmas consist of slightly raised, yellow, soft plaques on the eyelids. Although xanthelasmas are the commonest of the cutaneous xanthomas, they are also the least specific because they most frequently occur in persons with normal lipoprotein levels. We argue that xanthelasmas belong in the family of macrophage disorders because they rarely show extracellular lipids, frequently have giant cells, and do not typically disappear with appropriate lipid-lowering therapy.

Histopathology. The histologic appearance of xanthomas of the skin and the tendons is characterized by foamy cells, macrophages that have engulfed lipid droplets (131). Most of the xanthoma cells are mononuclear, but giant cells, especially of the Touton type with a wreath of nuclei, may be found. The most diagnostic finding suggesting that a xanthomatous lesion reflects an underlying lipid abnormality is the presence of free lipids that have not yet been taken up by macrophages. The lipid droplets can be better seen if frozen or formalin-fixed sections are stained with fat stains such as scarlet red or Sudan red. There may be varying degrees of fibrosis, giant cells, and clefts, depending on the type and site of xanthoma sampled, but most are surprisingly similar. All xanthomas are characterized by a degree of fixation artifact. Formalin fixation and paraffin embedding remove lipids so that only their shadows are left behind. Larger extracellular deposits of cholesterol and other sterols leave behind clefts.

In the past, much emphasis was placed on the refractile nature of xanthomatous deposits. Frozen or formalin-fixed frozen sections can be examined under polarized light. Cholesterol esters are doubly refractile, whereas other lipids are not. Thus tendon and tuberous xanthomas tend to be doubly refractile, whereas other xanthomas are not. Chronic lesions are far more likely to show fibrosis.

Some differences exist in the histologic appearance of the various types of xanthoma. Eruptive xanthomas, when of recent origin, often show a considerable admixture of nonfoamy cells, among them lymphocytes, macrophages, and neutrophils, whereas the number of well-developed foamy cells may still be small (Fig. 26-11B, C) (132). Because the rapid transport of lipid, especially triglycerides, into the tissue overwhelms the

capacity of the macrophages, extracellular lipids are usually found (Fig. 26-10A, B). These pools of lipid surrounded by macrophages mimic granuloma annulare histologically. Fully developed eruptive xanthomas are rich in foamy cells. Some may show urate crystals, causing confusion with gout (133).

Tuberous xanthomas consist of large and small aggregates of foamy cells. In early lesions, there usually is a slight admixture of nonfoamy cells, among them lymphocytes, macrophages, and neutrophils. In well-developed lesions, the infiltrate is composed almost entirely of foamy cells. Ultimately, collagen bundles replace many of these cells. Cholesterol clefts may be found (Fig. 26-12). Tendon xanthomas are identical to tuberous xanthomas in histologic appearance but may be even larger and are often submitted without their overlying skin.

Plane xanthomas should be suspected when the overlying epidermis is thickened with hyperkeratosis and a stratum lucidum, indicating a palmar location (Fig. 26-13A, B). Plane xanthomas from other sites have no unique features.

Xanthelasmas located on the eyelids differ from tuberous xanthomas by the fairly superficial location of the foamy cells and the nearly complete absence of fibrosis. Superficial striated muscles, vellus hairs, small vessels, and a thinned epidermis all suggest location on the eyelid and serve as clues to the histologic diagnosis of xanthelasmas (Fig. 26-14A, B). Metastatic adenocarcinoma to the eyelids, most often of breast origin, and primary adnexal carcinomas (sebaceous and signet ring) can be mistaken for xanthelasmas.

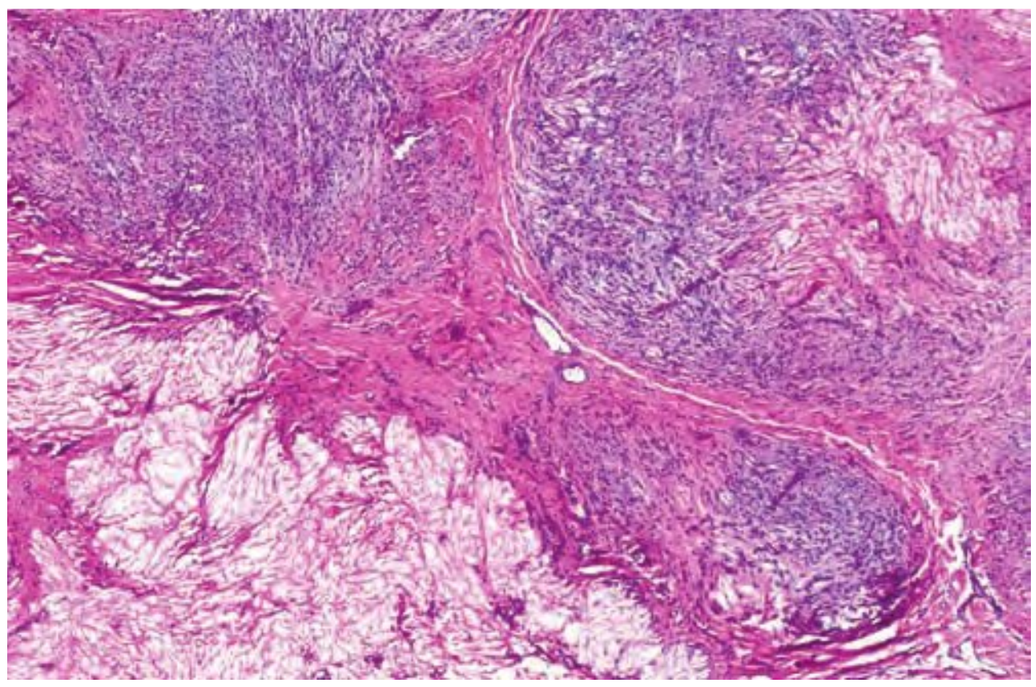
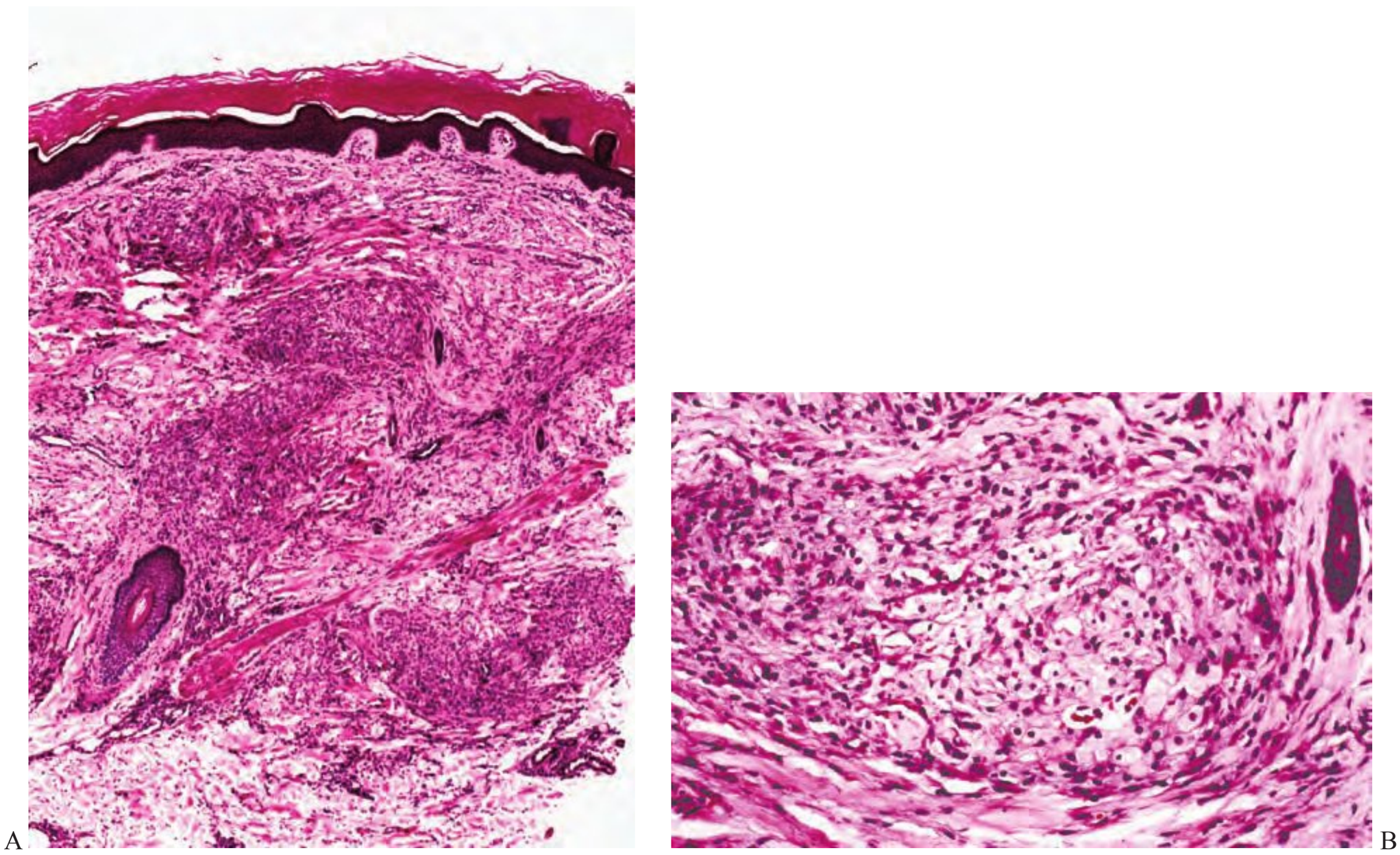


FIGURE 26-12. Tuberous xanthoma. Diffuse deposits of cholesterol probably occupied the pale area at the lower left, whereas clefts are more prominent in the upper right side.

Pathogenesis. Whereas the pathogenesis of many forms of hyperlipidemia is well understood, the formation of xanthomas is a complex process of dysregulation of macrophage sterol flux. Elevated levels of cholesterol-rich LDL and VLDL remnants tend to predispose to xanthomas. Under physiologic conditions, about 80% of LDL-cholesterol is taken up by specific LDL receptor–mediated endocytosis. The remaining LDL is removed from the circulation by the scavenger receptor pathways of



A B

FIGURE 26-13. Plane xanthoma. A: Acral skin with dermis replaced by multiple pale bulbous infiltrates. B: At higher power, numerous foamy macrophages with their nuclei displaced to the cell periphery can be seen.

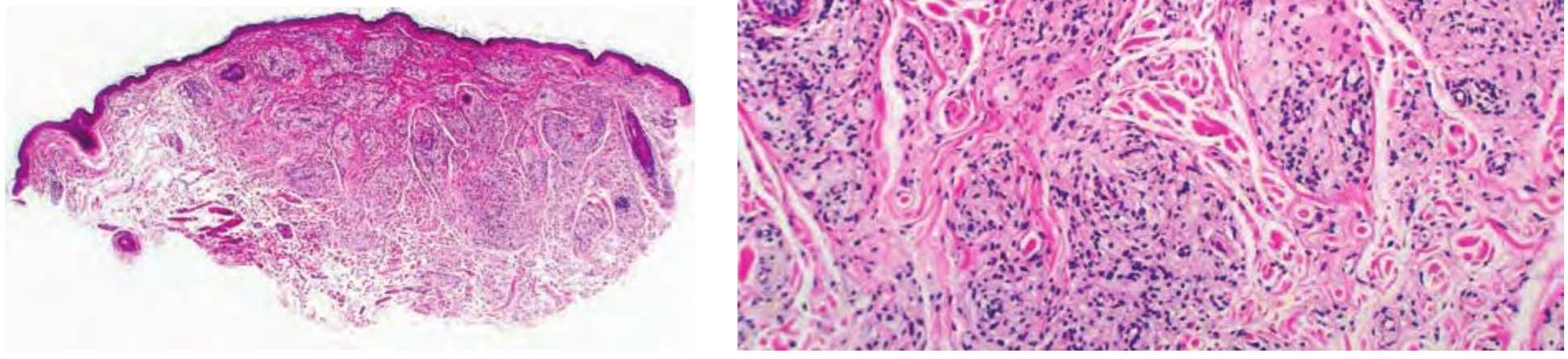


FIGURE 26-14. Xanthelasma. A: The thin epidermis and muscle fibers at the base are a clue to the eyelid location. B: Lobules of foamy cells in this location allow the specific diagnosis of xanthelasmas.

macrophages. In familial hypercholesterolemia and familial dysbetalipoproteinemia, the accumulating LDL and VLDL remnants are predominantly scavenged by macrophages, a pathway without feedback regulation, leading to continuous cellular lipid accumulation and foamy cells. Thus these xanthomas are caused by an increased load of altered sterol-rich lipoproteins.

On the other hand, xanthomas can also be caused by disturbed mechanisms of macrophage cholesterol reflux. Specific ATP-binding cassette (ABC) transporters play the key role in macrophage sterol efflux, regulation of HDL metabolism, and reverse cholesterol transport. Defective ABCA1 transporter has been shown to be the molecular cause of Tangier disease and familial HDL deficiency. Thus both overload of macrophages with altered and aged lipoproteins (increased scavenger pathway) and defective cholesterol efflux from macrophages (abnormal transporters) appear to play a crucial role in xanthoma formation.

NORMOLIPEMIC XANTHOMAS

A wide number of disorders must be considered if xanthomas are identified in a normolipemic patient. They can arise because of the presence of the following:

1. Another source of excess sterol (such as cholestanol in cerebrotendinous xanthomatosis or sitosterol in phytosterolemia). In both cases, tuberous and tendon xanthomas are most common, with marked amounts of extracellular lipids.
2. An abnormal apoprotein, which selectively binds cholesterol or triglyceride that is present nonetheless in normal amounts. These disorders are for convenience grouped with the traditional lipid-related xanthomas.
3. Lymphoproliferative disease (diffuse plane xanthomas and necrobiotic xanthogranuloma).

In some instances there is no lipoprotein abnormality or associated lymphoproliferative disease; many are idiopathic and others posttraumatic. In addition to those xanthomas in the xanthogranuloma family (xanthoma disseminatum and papular xanthoma) and rarely in LCD, one must consider verruciform xanthoma, postinflammatory and posttraumatic xanthomas, and a variety of rare syndromes.

Necrobiotic Xanthogranuloma with Paraproteinemia

Necrobiotic xanthogranuloma with paraproteinemia can usually be recognized clinically and histologically (134–136) but may overlap with diffuse normolipemic plane xanthoma. Large, often yellow, indurated plaques are found with atrophy, telangiectasia, and occasionally also ulceration. The most common location is periorbital; in one review, 21 of 22 patients had skin findings in this area (137). The thorax is also commonly involved. Systemic involvement includes a cardiac myopathy with giant cell infiltrates and hematologic malignancies (138).

Histopathology. Infiltrates containing macrophages, foamy cells, and often also an admixture of other inflammatory cells are present either as focal aggregates or as large, intersecting bands occupying the dermis and subcutaneous tissue (Fig. 26-15A). The intervening tissue shows extensive necrobiosis (degeneration of collagen imparting unique staining characteristics) (Fig. 26-15B). Another characteristic finding is B-cell follicles. A distinctive feature is the presence of numerous large giant cells, both of the Touton type with a peripheral rim of foamy cytoplasm and of the foreign-body type (Fig. 26-15C). Cholesterol clefts are also common. Sometimes all other features are present, but no necrobiosis is found (139).

Pathogenesis. In most patients, serum protein electrophoresis shows an immunoglobulin G monoclonal gammopathy that

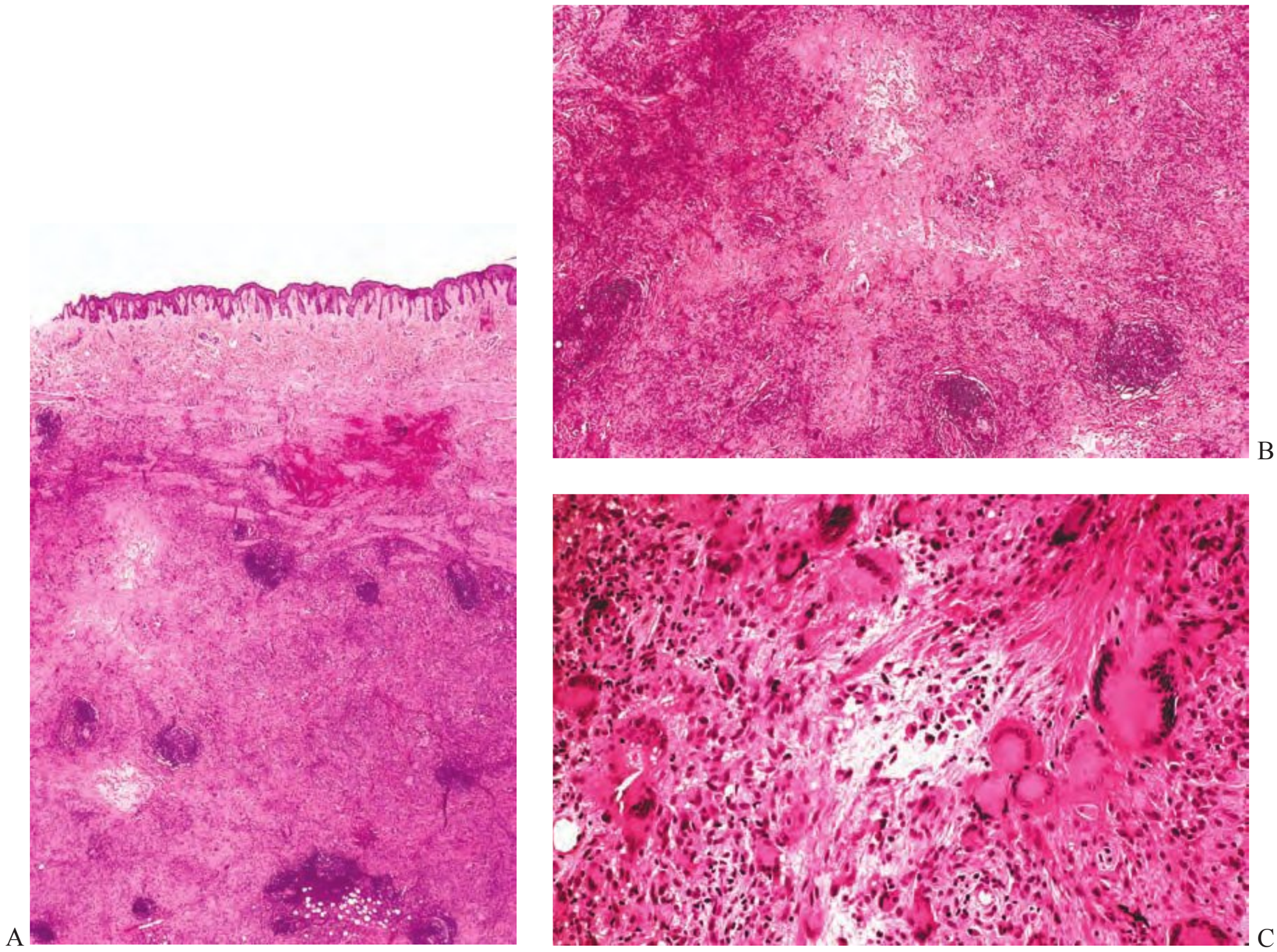


FIGURE 26-15. Necrobiotic xanthogranuloma. A: Low-power view showing a diffuse infiltrate with amorphous necrobiotic areas, cellular regions rich in giant cells, and a nodular lymphocytic infiltrate. B: Higher magnification, showing prominent B-cell follicles and pale necrobiotic regions. C: Another view, showing numerous bizarre foreign-body and Touton giant cells and extensive necrobiosis.

usually consists of κ light chains. Bone marrow examination has revealed multiple myeloma. The xanthomas seen in POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes, which may include xanthomas and angiomas; see Chapter 33) may have a similar etiology.

Differential Diagnosis. Other necrobiotic disorders, especially necrobiosis lipoidica diabeticorum and subcutaneous granuloma annulare or rheumatoid nodule, may be considered. In necrobiotic xanthogranuloma, the necrobiosis is far more extensive and often occurs in broad bands, associated with extensive infiltrates of Touton giant cells, foamy macrophages, and lymphocytes. Vascular involvement is rare, but panniculitis is common. Thus the cellularity and extent of necrobiosis usually serve as reliable clues, as does the usual periorbital location.

Diffuse Normolipemic Plane Xanthoma

In diffuse normolipemic plane xanthoma (DNPX), another rare disorder, one observes papules, patches, or, most commonly, even larger diffuse areas of orange-yellow discoloration of the skin (140–142). Whereas the smaller lesions are distinct, the diffuse areas have a poorly defined border. The face, particularly the periorbital areas, and the upper trunk are sites of predilection. The disorder may mimic xanthelasmas initially but progresses to involve wide areas of skin. The lesions usually persist indefinitely. By definition, the patient has no lipid abnormalities. Many but not all cases of diffuse normolipemic plane xanthoma are associated with hematologic disorders, most commonly paraproteinemias, including multiple myeloma, benign monoclonal gammopathy (often immunoglobulin A), Castleman's disease, and cryoglobulinemia (143). The skin disorder may precede the hematologic problem by many years (144,145).

Generalized papular xanthomas and eruptive normolipemic xanthomas are probably variations on the same theme; both have been reported in association with many of the conditions associated with diffuse normolipemic plane xanthomas. In addition, DNPX has many features in common with necrobiotic xanthogranuloma, including the presence of large patches and plaques, periorbital involvement, and association with paraproteinemias.

Histopathology. Histologic examination reveals large sheets and clusters of foamy cells, diffusely scattered throughout the dermis, as well as singly and in small groups, (Fig. 26-16). In some areas, the foamy cells lie in thin streaks between collagen bundles,

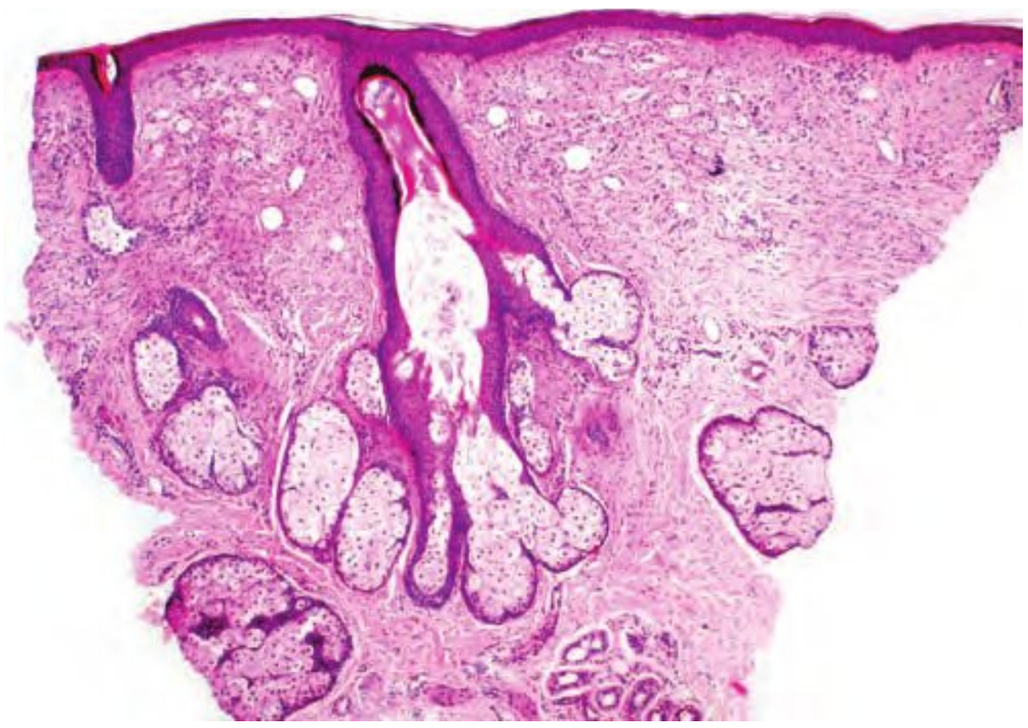


FIGURE 26-16. Diffuse normolipemic plane xanthoma. Accumulations of foamy cells in the superficial dermis.

and occasionally a perivascular arrangement is noted. There may be an admixture of macrophages and lymphocytes; rarely, Touton giant cells are seen. Scattered foamy cells have been observed even in clinically normal skin.

Pathogenesis. The mechanism of xanthoma formation is unclear. Possible explanations include the secretion of cytokines or immunoglobulins by the underlying lymphocytic proliferation, which in turn could stimulate macrophages or alter lipoprotein activity. This theory fails to explain why the skin involvement so often occurs first. The immunohistochemical phenotyping of the macrophages has yielded variable results.

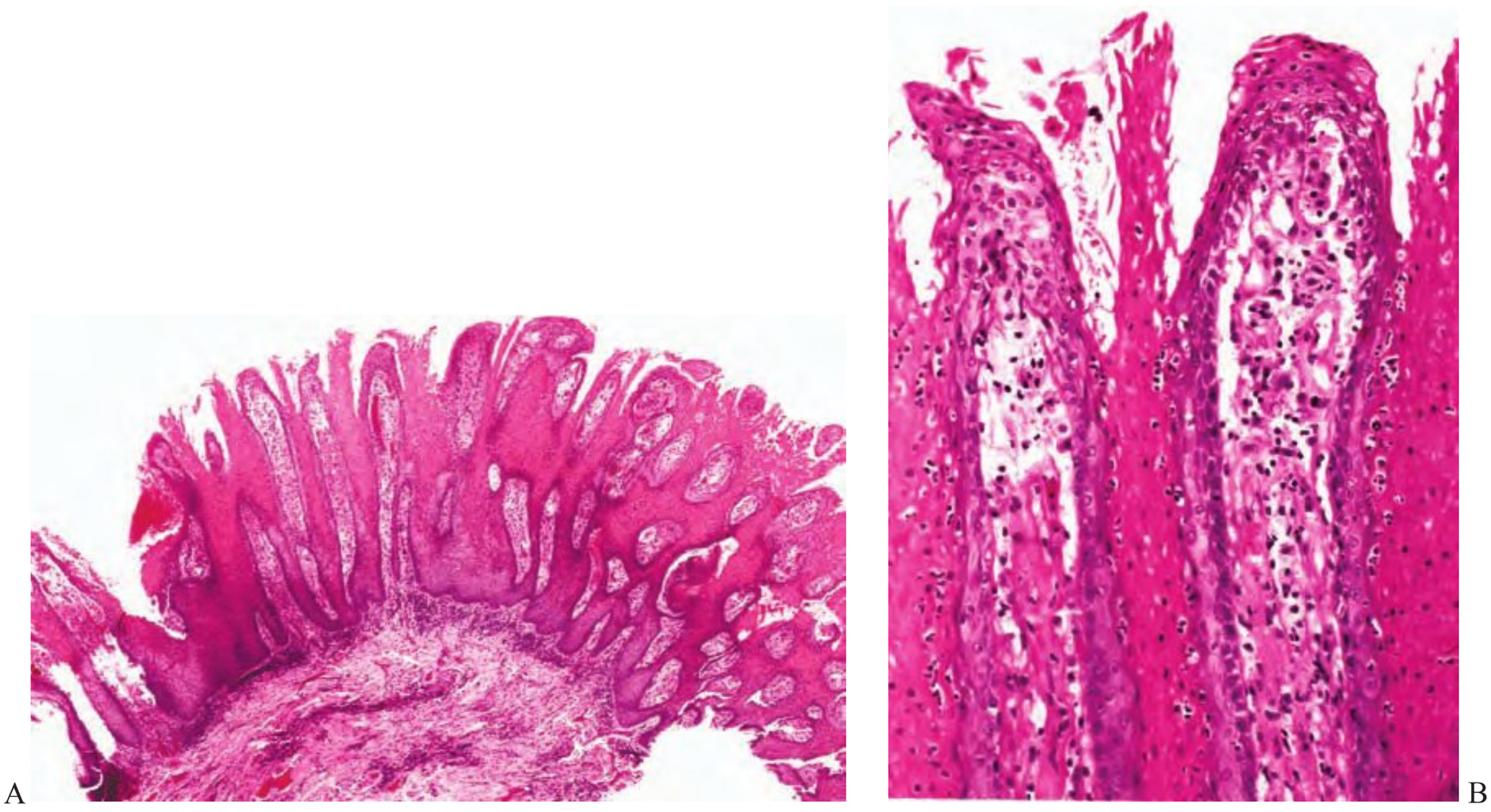
Differential Diagnosis. A single lesion cannot be distinguished from other small xanthomas. If marked necrobiosis or giant cell formation is present, necrobiotic xanthogranuloma should be considered.

Verruciform Xanthomas

Verruciform xanthoma (VX) occurs most commonly in the oral cavity, where it was first described by Shafer (146). Lesions are typically solitary, asymptomatic hyperkeratotic papillomatous nodules. Most cases involve the gingival or alveolar mucosa, although other oral sites may be affected (147). Although the process is usually benign, it has been associated with carcinoma *in situ* (148).

In addition, VX may occur in the skin in several settings (149). The most predictable situation is as part of a CHILD nevus, one type of epidermal nevus (congenital hemidysplasia with ichthyosiform erythroderma and limb defects; see Chapter 6) (150). Idiopathic cutaneous VX is usually anogenital or perioral; trauma is probably the triggering agent. Similar changes have been seen in sun-damaged skin, again associated with carcinoma *in situ* (151). VX has been reported secondary to a variety of inflammatory lesions, including discoid lupus erythematosus (152), lichen planus, and bullous diseases, and following psoriasiform inflammation in AIDS (153).

Histopathology. The low-power picture is that of a verruca, often leading to a mistaken diagnosis. There is marked elongation of the rete ridges extending to a uniform level in the dermis (Fig. 26-17A). An infiltrate of foamy cells is confined to the elongated dermal papillae located between the rete ridges



A B

FIGURE 26-17. Verruciform xanthoma. A: Papilloma with marked elongation and thinning of the dermal papillae. There is prominent hyperkeratosis, with a modest lymphocytic infiltrate at base. B: Higher magnification showing foamy cells in the papillae with polymorphonuclear leukocytes in the adjacent crust.

(Fig. 26-17B). Sometimes the xanthomatous cells may appear granular. The vessels in the papillae are also more prominent. The overlying epithelium is parakeratotic, and candidal hyphae or bacteria may be found.

Pathogenesis. Degenerating keratinocytes or perhaps even melanocytes are believed to be the source of the lipid material (154). Although human papilloma virus has been searched for, it has not been unequivocally identified in more than a few scattered cases. Trauma and inflammation are the two best-established triggers. The foamy cells are positive for macrophage markers and express scavenger receptors similar to those found in xanthomas associated with hyperlipidemia (155).

Miscellaneous Xanthomas

It is difficult to make rhyme or reason of the many other causes of normolipemic xanthomas. One recurrent theme is trauma, as in VX. Xanthoma have developed in areas of chronic inflammation, such as atopic dermatitis (156), persistent light eruption, mycosis fungoides (157), or even contact dermatitis (158), although the illustrations in many of these reports fail to convincingly demonstrate a nodule made up of foamy cells.

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CHAPTER 27

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Pigmentary Disorders of the Skin

CONGENITAL DIFFUSE MELANOSIS

Congenital diffuse melanosis, also termed *melanosis diffusa congenita* (1) or *generalized cutaneous melanosis* (2,3), is thought to be recessively inherited, appears at or shortly after birth, and demonstrates progressive diffuse hyperpigmentation. The pigmentation is most intense on the abdomen and back and may be reticulate in the axillae and groin. Thin nails (3) and yellow-white hair (1) have been noted.

Histopathology. Increased melanization is seen in both the basalar and midepidermal keratinocytes, along with melanophages in the superficial dermis.

Histogenesis. On electron microscopic examination, Braun-Falco and colleagues (1) noted increased numbers of single melanosomes in the keratinocytes, and Klint and associates (3) described dispersion of melanosomes throughout the keratinocyte cytoplasm.

RETICULATE PIGMENTARY ANOMALIES

Numerous cutaneous disorders have been documented that are characterized by hyperpigmentation that is clinically seen in a reticulate, retiform, or fishnet-like pattern. These disorders are unified by the presence of increased melanin within the epidermis and exclude postinflammatory pigmentary alterations and conditions displaying reticulation secondary to vascular phenomena, such as livedo reticularis.

Dyskeratosis congenita is characterized by an acquired reticulated brown hyperpigmentation, beginning in the first decade of life, which spreads across the neck, upper chest, and arms. This syndrome demonstrates genetic and clinical heterogeneity but is most commonly associated with nail dystrophy, leukoplakia, bone marrow failure, and a predisposition to malignancy (4).

Progressive cribriform and zosteriform hyperpigmentation begins in the second decade of life with tan cribriform macular hyperpigmentation of the lower half of the trunk or thighs in a dermatomal distribution (5,6). Linear and whorled nevoid hypermelanosis has a similar clinical appearance, except the pigmentation appears within the first year of life and is present along the lines of Blaschko.

Several entities are characterized by the presence of acral hyperpigmentation. *Acropigmentation symmetrica of Dohi* (dyschromatosis symmetrica hereditaria) is a progressive autosomal dominant disorder that appears as reticulate hyperpigmented and hypopigmented macules on the face and dorsa of the hands and feet, progressing to cover acral areas (7,8). *Reticulate acropigmentation of Kitamura* is an autosomal dominant disorder that presents as slightly depressed hyperpigmented macules on the dorsal hands and feet that evolve to a reticulate pattern as the individual ages. There is progression to involve the extremities, lateral neck, and occasionally the trunk and face. There has been an association with palmar and plantar pits (9).

Reticulate acropigmentation of Kitamura and *Dowling-Degos disease* (reticulate pigmented anomaly of the flexures) may appear together (10), supporting the concept that they are different expressions of one disorder. In Dowling-Degos disease, a dominantly inherited dermatosis, heavily pigmented macules are arranged in a reticulate pattern with a tendency to coalesce on flexural skin, including the axillae, lateral neck, inframammary and inguinal folds, antecubital and popliteal fossae, and intergluteal clefts. Other sites that may be involved include the genitalia, inner thighs, chest, face, and abdomen. Extensive areas of the skin may be affected. Pitted perioral scars, hyperpigmented comedones, hidradenitis suppurativa, multiple cysts and abscesses, and keratoacanthomas have been associated (11). *Galli-Galli disease* is considered an acantholytic variant of Dowling-Degos disease, but they are clinically indistinguishable (12).

The *Naegeli-Franceschetti-Jadassohn syndrome* (Naegeli's reticular pigmented dermatosis) and *dermatopathia pigmentosa reticularis* are autosomal-dominant inherited disorders that share key clinical features, such as reticulate pigmentation of the skin, absence of dermatoglyphics, palmoplantar keratoderma, hypohidrosis, and other hair and nail abnormalities. Dermatopathia pigmentosa reticularis is distinguished from Naegeli-Franceschetti-Jadassohn syndrome by lifelong persistence of skin hyperpigmentation, partial alopecia, and absence of dental anomalies (13).

Histopathology. Most of these conditions demonstrate hyperpigmentation of the basalar keratinocytes with either a normal or slightly increased number of melanocytes. Dyskeratosis

congenita is characterized by occasional atrophy of the epidermis, mild interface vacuolization with melanophages in the upper dermis, and telangiectasias of superficial vessels (14). Reticulate acropigmentation of Kitamura and, to a greater degree, Dowling-Degos disease demonstrate digitated elongations of the hyperpigmented rete ridges with a tendency to spare the suprapapillary epithelium. In Dowling-Degos disease, these thin, branching, heavily pigmented downward proliferations also involve the infundibula of follicles, and in some instances, horn cysts may be seen (11). Galli-Galli disease demonstrates similar thin, branching hyperpigmented rete ridges with foci of acantholysis (12). Although there is no preceding inflammatory dermatosis in dermatopathia pigmentosa reticularis, clumps of melanin-laden melanophages are seen in the papillary dermis in a patchy distribution without overlying epidermal hyperpigmentation (15).

Histogenesis. These conditions are thought to be inherited, although all of the genes responsible for their expression have not been definitively identified. Dyskeratosis congenita is a genetically heterogeneous disease of defective telomere maintenance that may demonstrate X-linked, autosomal recessive, or autosomal dominant patterns of inheritance (16). Dowling-Degos disease has been linked to mutations of the keratin 5 gene (17,18).

LINEAR AND WHORLED NEVOID HYPERMELANOSIS

Linear and whorled nevoid hypermelanosis is an occasionally familial disorder that appears within the first few weeks of life and progresses over 1 to 2 years before stabilization (19). This process presents with multiple hyperpigmented linear streaks and whorls composed of small homogeneous tan to brown macules that follow the lines of Blaschko (20,21). The pattern is the inverse of that found in hypomelanosis of Ito (21) and must be differentiated from resembling conditions including incontinentia pigmenti, epidermal nevus, and zebra-like hyperpigmentation (21,22).

Histopathology. There is hyperpigmentation of the basalar keratinocytes with prominent melanocytes and mild elongation of the rete ridges (19,21,22). Pigmentary incontinence with melanophages in the papillary dermis is variably present (22,23).

Histogenesis. The genetic abnormality has not been defined, but developmental somatic mosaicism has been proposed as an explanation for this patterned hypermelanosis (21,22).

MELASMA

Melasma is an acquired, localized, usually symmetrical hyperpigmentation of the face occurring in women. The forehead, cheeks, upper lip, and chin are affected. It often is associated with pregnancy or the ingestion of oral contraceptives and aggravated by sunlight.

Histopathology. An epidermal and a dermal type can be recognized, although frequently there is a combination of the two types. Melanin is significantly increased in all epidermal layers, and melanosomes are increased in number and more widely distributed among keratinocytes in lesional skin. Melasma skin often has more free melanin and melanophages in the dermis (24,25).

ADDISON'S DISEASE

Addison's disease represents a hypofunction of the adrenal cortex and is characterized by progressive weakness, malaise, weight loss, hypotension, joint and back pain, and darkening of the skin and mucous membranes (26). In some cases, hyperpigmentation is the initial clinical manifestation (27). The hyperpigmentation is generalized but most pronounced on sun-exposed skin, sites of friction, palmar creases, recent scars, and genital skin (26). Patchy oral mucosal pigmentation is often present.

Histopathology. The histologic findings simulate the normal findings in patients with naturally dark skin and are therefore not diagnostic. Increased amounts of melanin are seen in the basalar keratinocytes and often in the keratinocytes in the upper spinous layer. The number of melanocytes is not increased. Variable numbers of melanophages may be seen in the papillary dermis (28).

Histogenesis. Most commonly, Addison's disease is the result of an autoimmune destruction of the adrenal glands, with subsequent inadequate production of cortisol and aldosterone. Addison's disease is often associated with other autoimmune diseases, such as autoimmune glandular syndromes, insulin-dependent diabetes, vitiligo, and thyroid disease (26). Other causes of adrenal hypofunction include damage of adrenal glands by tuberculosis, metastatic carcinoma, and deep fungal infections.

The hyperpigmentation in Addison's disease is caused by an increased release of melanocyte-stimulating hormone (MSH) from the pituitary gland. Adrenocorticotropic hormone (ACTH) and MSH synthesis and secretion in the pituitary gland are linked. The increased production of ACTH and MSH in Addison's disease is a compensatory, feedback-controlled response to low adrenal gland activity.

POSTINFLAMMATORY PIGMENTARY ALTERATION

Pigment alteration in the skin from a preceding inflammatory disorder can produce clinical hypopigmentation, hyperpigmentation, or both. It occurs commonly in processes that affect the dermal–epidermal interface such as fixed drug eruptions, lichen planus, benign lichenoid keratosis, and erythema multiforme. In some individuals, the alteration can be

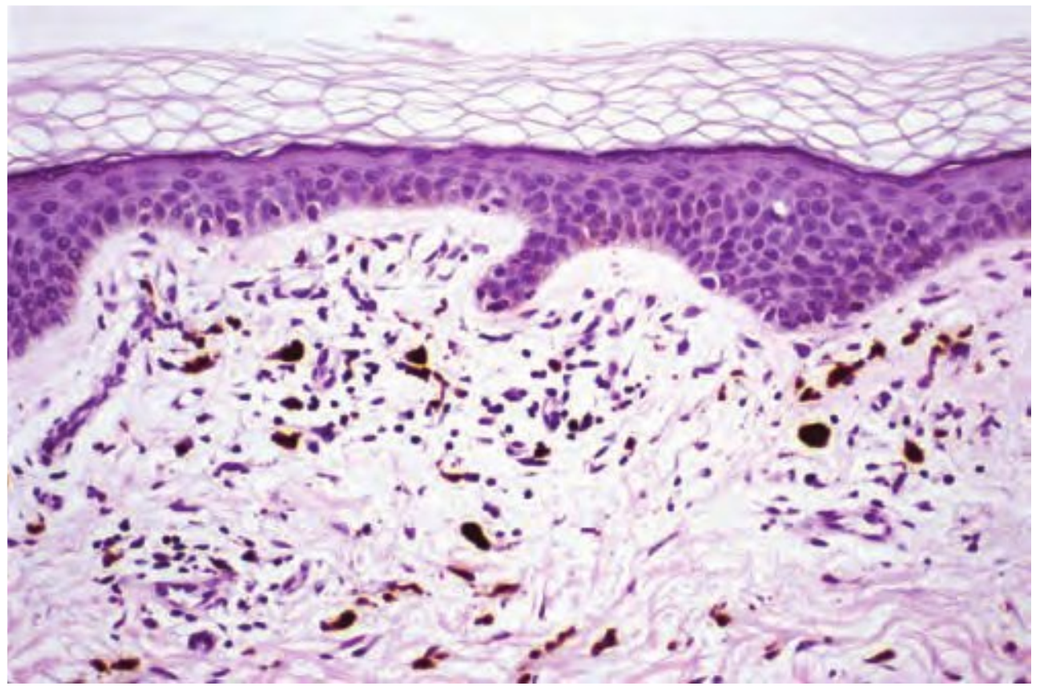


FIGURE 27-1. Postinflammatory hyperpigmentation. There are numerous melanophages in the papillary dermis along with a mild perivascular lymphocytic infiltrate. The epidermis is normal.

dramatic, producing dark pigmentation resembling primary melanocytic lesions or marked hypopigmentation resembling vitiligo. Wood's light examination accentuates epidermal melanin and is useful as a clinical tool in defining the nature and extent of pigmentary alteration.

Histopathology. Epidermal melanin is increased in clinical hyperpigmentation and decreased in clinical hypopigmentation. In both clinical forms of pigmentary alteration, melanophages are present in the superficial dermis, along with a variably dense infiltrate of lymphohistiocytes around superficial blood vessels and in dermal papillae (29) (Fig. 27-1). Necrotic keratinocytes and coarse collagen bundles in the papillary dermis are occasionally seen (29,30).

BERLOQUE DERMATITIS AND PHYTOPHOTODERMATITIS

Localized hyperpigmented patches produced by furocoumarin-containing oil of bergamot found in perfumes have a distinctive clinical presentation. The patches assume droplike shapes resembling pendants (French: *berloque*) and are usually located on the sides of the neck or retroauricular areas. Contact with plants containing furocoumarins may also produce hyperpigmented patches and include lime, wild and cow parsnip, wild carrot, bergamot orange, and fig (31).

Histopathology. Features identical to postinflammatory hyperpigmentation are found, including increased epidermal melanin and melanophages in the superficial dermis. Variable chronic inflammation is present.

CHEMICAL DEPIGMENTATION

Chemicals are capable of producing depigmentation resembling vitiligo. Hydroquinones and phenols are the most common causes and are found in bleaching agents, adhesives, cosmetics, photographic processing materials, and antioxidants used in the manufacture of rubber (32,33). Depigmentation may also occur in body sites remote from chemical contact, presumably from systemic absorption or inhalation.

Histopathology. Features indistinguishable from vitiligo are found (32). Decreased or absent melanocytes are present with a variable superficial perivascular lymphocytic infiltrate.

IDIOPATHIC GUTTATE HYPOMELANOSIS

Idiopathic guttate hypomelanosis is a commonly acquired disorder of unknown cause that produces few to numerous sharply circumscribed, 2- to 6-mm white macules. These lesions occur predominantly on the legs and forearms of persons over 30 years of age (34).

Histopathology. In sections stained with Fontana-Masson, the melanin content in lesional skin is markedly reduced. The lesional borders are sharply demarcated. Within the hypomelanotic epidermis, the melanin granules are irregularly distributed, and there is a significant reduction in the number of melanocytes (35,36).

Histogenesis. On electron microscopic examination, the scattered residual melanocytes in lesional skin are round and less dendritic with fewer melanosomes that are incompletely melanized (37).

PROGRESSIVE MACULAR HYPOPIGMENTATION

Progressive macular hypopigmentation is a disorder of unclear etiology that is characterized by hypopigmented macules on the central trunk, predominantly in young adults. These lesions are asymptomatic and occur without previous inflammation or skin disease. The lesions may be discrete or eventually become confluent (38).

Histopathology. Histologic features of lesional and nonlesional skin may be indistinguishable. A subtle decrease in melanin content may be present in lesional skin, and staining with Fontana Masson may demonstrate reduction in melanin within the basal cell layer (38,39).

Histogenesis. *Propionibacterium acnes* has been cultured and identified histologically in follicles of lesional skin but not follicles or interfollicular areas of healthy appearing adjacent skin. It has been proposed that the bacteria may interfere with melanogenesis in these skin lesions (39).

PSORALEN AND ULTRAVIOLET A–INDUCED PIGMENT ALTERATIONS

Psoralen and ultraviolet A (PUVA) therapy consists of the oral ingestion or topical application of a furocoumarin-containing psoralen compound followed by patient exposure to high-intensity

UVA radiation in a controlled-light-box setting. It is widely used for treating psoriasis and cutaneous T-cell lymphoma and less commonly used for a variety of other dermatoses including repigmentation therapy of vitiligo.

A spectrum of clinical and histologic changes is seen during and after PUVA therapy. Acutely, the phototoxic erythema peaks at 48 to 72 hours. Hyperpigmentation (tanning) is delayed for several days and more pronounced and longer lasting than that induced by ultraviolet B (UVB) exposure (40). Prolonged therapy leads to photoaging with cutaneous atrophy, fine wrinkling, mottled hyperpigmentation and hypopigmentation, telangiectasias, and loss of elasticity (41). Stellate lentigines or PUVA freckles often develop after prolonged therapy (42). There is also a dose-dependent increase in the risk of squamous cell carcinoma (43), especially in the genital areas (44).

Histopathology. The histologic changes of PUVA-induced acute phototoxicity are similar to a sunburn, with numerous pink apoptotic cells ("sunburn cells") scattered throughout the epidermis. Early in the therapeutic course, the melanocytes in the basalar epidermis and keratinocytes in the mid spinous layer are heavily melanized. Prolonged therapy leads to gradual flattening of the rete ridges, telangiectasias, increased papillary dermal acid mucopolysaccharide deposition, thinning and basophilic degeneration of elastic fibers, and hyperplasia and fragmentation of elastic fibers (45). Hyperpigmented skin without other clinical changes frequently demonstrates small foci of keratinocytic nuclear atypia and loss of the normal maturation pattern (46). Actinic keratoses, Bowen's disease, and squamous cell carcinomas may develop. PUVA freckles or lentigines show increased numbers of melanocytes and elongation of the rete ridges with focal atypical melanocytes (47).

Histogenesis. On electron microscopy, melanosomes are diffusely distributed throughout the epidermis (48). There is basement membrane thickening with focal dissolution. Elastic fibers in the dermis appear homogenized and fragmented (49). In the deep dermis, there is reduplication of the basal layer of capillaries and increased pinocytosis of endothelial cells (50).

DRUG-INDUCED PIGMENTARY ALTERATIONS

Drug-induced pigmentary alterations are quite common. Implicated agents include nonsteroidal anti-inflammatory drugs, antimalarials, tetracyclines, psychotropics including phenothiazines, antineoplastic agents including cytotoxics, heavy metals including gold, amiodarone, amitriptyline, and clofazimine (51,52). A variety of pathogenic mechanisms are seen, including increased production of melanin leading to hyperpigmentation of basalar keratinocytes, vacuolar change at the dermal–epidermal junction with pigmentary incontinence and dermal melanophages, binding of the drug to melanin and deposition of stable complexes, and deposition of the drug itself as granules in the dermal extracellular matrix or in macrophages. In addition, drugs may induce the synthesis of special pigments, such as lipofuscin, or damage blood vessels leading to red blood cell extravasation and hemosiderophages (51,52). Clinical features vary from generalized hyperpigmentation to specific patterns attributed to individual drugs such as the flagellated streaks attributed to bleomycin (53).

Histopathology. Minocycline may cause generalized bluish-brown pigmentation in a photodistribution due to increased basalar keratinocytic melanin, blue-black pigmentation of acne and other scars due to hemosiderin deposition in dermal macrophages, or gray-blue pigmentation of the anterior legs and arms due to deposition of drug complexes and protein extracellularly in the dermis and deposition on elastic fibers.

Antimalarial agents deposit pigment granules in dermal macrophages and extracellularly (51). Phenothiazines commonly deposit electron-dense granules in dermal macrophages. The granules are composed of a drug metabolite and melanin leading to progressive blue pigmentation on sun-exposed skin (54). Amiodarone may provoke a photoallergic reaction with blue-gray pigmentation due to the deposition of lipofuscin granules in macrophages around superficial dermal blood vessels. These are accentuated by periodic acid-Schiff (PAS) staining. Lipofuscinosis may also be caused by antibiotics (51).

Chemotherapy agents commonly produce both generalized and localized hyperpigmentation of the basalar keratinocytes. Bleomycin, busulfan, doxorubicin, daunorubicin, fluorouracil, cyclophosphamide, and carmustine additionally may demonstrate melanophages in the superficial dermis (53). Globules of mercury have been found in dermal and subcutaneous abscesses after oral ingestion (55).

PIGMENTARY PRESENTATIONS OF CUTANEOUS AND SYSTEMIC DISEASES

Mycosis fungoides may present with hypopigmented (56,57) or hyperpigmented (58) lesions. The former occurs in children and young adults, is slowly progressive, and often is present for many years before diagnosed. Sarcoidosis (59) may display hypopigmented skin lesions but usually demonstrates some degree of clinical induration. Darier's (60) disease may also present with hypopigmentation. Although pigmented variants of basal cell carcinoma are not uncommon, pigmented Bowen's disease (61), pigmented Paget's disease (62), and depigmented extramammary Paget's disease (63) can be difficult to recognize clinically. Skin metastases from breast carcinoma may be pigmented and can even simulate malignant melanoma (64). As well, generalized hyperpigmentation may be the presenting sign of metastatic malignant melanoma and primary pituitary tumors.

Histopathology. The histologic changes are those of the primary dermatosis. In hypopigmented mycosis fungoides, variable melanin pigmentary incontinence occurs (57), whereas hyperpigmented mycosis fungoides shows striking melanin pigment in the basal layer and giant melanin pigment granules throughout the spinous layer (58). No alteration of melanocytes is

present in hypopigmented sarcoidosis, and no appreciable change in melanin pigment is noted (59). Decreased melanin pigment is seen in the basal layer of hypopigmented Darier's disease (60). Pigmented Bowen's disease shows abundant melanin pigment in basal keratinocytes, highly dendritic melanocytes, and numerous melanophages (61). Pigmented Paget's disease and pigmented epidermotropic metastatic breast carcinoma demonstrate dendritic melanocytes at the dermal–epidermal junction with variable melanin pigment in the cytoplasm of tumor cells (62). Normal numbers of melanocytes are present in depigmented extramammary Paget's disease, but epidermal melanization is markedly reduced (63). In generalized hyperpigmentation from metastatic melanoma or endocrinopathy, variable epidermal pigment and melanophages are present.

Histogenesis. Electron microscopy of hypopigmented mycosis fungoides shows degenerative changes in melanocytes. The melanocytes demonstrate dilatation of rough endoplasmic reticulum, mitochondrial swelling, incompletely melanized melanosomes, and vacuolization and disintegration of the cytoplasm (65). Giant melanosomes are seen in keratinocytes of hyperpigmented mycosis fungoides, and melanin granules are also present in the cytoplasm of tumoral and Langerhans cells (58). Fewer melanosomes are present within keratinocytes in hypopigmented sarcoidosis, and melanocytes feature variable degenerative changes (59).

ALBINISM

Albinism is a heritable disorder causing a generalized lack of pigmentation of the skin, hair, and eyes. Involvement of only the eyes is known as *ocular albinism* and is X-linked recessive. Oculocutaneous albinism (OCA) affects both the eyes and skin and is autosomal recessive.

There are at least 10 types of OCA based on the degree of tyrosinase activity, hair color, and associated systemic disorders. Tyrosinase is a copper-containing enzyme responsible for the biosynthesis of melanin. Mutations in the tyrosinase gene result in inactivity of the enzyme (tyrosinase-negative OCA) and cause the most severe subtype (66,67). In tyrosinase-positive OCA, synthesis of melanin pigment is reduced, and patients acquire some melanin pigment in the hair, skin, and eyes beginning in childhood. Hair color varies from yellow (yellow-mutant OCA) to red (rufous OCA) to platinum (pt OCA) to brown (brown OCA) to black (blacklocks-albinism-deafness syndrome [BADS]). Associated systemic disorders include platelet defect and ceroid storage (Hermansky-Pudlak syndrome), defects in immunity (Chédiak-Higashi and Griscelli syndromes), and microphthalmia and mental retardation (Cross syndrome). Cutaneous malignancies, particularly squamous cell carcinoma, are frequent in all forms of albinism.

Prenatal diagnosis of OCA can be made by analysis of fetal skin biopsy for the tyrosinase gene in fetal cells obtained by amniocentesis (68).

Histopathology. Histologic examination of skin from patients with OCA shows the presence of basal melanocytes in the epidermis and hair bulb; however, Fontana-Masson stain fails to show any melanin. In patients with the tyrosinase-positive type of albinism, the epidermal melanocytes form pigment if sections of skin are incubated with dopa.

Hermansky-Pudlak syndrome is a disorder in melanosome formation that histologically demonstrates giant melanosomes in the epidermis along with melanophages in the dermis (69,70).

Histogenesis. OCA is a disorder of melanin synthesis within the melanosome. Electron microscopic examination in OCA shows normally structured melanocytes in the epidermis; however, there is a reduction in the melanization of melanosomes (71). For example, in tyrosinase-positive albinism, there are fewer melanized stage III and IV melanosomes, whereas in tyrosinase-negative albinism, the melanosomes contain no melanin and represent stage I and II melanosomes. Melanosome transfer to keratinocytes is not altered.

The tyrosinase gene has been localized in the long arm of chromosome 11 (72). Mutations in the protein-coding region of the gene are responsible for the tyrosinase-negative OCA. In contrast, tyrosinase-positive OCA has been mapped to the P gene on chromosome 15, and mutations of this gene are associated with a wide range of clinical manifestations (73).

PIEBALDISM (PATTERNED LEUKODERMA)

Piebaldism is an autosomally dominant disorder characterized by irregularly shaped depigmented patches that are present from birth and are associated in about 85% of the cases with a white forelock arising from a depigmented area in the center of the forehead. Depigmentation has a predilection for the ventral skin, that is, the center of the face, the ventral chest, and the abdomen. Small islands of hyperpigmentation, 1 to 5 cm in diameter, are usually present within the depigmented areas. The condition used to be called *partial albinism*, but this term is no longer used because of the difference in pathogenesis between OCA and piebaldism.

Waardenburg syndrome, also dominantly inherited, is a variant of piebaldism that is characterized by lateral displacement of the inner canthi of the eyes, heterochromia of the irides, and congenital deafness. About half of the patients have a white forelock, and approximately 12% have patches of depigmentation from birth.

Histopathology. The depigmented skin and hair usually have significantly reduced to no melanocytes (74,75). Melanocytes are normal in number in associated hyperpigmented areas (75). In some cases, white forelock epidermis may show a few melanocytes that are dopa positive (76).

Histogenesis. Electron microscopic examination of the depigmented skin usually reveals a complete absence of melanocytes (76). In some instances, an occasional melanocyte is seen with unmelanized ellipsoidal or spherical melanosomes. Electron microscopy of plucked forelock hair reveals absence of melanin

in the cortex, cuticle, and inner root sheath (76). The small hyperpigmented islands show many abnormal spherical, granular melanosomes.

A mutation of the *KIT gene* that encodes melanocytic migration into the hair follicle and epidermis during embryonic development has been implicated in piebaldism (72). In the Waardenburg syndrome, four types have been described involving three transcription factors, MITF, SOX-10 and PAX-3, all of which affect expression of the KIT gene (77).

VITILIGO

Vitiligo is an acquired, disfiguring, patchy, total loss of skin pigment. Stable patches often have an irregular border but are sharply demarcated from the surrounding skin. There may be surrounding hyperpigmented skin. In expanding lesions, there may rarely be a slight rim of erythema at the border and a thin zone of transitory partial depigmentation. Hairs in patches of vitiligo are often white. The scalp and eyelashes are rarely affected. In generalized vitiligo, the face, upper trunk, dorsal hands, periorificial areas, and genitals are most commonly affected in a symmetrical fashion. Localized disease can occur as a linear, dermatomal patch (segmental vitiligo). Induction with trauma (Koebner phenomenon) and association with halo nevi occurs with generalized but not segmental vitiligo.

In *Vogt-Koyanagi-Harada syndrome*, an aseptic meningitis is often the initial symptom, followed by uveitis and dysacousia. Patches of vitiligo involving the skin, and frequently the eyelashes and scalp, develop. There is often an association with alopecia areata.

Histopathology. The most prominent feature in vitiligo is the alteration of melanocytes at the dermal–epidermal junction. With silver stains or the dopa reaction, well-established lesions of vitiligo are totally devoid of melanocytes. The periphery of expanding lesions, which are hypopigmented rather than completely depigmented, still show a few dopa-positive melanocytes and some melanin granules in the basal layer (78). In the outer border of patches of vitiligo, melanocytes are often prominent and demonstrate long dendritic processes filled with melanin granules. Early lesions show a superficial perivascular and occasionally lichenoid mononuclear cell infiltrate at the border. Focal areas of vacuolar change at the dermal–epidermal junction in association with a mild mononuclear cell infiltrate have been seen in the normal-appearing skin adjacent to vitiliginous areas (79,80). In long-standing lesions, degenerative changes in cutaneous nerves and adnexal structures have been reported (81).

Histogenesis. Electron microscopic studies (80,82) and immunohistochemistry studies using a panel of 17 monoclonal antibodies directed against melanocytes (83) confirm the complete absence of melanocytes in areas of long-standing vitiligo (Fig. 27-2). In the hypopigmented zone of expanding lesions, most melanocytes show signs of degeneration. Some studies have demonstrated peripheral damage to keratinocytes and melanocytes (84). A combination of hair follicle split-dopa stains and hair follicle split-scanning electron microscopy showed inactive, dopa-negative melanocytes in the outer root sheaths of normal hair follicles. These inactive melanocytes are also present in the outer root sheaths of hair follicles from vitiliginous patches. Treatment of vitiligo stimulates these inactive melanocytes in the middle and lower parts of the outer root sheaths to divide, proliferate, and migrate upward to the dermal–epidermal junction of overlying skin. Melanocytes then radiate to form the pigmented islands clinically visible in repigmented lesions (85,86).

Autoimmune mechanisms with an underlying genetic predisposition are the most likely cause of vitiligo, although neurohumoral and autocytotoxic hypotheses are alternative theories or contributing mechanisms. Antibodies to melanocytes have been found by immunoprecipitation in the sera of patients with vitiligo but not in normal sera (87). As well, sera from patients with vitiligo causes damage to melanocytes in cell cultures, suggesting that the antibodies present in these sera may be involved in the pathogenesis of vitiligo (88). Patients with metastatic malignant melanoma may develop vitiligo, which is postulated to be secondary to the development of antibodies that react with both melanocytes and melanoma cells, as a result of cross-antigenicity (89). Vitiligo patients also have an increased association of known autoimmune disorders including thyroiditis, pernicious anemia, Addison's disease, diabetes, and alopecia areata. A recent study suggests that variants of the *NALP1 gene*, a regulator of the innate immune system, confers susceptibility to autoimmune and autoinflammatory diseases that are associated with vitiligo (90). Evidence of cellular mechanisms in the pathogenesis include the finding of T cells expressing a cutaneous lymphocyte-associated antigen typical of skin-homing T cells that are found at the edge of vitiligo patches. This finding is consistent with a hypothesis that lesional T cells rather than circulating antimelanocytic antibodies may be responsible for the patchy destruction of cutaneous melanocytes in vitiligo (91). Another study showed striking aberrations of T-cell subtypes in active areas of vitiligo when compared with static patches of disease (92).

CHÉDIAK-HIGASHI SYNDROME

Chédiak-Higashi syndrome is a rare autosomally recessive disorder characterized by cutaneous, ocular, neurologic, and hematologic abnormalities. There is a greatly increased susceptibility to bacterial infections and a unique "accelerated phase" that often leads to death (93). The accelerated phase is manifested by fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia, and widespread lymphohistiocytic organ infiltrates. Viruses, particularly Epstein-Barr virus, have been associated with triggering the accelerated phase. Giant lysosomal granules in the cytoplasm of circulating white blood cells are typical.

Chédiak-Higashi syndrome is a subtype of OCA, and patients demonstrate fair skin with susceptibility to severe



FIGURE 27-2. Vitiligo. A: Patchy loss of pigment in a patient with vitiligo. B: There is a total loss of melanocytes in the depigmented skin near the border of this patch. C: S-100 protein immunoperoxidase staining confirms the loss of melanocytes, although Langerhans and dermal dendritic cells stain positively.

sunburn, silvery colored hair, and pale irides with photophobia and nystagmus. Severe and recurrent infections of the respiratory tract and skin are common.

Histopathology. Light microscopic features of skin sections show normal findings (94). Fontana-Masson stain shows sparse melanin granules, some of which are grouped and others of which are larger than normal (94). Similar large, irregularly shaped melanin granules are scattered in the upper dermis within melanophages. Hair shafts also demonstrate abnormal aggregates of melanin (95).

The giant lysosomal granules can be demonstrated in peripheral blood, in skin (melanocytes or Langerhans cells), and other organs. A blood smear stained with Giemsa or Wright stain shows the granules are azurophilic. They are found in all white blood cell lines but are most easily seen in neutrophils.

Histogenesis. Within melanocytes, electron microscopic examination reveals giant melanosomes of irregular shape surrounded by a limiting membrane. They further increase in size by fusing with other giant particles. Within the giant melanosomes, a granular matrix and filaments showing periodicity and varying degrees of pigmentation are observed. The largest melanosomes show signs of degeneration leading to vacuolization and the formation of residual bodies. In addition, normal melanosomes are present in the melanocytes and are transferred to keratinocytes; however, they are packaged into abnormally large lysosomes. Similar abnormally large, membrane-bound lysosomes are found in the hair. The giant melanosomes in melanocytes and the giant lysosomes in keratinocytes form because of a defect in membrane or microtubule function. Hypopigmentation occurs because the melanosomes within keratinocytes are found within a relatively few large lysosomes rather than dispersed throughout the cell cytoplasm.

The giant granules in the cytoplasm of white blood cells develop by the fusion of primary lysosomes with one another and with cytoplasmic material. Even though microorganisms are phagocytized into phagocytic vacuoles in a normal fashion, their intracellular killing is delayed because of the unavailability of primary lysosomes to discharge their bacterial enzymes into the phagocytic vacuoles. Also, cathepsin G, a potent antimicrobial protease in neutrophils, is absent in Chédiak-Higashi syndrome.

Mutations in the *CHS1/LYST gene* are associated with Chédiak-Higashi syndrome. CHS1 protein is thought to be a cytosolic protein with a role in vesicle transport (70,96).

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CHAPTER 28

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Benign Pigmented Lesions and Malignant Melanoma

Melanocytic proliferations are composed of one or more of three related types of cells: melanocytes, nevus cells, and melanoma cells, each of which may be located in the epidermis, the dermis, or occasionally also in the subcutis. Melanocytes are solitary dendritic cells that generally are separated from one another by other cells (keratinocytes or fibroblasts). Localized proliferation of melanocytes may occur, giving rise to benign or malignant melanocytic neoplasms, characterized by melanocytes that lie in contiguity with one another to form a tumor. Benign tumors of melanocytes are generally called melanocytic nevi, whereas malignant tumors are called malignant melanomas, and the cells of these lesions are called nevus cells and melanoma cells, respectively. Although the term "melanoma" was at one time taken to include benign pigmented lesions, this is now considered to be synonymous with "malignant melanoma," and the two terms are used interchangeably in this chapter. Major morphologic differences among melanocytes, nevus cells, and melanoma cells are summarized in Table 28-1.

Melanocytic lesions are important primarily because of malignant melanoma, which is the most common potentially lethal neoplasm of the skin. The incidence of melanoma has risen dramatically over the last several decades. However, the mortality has risen less dramatically than the incidence, likely due to earlier diagnosis. There is considerable geographic variation in the incidence of melanoma, related to exposure to sunlight and the susceptibility of the population. Thus, the global incidence is highest in the Australian tropics but very low in most other tropical countries, with their less susceptible populations.

Benign melanocytic nevi occur in all ethnic groups, although there is evidence for shared etiologic factors with melanoma, with a greater incidence in susceptible populations living in sunny climates. Nevi and other benign pigmented lesions are occasionally of cosmetic significance, especially in the case of giant or so-called "garment" congenital nevi. Other than cosmetically, nevi are important primarily in relation to melanoma. Thus, nevi are important as simulants of melanoma, as potential precursors of melanoma, and as markers of individuals at increased risk for melanoma. Because nevi are simulants of melanoma both clinically and histologically, criteria that distinguish between nevus and melanoma are of critical importance. This differential diagnosis, especially at the histologic level, is the primary topic of this chapter.

BENIGN PIGMENTED LESIONS

Benign pigmented lesions composed of epidermal melanocytes include freckles, solar lentigines ("actinic" or formerly senile lentigo), the melanotic macules of Albright's syndrome, and Becker's melanosis. The café-au-lait patches of neurofibromatosis have been described elsewhere. Benign pigmented lesions derived from dermal melanocytes include the Mongolian spot, the nevi of Ota and of Ito, and the blue nevus. Benign tumors of nevus cells are called melanocytic nevi. They can be divided into junctional nevi, including lentigo simplex, compound nevi, and intradermal nevi. There are special variants of melanocytic nevi, the more important of which include the Spitz nevus, the pigmented spindle cell nevus, the congenital melanocytic nevus, and the dysplastic nevus.

Dermal Melanocytoses and Hamartomas

It is important to distinguish dermal melanoses (implying only increase in dermal melanin pigment) caused by the presence of melanocytes in the dermis (melanocytoses) from those produced by the presence of melanin within nonmelanocytic cells (e.g., macrophages) within the dermis. Clinically, the two different processes may have very similar appearances (1). In this section we consider the former condition. Dermal melanosis associated with metastatic melanoma is discussed in a later section of this chapter (Generalized Melanosis in Metastatic Melanoma), whereas inflammatory disorders associated with pigmentary alterations are discussed in Chapter 27.

Mongolian Spot

The typical Mongolian spot occurs in the sacrococcygeal region as a uniformly blue discoloration resembling a bruise. It consists of a noninfiltrated, round or ovoid, rather ill-defined patch of varying size. It is found very frequently in Mongoloid and Negroid infants, but it also occurs occasionally in Caucasoid infants. It is present at birth and usually disappears spontaneously within 3 to 4 years (2).

Occasionally, Mongolian spots occur outside the lumbosacral region as aberrant Mongolian spots, such as on the middle or upper part of the back; they may then be multiple and bilateral and persist. Extensive and persistent Mongolian spots are commonly seen in patients with bilateral nevus of Ota (3).

TABLE 28-1 Melanocytes, Nevus Cells, and Melanoma Cells

Melanocytes	Nevus cells	Melanoma cells
Cytoplasm is dendritic	Rounded or spindle	Rounded or spindle
Cells are solitary	Arranged in clusters	In clusters and large sheets
Nuclei are small and regular	Nuclei of most cells are small and regular	Most nuclei are large, irregular, and hyperchromatic
Mitoses are rare	Mitoses are rare	Mitoses are usually present

Histopathology. In the Mongolian spot, the dermis shows in its lower half or two thirds greatly elongated, slender, often slightly wavy dendritic cells containing melanin granules that are distributed within the dendrites, rendering them visible. These cells are present in a low concentration and lie widely scattered between the collagen bundles, and like the collagen bundles, they generally lie parallel to the skin surface. No melanophages are seen.

Nevi of Ota, Ito, and Hori; Dermal Melanocyte Hamartoma

Nevi of Ota and Ito and dermal melanocyte hamartoma are types of dermal melanocytosis that differ from the Mongolian spot by usually having a speckled rather than a uniform blue appearance and by showing a greater concentration of dermal melanocytes, with location in the upper rather than in the lower portion of the dermis (3,4).

The *nevus of Ota* is most often a unilateral discoloration of the face composed of blue and brown, partially confluent macules. The periorbital region, temple, forehead, malar area, and nose are usually involved. Because of this usual distribution, Ota called the lesion nevus fuscocaeruleus ophthalmomaxillaris. There is frequently also a patchy blue discoloration of the sclera of the ipsilateral eye and occasionally also a similar discoloration of the conjunctiva, cornea, and retina. In some instances, the oral and nasal mucosa is similarly affected. In about 10% of the cases, the lesions of the nevus of Ota are bilateral rather than unilateral. They may be present at birth; they may also appear during the first year of life or during adolescence but only rarely in childhood. They have a tendency toward gradual extension. Malignant change in the cutaneous lesions of a nevus of Ota is extremely rare (3).

In the nevus of Ota, the involved areas of the skin show a brown to slate-blue, uniform or mottled discoloration, usually without any induration. Occasionally, however, some areas are slightly raised. In some patients, discrete nodules varying in size from a few millimeters to a few centimeters and having the appearance of blue nevi are found within the areas of discoloration. Persistent Mongolian spots are quite common in association with the nevus of Ota. Extensive Mongolian spots are typically found in bilateral cases of nevus of Ota (3).

The *nevus of Ito* differs from the nevus of Ota by its location in the supraclavicular, scapular, and deltoid regions. It may occur alone or in association with an ipsilateral or bilateral nevus of Ota (5). Like the nevus of Ota, it has a mottled, macular appearance.

Nevus of Hori is a form of acquired dermal melanocytosis. It is also known as acquired bilateral nevus of Ota-like macules and acquired symmetric dermal melanocytosis (6–8). The patients present with speckled blue-brown or gray macules that are located bilaterally in the malar region. The vast majority of the reported cases have been seen in Asian women. Histology reveals dendritic pigmented melanocytes in the mid and upper dermis. The dermal pigment stains positively with Fontana Masson staining, and the melanin-containing cells are 3,4-dihydroxy-L-phenylalanine (DOPA) positive. Electron microscopy has revealed a predominance of stage IV melanosomes and melanocyte dendrites encircling elastic fibers.

In the *dermal melanocyte hamartoma*, there may be a single, very extensive area of gray-blue pigmentation present from the time of birth. Histologic and ultrastructural examinations reveal numerous dermal melanocytes (9). The involvement may be nearly generalized (10). In other instances, there are several coalescing blue macules that have gradually extended within a circumscribed area from the time of childhood (11).

Histopathology. The noninfiltrated areas of the nevus of Ota, as well as the nevus of Ito and the dermal melanocyte hamartoma, show, like the Mongolian spot, elongated, dendritic melanized melanocytes scattered among the collagen bundles. However, in these three forms of dermal melanocytosis, the melanocytes generally are more numerous and more superficially located than in the Mongolian spot. Although most of the dendritic melanocytes lie in the upper third of the reticular dermis, melanocytes may also occur in the papillary layer and may extend as far down as the subcutaneous tissue. Melanophages are seen in only few lesions (9,10). A histologic classification of Ota's nevus has been proposed according to the distribution of the dermal melanocytes from superficial to deep. This correlates with the color and location of the nevus and probably with response to therapy (12).

Slightly raised and infiltrated areas show a larger number of elongated, dendritic melanocytes than do noninfiltrated areas, thus approaching the histologic picture of a blue nevus, and nodular areas are indistinguishable histologically from a blue nevus (13).

Malignant changes in lesions of nevus of Ota have been reported in a handful of cases (14). The histologic appearance of the tumors may be that of a malignant or cellular blue nevus (15). In a few instances, a primary melanoma of the choroid, iris, orbit, or brain has developed in patients with a nevus of Ota involving an eye (16,17). A benign or low-grade lesion termed a melanocytoma of the meninges may also occur (18).

Histogenesis of the Dermal Melanocytoses. The blue color of the dermal melanocytoses depends on the phenomenon whereby light passing through the skin is scattered as it strikes dark particles, such as melanin. Owing to this scattering phenomenon, which is termed the Tyndall effect, the colors of light that have a longer wavelength, such as red, orange, and yellow, tend to be less scattered and therefore continue to travel in a forward direction, but the colors of shorter wavelength, such as blue, indigo, and violet, are scattered to the side and backward to the skin surface. This phenomenon is also responsible for the distinctive color of blue nevi and of blood in veins.

The Mongolian spot is believed to be the result of the delayed disappearance of dermal melanocytes during embryogenesis. On electron microscopy, the dermal melanocytes are seen to contain numerous fully melanized melanosomes. Only a few melanocytes show premelanosomes as evidence of ongoing melanogenesis (2).

Because the concentration of melanocytes in the nevi of Ota and Ito and in the dermal melanocyte hamartoma is greater than in the Mongolian spot, it has been suggested that these lesions are nevoid or hamartomatous, rather than reactive or neoplastic. Although the lesional cells are considered to be melanocytes, the DOPA reaction may be negative, likely due to all of the melanogenic enzyme having been consumed in heavily pigmented melanocytes (9).

Blue Nevi

Blue nevi are benign, localized pigmented lesions that generally occur on the skin, although, occasionally, they may be observed in mucous membranes (19). On the skin, three types of benign blue nevi are recognized: the common blue nevus, the cellular blue nevus, and the combined nevus. In addition, there are malignant blue nevi, discussed in a later section.

Histologically, the common feature of blue nevi is the presence of pigmented spindle and dendritic melanocytes in a focal area of the reticular dermis, associated (unlike the dermal melanocytoses) with alterations in the dermal collagen architecture. This deeply situated pigment differs from that in acquired nevi, which is typically superficial only, and accounts for the blue color of these lesions due to the light-scattering Tyndall effect.

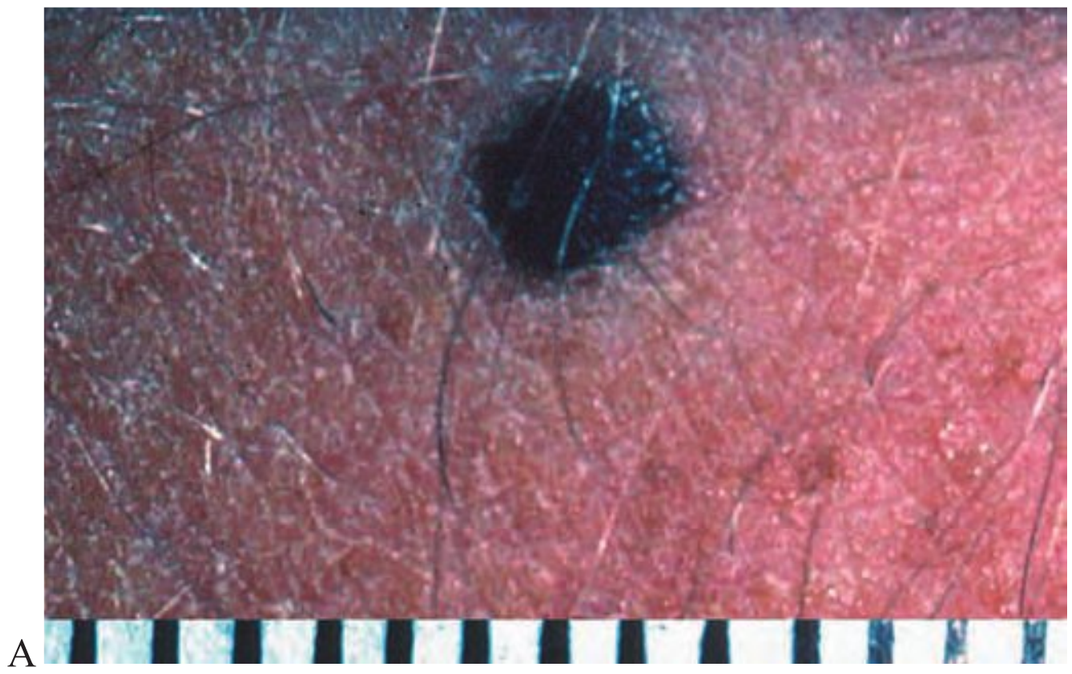
In a recent study, persistence and recurrence of blue nevi were discussed, demonstrating that blue nevi of all histologic types and combinations are capable of persistence with clinical recurrence (20). The persistence usually is histologically similar to the original but in some cases is more "cellular" and/or atypical. Limited follow-up of these cases has not demonstrated frankly malignant behavior. Clinical recurrence may also be associated with malignancy of a blue nevus–like lesion, but this study demonstrated that tumor progression to malignancy is not necessarily the case. In the absence of necrosis en masse, marked cytologic atypia, and frequent mitotic figures, recurrence of a blue nevus or a cellular blue nevus is likely to be a benign phenomenon (20). However, we recommend complete excision and follow-up for such recurrent lesions.

Common Blue Nevus

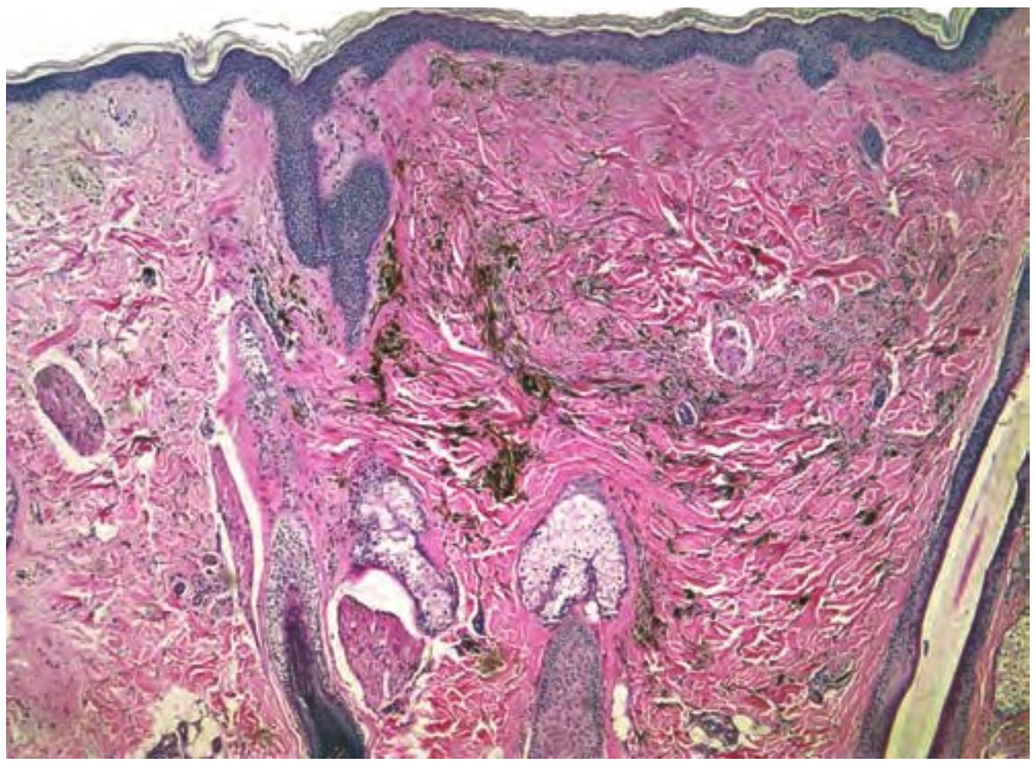
The common blue nevus occurs as a small, well-circumscribed, dome-shaped nodule of slate-blue or blue-black color (Fig. 28-1A). The lesion rarely exceeds 1 cm in diameter. Common blue nevi are frequently found on or near the dorsa of the hands and feet, as well as on the scalp. Usually, there is only one lesion, but there may be several. A rare manifestation is the plaque type of blue nevus, which shows numerous macules and papules within a circumscribed area. This type of lesion may be present at birth or may become clinically apparent later in life (21). Malignant degeneration has not been reported in the common blue nevus.

Histopathology. In the *common blue nevus*, the melanocytes have a similar appearance to those in the Mongolian spot and in the nevus of Ota but they are typically larger and their density is much greater. Greatly elongated, slender, often slightly wavy melanocytes with long, occasionally branching dendritic processes lie grouped in irregular bundles in the dermis (Fig. 28-1B–D). The bundles of cells may extend into the subcutaneous tissue or lie close to the epidermis. However, the epidermis is normal, except in the combined nevus (see section Combined Nevus). The greatly elongated melanocytes lie predominantly with their long axis parallel to the epidermis. Most of them are filled with numerous fine granules of melanin, often so completely that their nuclei cannot be visualized. The melanin granules also characteristically fill the long, often wavy, occasionally branching dendritic processes. Wavy fiber bundles similar to nerves may be present, indicative of schwannian differentiation (22). Occasionally, lesional cells are seen in the perineurium of authentic nerves, a finding that is not indicative of malignancy. Melanophages may be seen near the bundles of melanocytes but are usually not numerous or dense. The melanophages differ from the melanocytes by being more round to ovoid, by showing no dendritic processes, and by containing larger granules. The melanocytes of blue nevi are positive for S100 and HMB-45 (23) and for Melan-A (24). The number of fibroblasts and the amount of collagen are generally increased in blue nevi, resulting in disruption of the normal architecture of the connective tissue. In some lesions, the collagen is unusually prominent, and these have been termed *desmoplastic blue nevi* (or cellular blue nevi) (25,26).

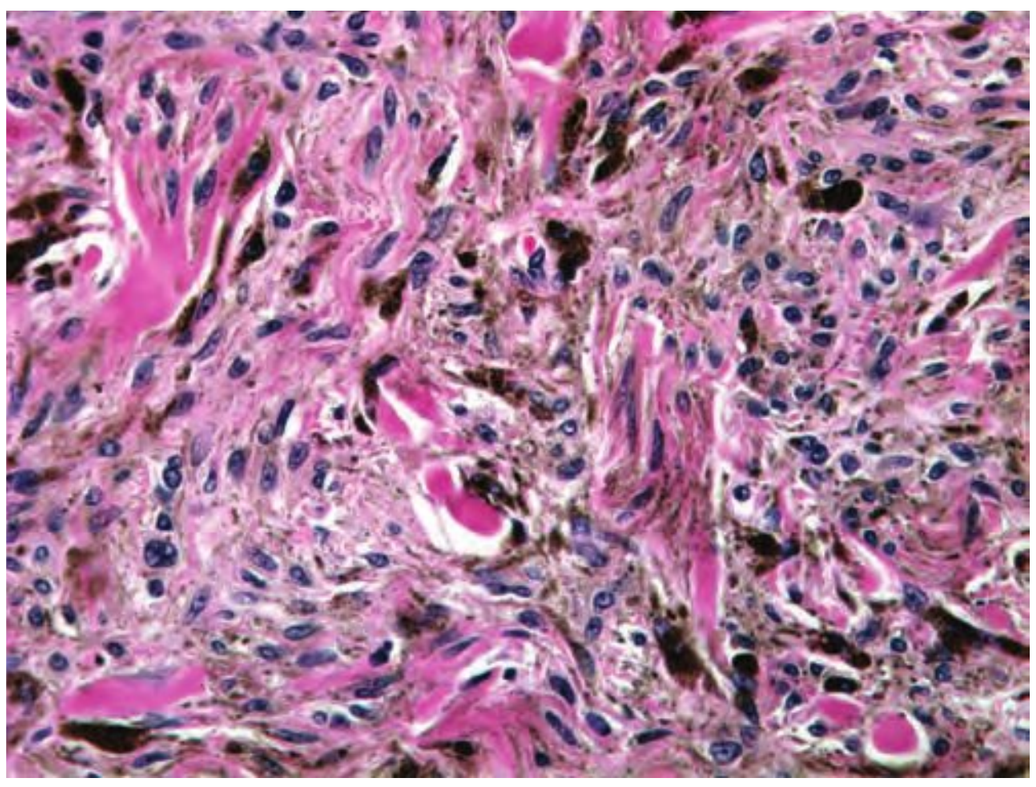
If melanocytes are relatively sparsely distributed and minimally pigmented, these lesions may be mistaken for a fibrohistiocytic lesion such as a *dermatofibroma*. A few blue nevi are hypopigmented or even amelanotic (27,28), requiring immunohistochemistry for their confirmation. Although blue nevi are usually strictly dermal, rare *compound blue nevi* have been described in which there are pigmented dendritic melanocytes in the epidermis near the dermal–epidermal junction (29). Junctional melanocytes may also be seen in the setting of combined nevi (see later discussion). Recurrences of benign blue nevi after excision have been described; although this phenomenon is



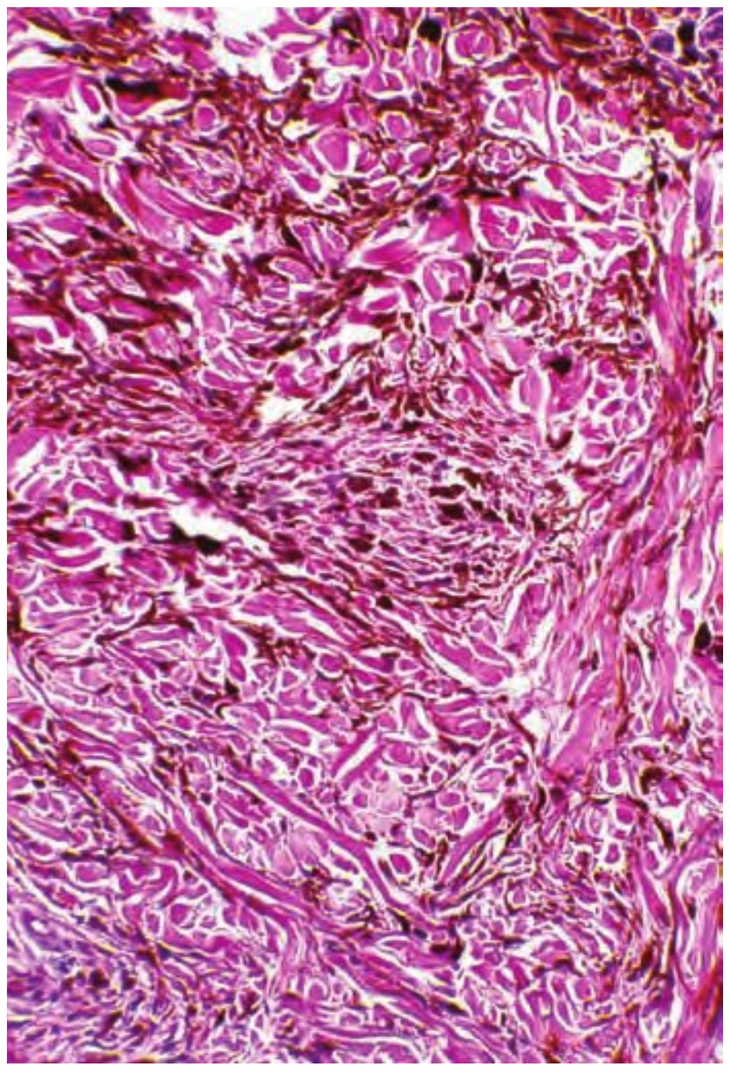
A



B



C



D

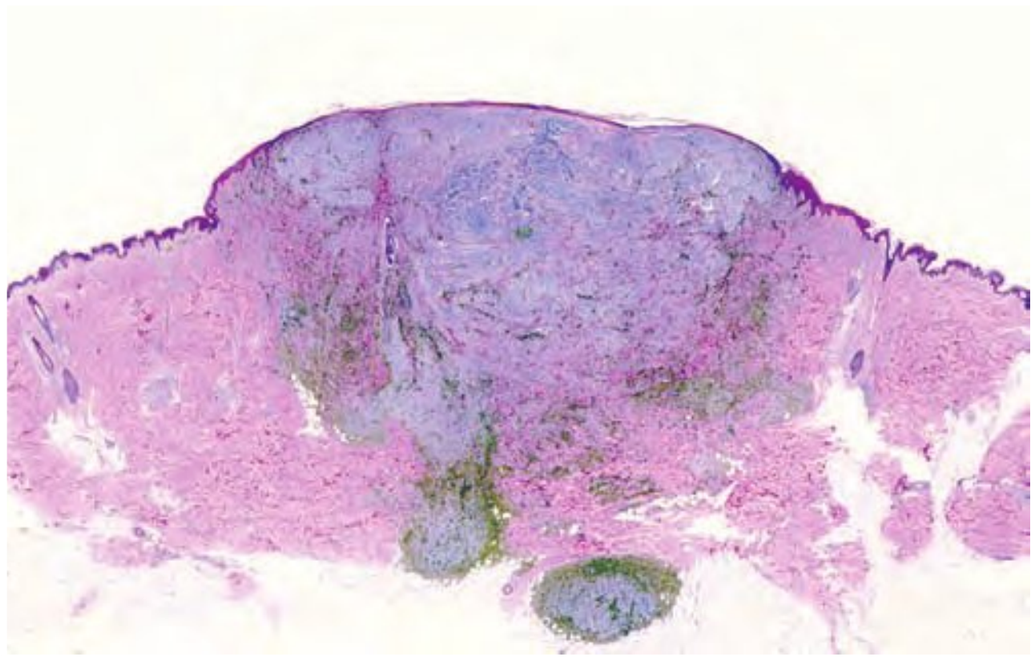
FIGURE 28-1. A: Blue nevus. A relatively small, well-circumscribed, slightly elevated blue-black pigmented lesion. B: Spindle-shaped or dendritic melanocytes are placed among reticular dermis collagen bundles, which are often, as here, slightly thickened. C: Unlike the cells of most common or congenital nevi that involve the reticular dermis, the cells of blue nevi are usually heavily pigmented, with coarsely divided melanin granules. D: Especially at the periphery of the lesion, the cells are arranged as single cells placed among collagen bundles rather than sheets or fascicles.

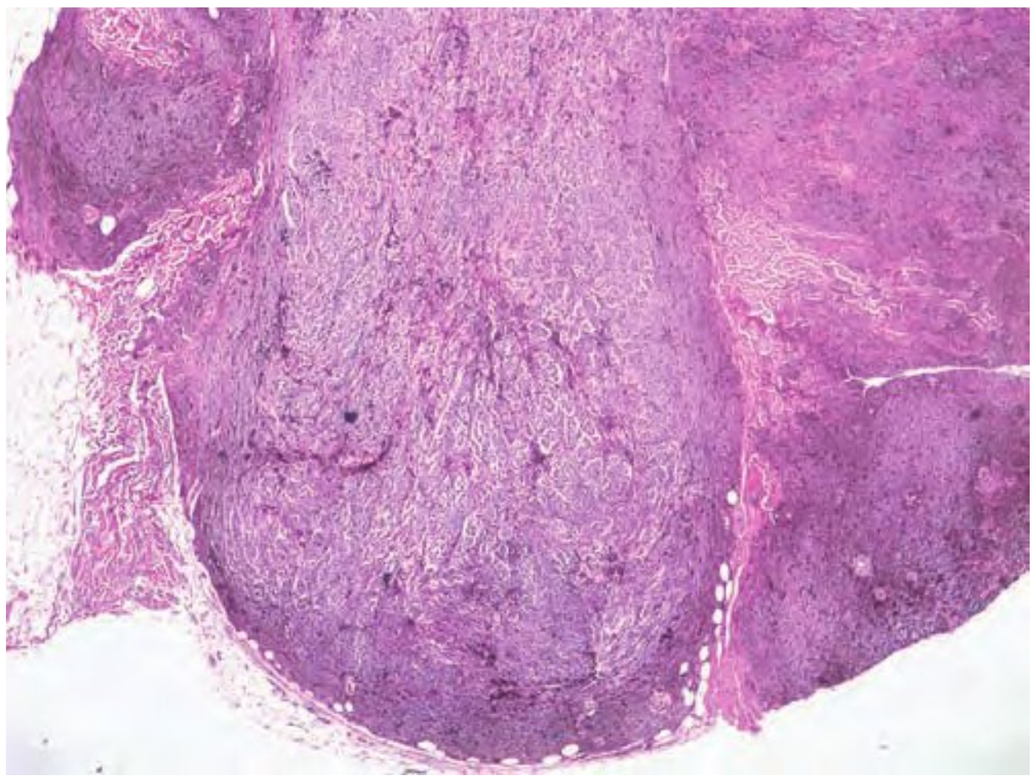
suggestive of malignancy and the recurrences tend to be more cellular than the original lesions, the behavior may be benign in the absence of compelling indicators of malignancy, such as necrosis, high-grade atypia, and mitoses (20).

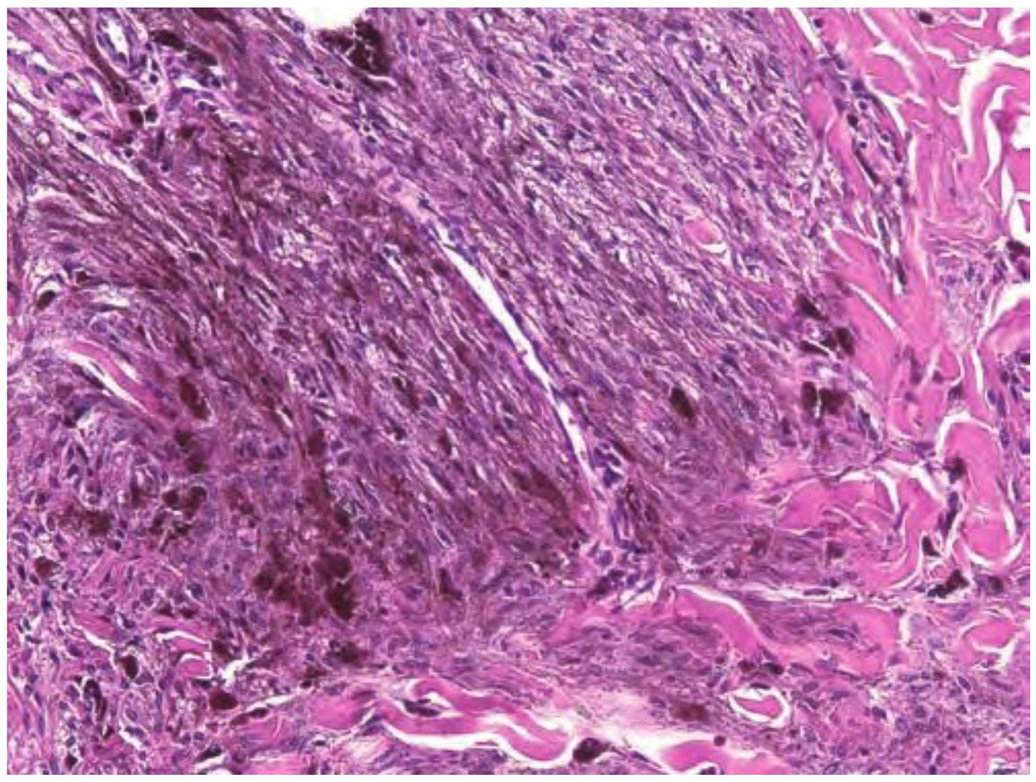
Cellular Blue Nevus

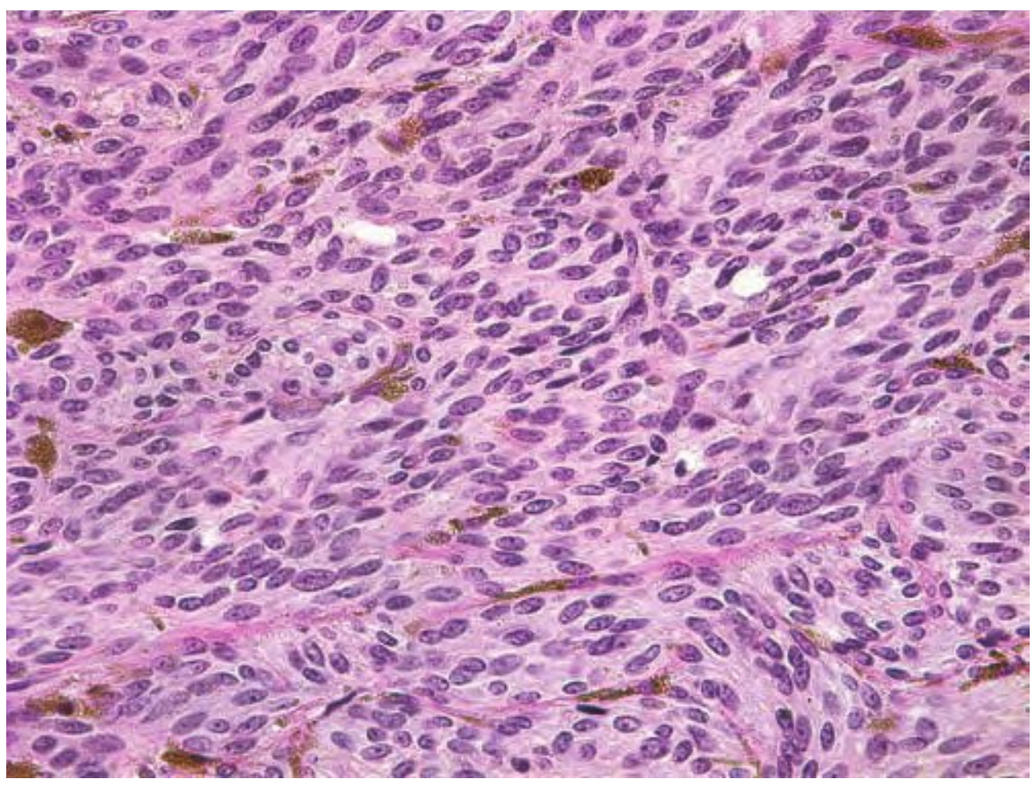
The cellular blue nevus (CBN) consists of a blue nodule that is usually larger than the common blue nevus. It generally measures 1 to 3 cm in diameter, but it may be larger. It shows either a smooth or an irregular surface. About half of all cellular blue nevi have been located over the buttocks or in the sacrococcygeal region (30–32). Although rare, malignant degeneration of cellular blue nevi can occur (31) (see section Malignant Blue Nevis).

Histopathology: The profile of a CBN is often distinctive at scanning magnification, with a bulky, heavily pigmented cellular tumor often spanning the reticular dermis and not associated with an overlying *in situ* melanoma (Fig. 28-2A–E). In


A


B


C


D

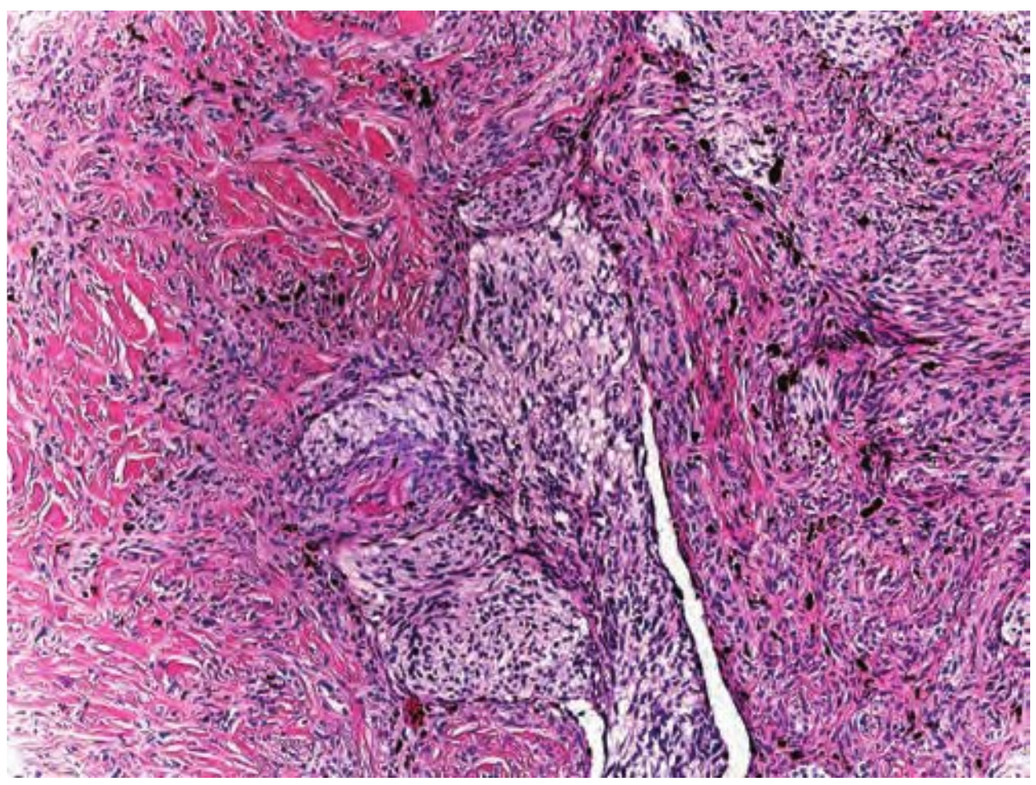

E

FIGURE 28-2. A: Cellular blue nevus. Usually broader at its surface than its base, the cellular blue nevus spans the reticular dermis, usually involving the superficial panniculus. Often, there is a region of increased cellularity that may form a bulbous expansion at the base. A small satellite lesion, as seen here, is an unusual finding. B: The bulbous expansion where the lesion meets the panniculus at the base is a characteristic but not invariable finding. C: Spindle cells usually predominate in cellular blue nevi. They lie in contiguity with one another, unlike the cells of common blue nevi, most of which are separated from one another by collagen bundles. D: In other areas, it is common to find sheets of cuboidal cells with pale cytoplasm in a cellular blue nevus. E: This mixed-biphasic pattern is a distinctive feature of many cellular blue nevi, with ovoid islands of polygonal cells with somewhat clear cytoplasm alternating with spindle cells, the latter often pigmented. Mitoses are very rare in most examples. Changes at the periphery may be indistinguishable from those of a common blue nevus.

lesions that enter the subcutis there is often a cellular nodule at the base, connected to the overlying tumor in a dumb-bell pattern. Areas of deeply pigmented dendritic melanocytes, as seen also in the common type of blue nevus, are admixed with cellular islands composed of closely aggregated, rather large, spindle-shaped or more-epithelioid cells with ovoid nuclei and abundant pale cytoplasm often containing little or no melanin. Melanophages with abundant melanin may be present between the islands. Although pigment is usually prominent, amelanotic CBN have been described (33). Four histologic subtypes have been recognized: mixed-biphasic, alveolar, fascicular or neuronevoid (also known as the monophasic spindle cell type), and atypical varieties (31). In the common mixed-biphasic type, there are clusters of epithelioid cells with somewhat clear cytoplasm, between which there are fascicles of spindle cells (Fig. 28-2E). Pigment is usually more prominent in the latter. The alveolar type is distinctive, characterized by rounded nests of clear spindle cells embedded in a matrix of dendritic and spindle-shaped, more heavily pigmented melanocytes similar to those of the mixed-biphasic pattern. The monophasic spindle cell type is somewhat more problematic and may overlap with *pigmented epithelioid melanocytomas*, *spindle cell tumorigenic melanomas*, and *malignant blue nevi* (see the respective sections). The absence of an overlying *in situ* component may help to rule out a melanoma. Attributes that may suggest malignancy in a CBN are discussed in the section on malignant blue nevi. They include frequent mitoses, high-grade cytologic atypia, and spontaneous tumor necrosis or ulceration.

Lesions termed *atypical cellular blue nevi* have become recognized as a variant of cellular blue nevi, characterized by unusual features including architectural atypia (infiltrative margin and/or asymmetry) and/or cytologic atypia (hypercellularity, nuclear pleomorphism, hyperchromasia, occasional mitotic figures, and/or subtle necrosis) (30,31,34). Although most of these lesions have a benign course, a few cellular blue nevi (not necessarily all "atypical") have been locally aggressive (35,36) or have metastasized at least to regional lymph nodes (37,38), and a guarded prognosis is appropriate in the presence of more than a few mitoses (see section Superficial Atypical Melanocytic Proliferation of Uncertain Significance). The absence or scarcity of mitotic figures and the absence of areas of necrosis or of high-grade atypia are evidence against a diagnosis of malignant blue nevus, and the presence of areas of dendritic blue nevus–type cells elsewhere in the tumor and the lack of a characteristic intraepidermal (*in situ* melanoma) component argue against a diagnosis of melanoma.

In several instances in which cellular blue nevi were excised with regional lymph nodes under the mistaken diagnosis of melanoma or because of an "atypical" or "uncertain" diagnosis, moderately or severely atypical cells of cellular nevus were found in the regional lymph nodes, often in the marginal sinuses or in the capsule (39), but sometimes more massively involving the node (38). It is sometimes assumed that these cells do not represent true metastases but were passively transported to the lymph nodes and lodged there as inert deposits. However, some examples of this phenomenon in our experience have shown high-grade uniform atypia, necrosis, and fairly numerous mitoses, apparently indicative of an active neoplasm. Some of these lesions may best be interpreted as metastatic tumors of uncertain potential (see later section).

Combined Nevus

The term *combined nevus* is applied to the association of a blue nevus with an overlying melanocytic nevus (40) or to other combinations of benign nevi (41). Clinically, combined nevi often present with a focal area of deep pigmentation.

Histopathology: In a combined nevus, one component is often a congenital pattern nevus in which pigmented spindle cells form a focal collection of fascicles among nests of ordinary nevus cells. The fascicles tend to be organized along the lines of a blue nevus, which may be either a common or a cellular blue nevus. The other component may be an overlying nevus of the junctional, compound, or intradermal type, or, rarely, a Spitz nevus (41). Such lesions may simulate melanoma clinically because of the appearance of a very darkly pigmented spot within a background nevus. Histologically, the pigmented spindle cells of the blue nevus component may give rise to suspicion based on apparent asymmetry of pigment distribution, but mitoses and high-grade atypia are absent, and the pigmented cells often blend with the background nevus rather than displacing or destroying it. Furthermore, it is extremely unusual for a melanoma to arise in the dermal component of a nevus in the absence of a characteristic intraepidermal component.

Histogenesis of Blue Nevi. There is general agreement that the cells of the common blue nevus are melanocytes, which may show evidence of Schwannian differentiation. This occasional resemblance to neural tumors had led to suggestions of neural origin for blue nevi (42). However, the lesional cells of blue nevi and their variants react positively with antibodies to the S100, HMB-45, and Melan-A/MART-1 antigens, the last two in this context being quite specific for melanocytic differentiation, and also serving to help differentiate these lesions from desmoplastic melanomas, which are typically negative for these markers (26,43). In addition, melanosomes are present by electron microscopy (EM 48), and the electron microscopic DOPA reaction indicates that the spindle-shaped cells of the cellular blue nevus have melanogenic potential (44).

Freckles and Hyperpigmentations

By definition, a freckle (ephelide) is a small, flat, tan or brown lesion that histologically shows increased pigment in keratinocytes but no increase in the number of melanocytes. Hyperpigmentations may be described as larger, macular, pigmented lesions that show increased melanin pigment in keratinocytes without melanocytic proliferation. Lentigines are macular hyperpigmentations that differ from freckles and hyperpigmentations in that the number of epidermal melanocytes is increased within the basal cell layer. However, in common parlance, the term "freckle" is often used to refer both to ephelides and to solar lentigines, as well as other forms

of macular hyperpigmentations. Ephelides appear early in childhood and are associated with fair skin type and red hair. Solar lentigines appear with age and are a sign of photodamage. Both lesions are strong risk indicators for melanoma and nonmelanoma skin cancer. Melanocortin-1–receptor (MC1R) gene variants are also associated with fair skin, red hair, and melanoma and nonmelanoma skin cancer. In a large case–control study, carriers of MC1R gene variants had a markedly increased risk of developing ephelides, whereas the risk of developing severe solar lentigines was moderately increased, suggesting that MC1R is a major gene controlling susceptibility to the development of these forms of macular hyperpigmentations (45).

Ephelide (Freckle)

Freckles, or ephelides, are small, red-brown macules scattered over skin exposed to the sun. Exposure to the sun deepens the pigmentation of freckles, in contrast to lentigo simplex, whose already deep pigment does not change. Ephelides, simple lentigines, and solar lentigines are difficult to distinguish from one another clinically and are considered together in most clinical and epidemiologic studies. Taken together, these lesions constitute a significant risk factor for the development of melanoma (46).

Histopathology. Freckles show hyperpigmentation of the basal cell layer, but in contrast to lentigo simplex, there is no elongation of the rete ridges and, by definition, no obvious increase in the concentration of melanocytes. However, in a quantitative study of lesions from children, melanocyte frequencies in freckles were significantly greater than in adjacent nonpigmented skin. Cellular atypia of melanocytes and reactivity of melanocytes for HMB-45 were noticed in some freckles (47). It is likely that freckles represent a hyperplastic and hyperactive response of melanocytes to ultraviolet (UV light).

Histogenesis. On electron microscopy, the melanocytes within freckles are found to be essentially similar to those of dark-skinned persons. Melanocytes of the surrounding epidermis, by contrast, show constitutionally few and minimally melanized melanosomes, many of which are rounded rather than elongated (48). Such rounded melanosomes (so-called pheomelanosomes) are characteristic of the lightly pigmented skin of individuals with red hair and/or blue eyes and a cutaneous phenotype that is prone to freckles. As noted earlier, the tendency to develop freckles appears to be closely related to MC1R gene polymorphisms (45).

Melanotic Macules of Albright's Syndrome

Albright's syndrome usually is characterized by unilateral polyostotic fibrous dysplasia, precocious puberty in females, and melanotic patches. The patches generally are large and few, are located on only one side of the midline, often on the same side as the bone lesions, and have a jagged, irregular border, like the coast of Maine, in contrast to the smooth, coast of California–type of border of the café-au-lait patches of neurofibromatosis.

Histopathology. Except for hyperpigmentation of the basal layer, there is no abnormality, and both the number and the size of the melanocytes are normal (49).

Differential Diagnosis. The melanotic macules of Albright's syndrome only rarely show the "giant" melanin granules (macromelanosomes) that are commonly seen in some of the melanocytes and keratinocytes within the café-au-lait patches of *neurofibromatosis*. Histologically, the melanotic macules may be indistinguishable from ephelides without correlative clinical information.

Mucosal Melanotic Macules (Mucosal Lentigines)

These benign lesions present as a pigmented patch on a mucous membrane. Common locations include vermilion border of the lower lip, the oral cavity, the vulva, and, less often, the penis. These lesions may simulate melanoma clinically, but histologically there is no contiguous melanocytic proliferation and no significant atypia. Because there may be a slight increase in number of melanocytes, although there is no nest formation, the term genital lentiginosis has been proposed for those lesions affecting genital paramucosae (50). The lesions may be synonymously referred to as mucosal lentigo or mucosal melanotic macule.

In the common location on the vulva (vulvar lentigo), this process may appear quite alarming clinically, presenting as a broad, irregular, and asymmetric patch of brown to blue-black hyperpigmentation, often meeting the "ABCD" criteria for melanoma discussed later (51). Similar lesions may also be seen on penile skin (50). The lesions may be multicentric, with alternating areas of normal and pigmented mucosa resembling areas of partial regression of a melanoma. The lesions are entirely macular, which would be unusual in an invasive melanoma. The so-called labial lentigo (also known as labial melanotic macule or labial melanosis), a hyperpigmented macule of the lip, is closely related to the lesions of genital skin. It is rarely biopsied because the clinical appearances are characteristic and do not suggest malignancy. These lesions are uniformly pigmented light to dark brown, usually completely macular, and usually less than about 6 mm in diameter. These macules are biologically indolent (52).

Histopathology. On initial inspection, a biopsy specimen may appear normal. The findings include mild acanthosis without elongation of rete ridges and hyperpigmentation of basal keratinocytes, often best recognized in comparison with surrounding epithelium, in association with scattered melanophages in the dermis. Although melanocytes may be normal in number, in most instances they are slightly increased (50,53). Because of this slight increase in number, the lesions are termed lentigines (as opposed to ephelides) by strict histologic criteria (50). In contrast to true melanocytic neoplasms (nevi or melanomas), the cell bodies of the lesional melanocytes are separated by those of keratinocytes, that is, there is no contiguous proliferation of melanocytes. Occasionally, especially in the penile and vulvar lesions, there are prominent dendrites of melanocytes ramifying among the hyperpigmented keratinocytes. There

may be associated mild keratinocytic hyperplasia, and scattered melanophages in the papillary dermis, resulting from pigmentary incontinence, may account for the blue-black color and the pigmentary variegation that may simulate melanoma clinically.

Differential Diagnosis. The histologic distinction from radial-growth-phase melanoma is easy because of the absence of neoplastic (contiguous) melanocytic proliferation and cytologic atypia of melanocytes (54).

Pathobiology. The process appears likely to be one of reactive hyperplasia with some features of postinflammatory hyperpigmentation rather than a neoplasm (55). The phenomenon is benign, with associated lesional growth stabilization over time.

Becker's Melanosis

Becker's melanosis, also called Becker's pigmented hairy nevus, occurs most commonly as a large, unilateral patch showing hyperpigmentation and hypertrichosis on the shoulder, back, or chest of a male adult (56). Usually, the patch is sharply but irregularly demarcated. Occasionally, however, the lesion presents as coalescing macules instead of a solitary patch. The lesion commonly appears during the second decade of life. In some instances, Becker's melanosis affects areas other than the shoulder and chest. In addition, it may be multiple and bilateral and may occasionally be found in women.

In one report, nine cases of melanoma in association with Becker's nevus were described (57). Five of these were on the same body site as the nevus. It remains to be determined whether these reports represent a greater incidence than chance would suggest.

The hairiness always appears after the pigmentation, and, quite frequently, no hypertrichosis is seen. It is therefore possible that cases described as progressive cribriform and zosteriform hyperpigmentation represent a variant of Becker's melanosis without hypertrichosis (58).

Of interest is the association of a pilar smooth muscle hamartoma with Becker's melanosis. In such cases, the area of Becker's melanosis may show slight perifollicular papular elevations or slight induration (59).

Histopathology. The epidermis shows slight acanthosis and regular elongation of the rete ridges. There is hyperpigmentation of the basal layer, and melanophages are seen in the upper dermis. The number of melanocytes is increased within the basal cell layer. This increase is particularly evident when melanocytes are stained for dopa-oxidase activity in both involved and uninvolved skin nearby (60). The pilar structures appear normal or increased in number.

An increase in smooth muscle fibers exists in nearly all cases, although it may be slight (61). In cases with an associated smooth muscle hamartoma, irregularly arranged, thick bundles of smooth muscle are present in the dermis (59). The term Becker nevus syndrome has been proposed for a phenotype characterized by the presence of a particular type of organoid epithelial nevus showing hyperpigmentation, increased hairiness, hamartomatous augmentation of smooth muscle fibers (smooth muscle hamartoma), and other developmental defects such as ipsilateral hypoplasia of breast and skeletal anomalies including scoliosis, spina bifida occulta, and ipsilateral hypoplasia of a limb (62).

The few melanomas that have been described in association with Becker's nevus have been of the superficial spreading type, originating in the epidermis (57).

Lentigines

Lentigines are macular hyperpigmentations in which the number of epidermal melanocytes is increased and there are no nests of melanocytes as are present, by definition, in nevi. The term "lentigo" is derived from the Latin "*lenz*," meaning lens or lentil (63). Thus, the term in its original usage is clinical, referring to a small ovoid or lens-shaped pigmented spot. The term has come to be applied to larger pigmented lesions, especially those that recapitulate to a greater or lesser extent the histologic features of a lentigo simplex: basal proliferation of melanocytes arranged as single cells rather than in nests, typically but not always associated with elongation of the rete ridges. This pattern of melanocytic proliferation is termed "lentiginous." Lentiginous melanocytic proliferation is seen in the macules of solar lentigo and lentigo simplex and in the macular or plaque components of lentiginous junctional and compound nevi, of lentiginous dysplastic nevi, and of lentiginous melanoma, including lentigo maligna, acral and mucosal-lentiginous types.

Solar Lentigo (Actinic Lentigo)

Solar lentigines commonly occur as multiple lesions in areas exposed to the sun, such as the face and extensor surfaces of the forearms, but most commonly on the dorsa of the hands. The lesions increase in number with age, in contrast to nevi, which decline in number (64). Therefore, they are often referred to as senile lentigines (65). However, sun exposure, rather than age, is the eliciting factor (66). Thus, the lesions do not occur on sun-protected skin, even in the elderly. Solar lentigines are commonly seen in sun-exposed Caucasoids. They are not indurated, possess a uniform dark brown color, and have an irregular outline. They vary in diameter from minute to more than 1 cm and may coalesce. Solar lentigines, like ephelides, are risk markers for the development of melanoma (67) and are commonly numerous in the skin around melanomas, as seen in melanoma reexcision specimens. Lesions termed "sunburn freckles" by some clinicians may overlap clinically and histologically with actinic lentigines. They are blotchy macular areas of tan hyperpigmentation, often of the order of 1 cm in diameter, that often appear on the shoulders or other sun-exposed areas of a young person after a severe sunburn (68). Other potentially related lesions are intensely dark, perfectly macular reticulated lesions that have been called reticulated lentigo (69) or ink spot lentigo (70).

Solar lentigines differ from ephelides in that they are more prevalent, increase in prevalence and number with age (ephelides tend to decline in number), are most prevalent on

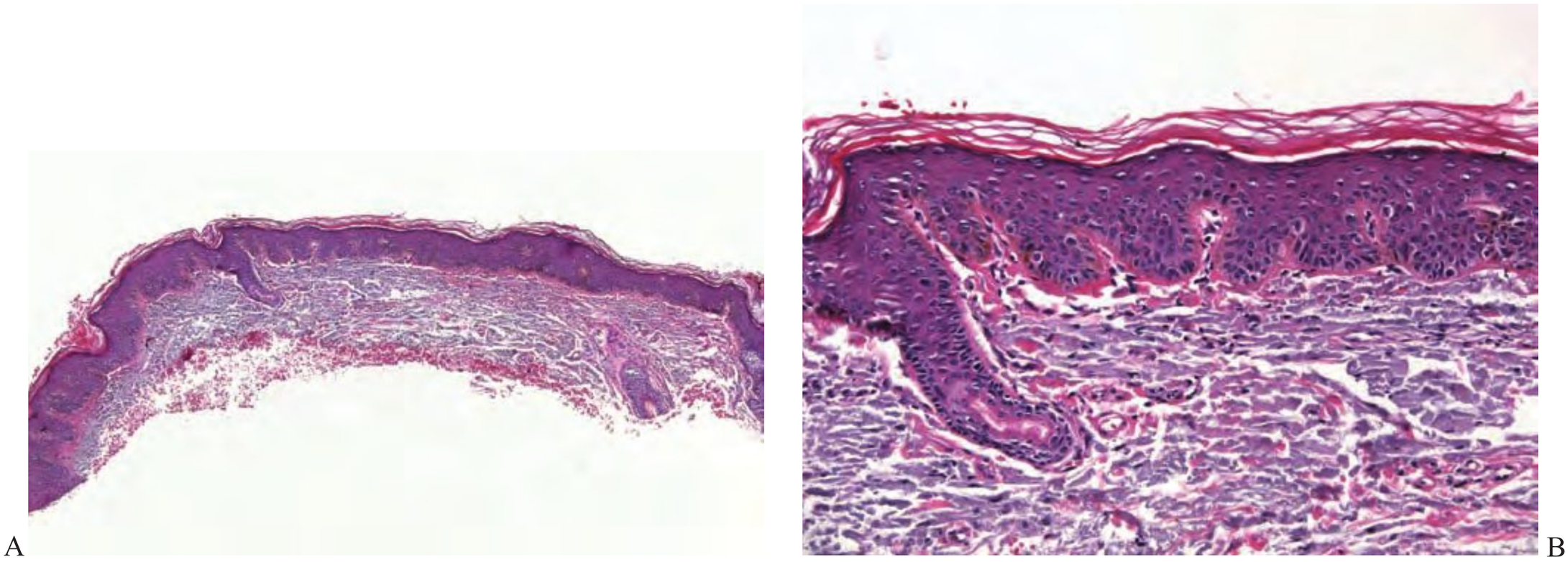


FIGURE 28-3. A: Actinic lentigo. Scanning magnification showing a localized area of elongated rete ridges in elastotic, actinically damaged skin. B: Actinic lentigo. Higher magnification shows basal hyperpigmentation and slight to moderate prominence of melanocytes, without contiguous proliferation. Sometimes there is slight atypia of randomly scattered melanocytes (mild random atypia).

the trunk, and occur more frequently in males than in females, unlike ephelides, which are more evenly distributed and are not related to sun exposure (71,72).

Solar lentigines and relatively flat seborrheic keratoses may resemble each other in clinical appearance, and both are commonly referred to as "liver spots" or "age spots." Seborrheic keratoses in general show more hyperkeratosis clinically. In contrast, lentigo maligna differs from solar lentigo in clinical appearance by its irregular distribution of pigment, often in a finely reticulated pattern, and by its greater asymmetry and border irregularity.

A recent microarray analysis of solar lentigines demonstrated upregulation of genes related to inflammation, fatty acid metabolism, and melanocytes and downregulation of cornified envelope–related genes; the authors suggested that solar lentigo may be induced by the mutagenic effect of repeated UV light exposures, leading to enhancement of melanin production along with decreased proliferation and differentiation of lesional keratinocytes on a background of chronic inflammation (73). It has been postulated that abnormal pigment retention in keratinocytes may be the primary disorder in solar lentigines (74).

Prolonged treatment with psoralen and ultraviolet light A (PUVA) can induce formation of pigmented macules ("PUVA lentigines") in the irradiated areas. These are similar to solar lentigines, but their color is darker and their pigment is more irregularly distributed (75).

Histopathology. The rete ridges are subtly or more significantly elongated. They either appear club shaped or are tortuous and show small, budlike extensions. The elongated rete ridges are composed, especially in their lower portion, of deeply pigmented basaloid cells intermingled with melanocytes, which are arranged mostly as single cells. Epidermal maturation may appear subtly perturbed in some lesions. The melanocytes appear significantly increased in number in some cases but only slightly or not at all increased in others (Fig. 28-3) (76). They possess a heightened capacity for melanin production, as shown by the fact that, on staining with DOPA, they display more numerous as well as longer and thicker dendritic processes than the melanocytes of control skin (77). The upper dermis shows elastosis and often contains scattered melanophages and occasionally a mild, perivascular lymphoid infiltrate.

Solar lentigines differ histologically from ephelides by definition, in having an increased number of epidermal melanocytes. However, in some lesions, the proliferation may be demonstrable only by formal counting (78). In contrast to lentigo simplex, lentiginous nevi, and lentiginous melanomas, the melanocytic proliferation is not contiguous and is nonnested.

In some lesions, the rete ridges are elongated to such an extent that strands of basaloid cells form anastomosing branches, resulting in a reticulated pattern closely resembling that seen in the reticulated pigmented type of seborrheic keratosis. However, unlike seborrheic keratoses, solar lentigines do not form horn cysts (76).

PUVA-induced pigmented macules represent actinic lentigines on the basis of irregular elongation of their rete ridges. They show an increased number of large melanocytes that may appear slightly atypical (79).

Large-cell acanthoma, which presents as a slightly scaly, tan macule on photodamaged skin, is identified histologically by having epidermal keratinocytes with nuclei roughly twice the size of adjacent keratinocytes but with minimal nuclear pleomorphism. There are clinical, histologic, and immunohistochemical overlapping characteristics with solar lentigo, suggesting that large-cell acanthoma should be considered as a related condition (80).

In the reticulated or "ink spot" lentigo, histologic evaluation, including electron microscopy and DOPA-incubated vertical sections, demonstrated lentiginous hyperplasia of the epidermis, marked hyperpigmentation of the basal layer with "skip" areas that involved the rete ridges, and a minimal increase in the number of melanocytes (70).

Histogenesis. By electron microscopy, the basal layer of keratinocytes contains increased melanosomes and melanosome complexes, and the melanosome complexes within keratinocytes appear larger than those found in uninvolved skin. Even in the upper layers of the epidermis, including the horny layer, numerous melanosomes are present, largely in a dispersed state rather than as complexes (74,76).

Differential Diagnosis. In lentigo simplex (see later discussion), the rete ridges are elongated, but, in contrast, the lesional melanocytes are more obviously increased in number and focally lie in contiguity with one another around the tips and sides of the rete but not between the rete. Lentigo maligna shows flattening or absence of the rete ridges together with contiguous and continuous proliferation and uniform atypia of its melanocytes; like lentigo simplex, however, it may be associated with a dermal lymphocytic infiltrate. In actinic lentigo, the rete are elongated and the lesional melanocytes do not lie in contiguity with one another, even though they may be increased in number. There is minimal cytologic atypia and no pagetoid spread of melanocytes above the basal layer. In contrast to a pigmented actinic keratosis, there is no keratinocytic atypia and usually no parakeratosis.

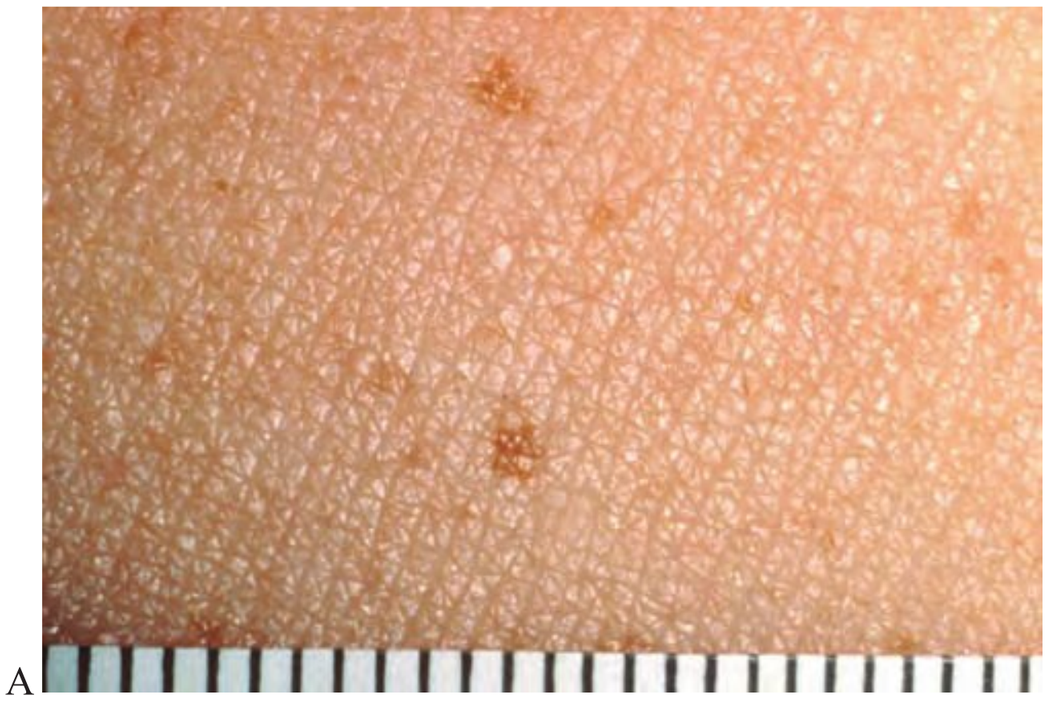
Lentigo Simplex and Related Lesions

Simple lentigines are macular hyperpigmentations in which the number of epidermal melanocytes is increased. In solar lentigines, as described previously, the cell bodies are separated from one another by those of keratinocytes, and the proliferation may be termed noncontiguous. The proliferation may be described as contiguous if the cell bodies at least focally touch one another, as in lentigo simplex (and also in lentiginous nevi and in lentiginous melanomas).

Lentigo simplex most frequently arises in childhood, but it may appear at any age (81). Usually there are only a few scattered lesions in lentigo simplex, without predilection for areas of sun exposure. They are small, symmetric, and well-circumscribed macules that are evenly pigmented but vary individually from brown to black (Fig. 28-4A). They are not indurated and usually measure only a few millimeters in diameter. Clinically a lentigo simplex is indistinguishable from a junctional nevus. Special forms of lentigo simplex are lentiginosis profusa, the multiple lentigines syndrome or LEOPARD syndrome, and speckled lentiginous nevus, also referred to as nevus spilus.

Lentiginosis profusa shows innumerable small, pigmented macules either from birth or starting in childhood or early adulthood without any other abnormalities. The mucous membranes are spared. There may be a family history (82,83). *Agminated* or *segmental lentigines* have been defined as a circumscribed group of small, pigmented macules arranged in a small or large group, often in a segmental pattern, each macule consisting of a lentiginous intraepidermal proliferation of melanocytes (84,85). The *speckled lentiginous nevus*, or *nevus spilus*, consists of a light brown patch or band present from the time of birth that in childhood becomes dotted with small, dark-brown macules (86,87).

The multiple lentigines syndrome, a dominant trait, is characterized by the presence of thousands of flat, dark-brown macules on the skin but not on the mucous surfaces. The


A

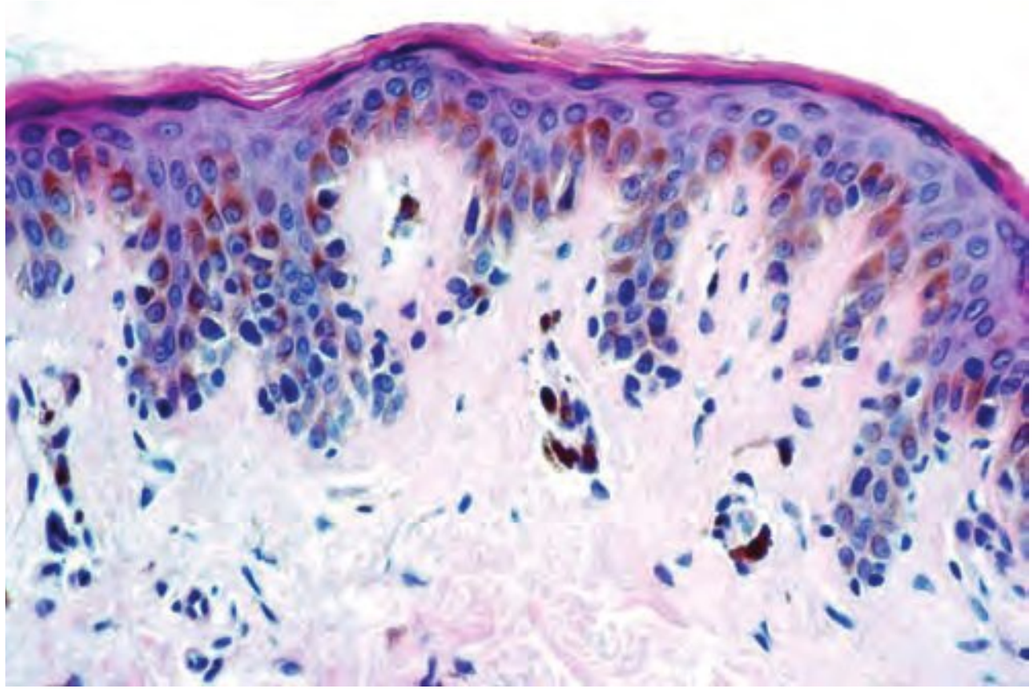

B

FIGURE 28-4. A: Lentigo simplex. Clinically, the lesions are small (usually less than 2 mm), fairly symmetric, and well circumscribed. It is not possible to distinguish clinically among ephelides, simple lentigines, and lentiginous junctional nevi. (Clinical photograph by Peter Wilson.) B: Lentigo simplex. Melanocytes are present in contiguity near the tips and sides of elongated rete ridges ("lentiginous proliferation"). There is no continuous proliferation between the rete. The presence of at least a single nest would define a lentiginous junctional nevus ("jentigo").

lentigines begin to appear in infancy and gradually increase in number. Although most macules vary from pinpoint dots to 5 mm in diameter, some dark spots are much larger, up to 5 cm in diameter. Features of this rare syndrome, known also by the mnemonic LEOPARD, in addition to the lentigines (L), may include electrocardiographic conduction defects (E), ocular hypertelorism (O), pulmonary stenosis (P), and abnormalities of the genitalia (A) consisting of gonadal or ovarian hypoplasia, retardation of growth (R), and neural deafness (D). Not all of these manifestations are present in every case. Cardiomyopathy may also be present and associated with significant mortality (88). Another syndrome associated with lentigines is known by the mnemonic NAME or LAMB or as myxoma syndrome (lentiginous nevi, atrial and/or mucocutaneous myxomas, myxoid neurofibromas, ephelides, blue nevi). It has been proposed that these mnemonics be dropped because the particular features encompassed within this syndrome are unclear, and the term cutaneous lentiginosis with atrial myxomas is an adequate description of this syndrome (89). The Carney complex, a familial multitumoral syndrome, comprises spotty skin pigmentation (lentigines and blue nevi), myxomas (heart, skin, and breast), endocrine overactivity usually manifested by endocrine tumors (adrenal cortex, pituitary, testis, and thyroid), schwannomas, and two unusual pigmented tumors, epithelioid blue nevus (skin) and psammomatous melanotic schwannoma (involving skin, viscera, or nerve tissue). Carney complex has been linked to chromosome 2p16 and the PRKAR1A gene at 17q22-24 (90).

The *Peutz-Jeghers syndrome* (PJS) shows dark-brown macules clinically resembling lentigines in the perioral region. Similar macules are seen on the vermilion border and the oral mucosa and, often, the dorsa of the fingers. Although a few cases of this dominantly inherited disorder have shown only the pigmentary anomaly, there are usually multiple polyps in the gastrointestinal tract, mainly in the small intestine (91,92). Although early reports did not demonstrate a predisposition to cancer in patients with this syndrome, more recent studies have described an increased risk for both gastrointestinal and extragastrointestinal cancers. Women with PJS have an extremely high risk for breast and gynecologic cancer. Recently, a PJS susceptibility gene, encoding the serine threonine kinase STK11 (also called LKB1), was identified in this syndrome (93). A complex of PJS-like pigmentation without polyposis, designated as isolated mucocutaneous melanotic pigmentation, has recently been described and also appears to be associated with increased risk of cancer in diverse organs (94).

Histopathology. Lentigines, in general, show a slight or moderate elongation of the rete ridges, an increase in the concentration of melanocytes in the basal layer, an increase in the amount of melanin in both the melanocytes and the basal keratinocytes, and melanophages in the upper dermis. The melanocytes in the epidermis lie in focal contiguity with one another near the tips and sides of the elongated rete, but the proliferation is not continuous between the rete (Fig. 28-4B). There are no nests by definition. In some instances, melanin is also seen in the upper layers of the epidermis, including the stratum corneum. A mild inflammatory infiltrate may be intermingled with the melanophages within the underlying papillary dermis. In lesions otherwise clinically characteristic of lentigo simplex, small nests of nevus cells are commonly seen at the epidermal–dermal junction, especially at the lowest pole of rete ridges. The lesions then combine features of a lentigo simplex and a junctional nevus, leading to their descriptive diagnosis as jentigo (84), or lentiginous junctional nevus. Because of the existence of these transitional forms, the lentigo simplex is regarded as a potential precursor of what may become a melanocytic nevus, and is discussed as such in the next section.

In *lentiginosis profusa* and the *multiple lentiginosis syndromes*, as a rule, the lesions are "pure" lentigines without the formation of nevus cell nests. In larger macules, however, there may be junctional nevus cell nests, and there may even be nevus cell nests in the upper dermis (95).

In *speckled lentiginous nevus*, or *nevus spilus*, the light-brown patch or band shows the histologic features of lentigo simplex. The speckled areas show junctional nests of nevus cells at the lowest pole of some of the rete ridges, diffuse lentiginous melanocytic proliferation, and dermal aggregates of nevus cells. Various types of nevi (e.g., junctional nevi, blue nevi, and Spitz nevi) may present in the same lesion over time, and histologic features of congenital melanocytic nevi may be present within the spots, suggesting that these lesions may be considered as variants of congenital nevi (87).

In the lesions of *Peutz-Jeghers syndrome*, the basal cell layer shows marked hyperpigmentation. Although the number of melanocytes may appear to be slightly increased, no increase has been found in DOPA-stained sections (96). The intestinal polyps appear to be hamartomas because glands are intermingled with smooth muscle bundles (93).

The presence of occasional giant melanin granules has been described in various forms of lentigines and lentiginous nevi, as well as in other conditions associated with hyperpigmentation, including the café-au-lait spots of neurofibromatosis and, less commonly, in café-au-lait spots without neurofibromatosis; on occasion, they have even been found in normal skin of healthy persons (97,98). Thus, they have no diagnostic specificity. Giant melanin granules vary in size from 1 to 6 mm. Because of their size and heavy melanization, the larger granules are readily recognized by light microscopy. Although seen largely within melanocytes, they also occur in keratinocytes and melanophages to which they have been transferred, although many are too large for conventional donation by affected melanocytes to keratinocytes. On electron microscopy, the giant melanin granules have been termed macromelanosomes, and are regarded as autolysosomes, referred to as melanin macroglobules, representing lysosome-mediated accumulation of melanosomes to form massive rounded to ellipsoid melanized bodies (99).

Table 28-2 summarizes some of the salient clinical and histologic features observed in the various forms of hyperpigmentations and lentigines.

TABLE 28-2 Hyperpigmentations and Lentigines

	Clinical	Basal layer	Melanocytes	Features
Ephelide	Sun-exposed skin, decrease with age, darker with exposure	Increased melanin	No increase by routine histology	HMB-45 reactivity, rounded melanosomes
Melanotic macule, Albright's syndrome	Fibrous dysplasia, precocious puberty, Albright's syndrome	Increased melanin	Normal in number and size	—
Mucosal lentigines	Lower lip, genital skin	Increased melanin	Appear normal to slightly increased	Mild acanthosis, pigment incontinence
Becker's melanosis	Unilateral, hypertrichosis	Increased melanin	Increased	Elongation of rete, smooth muscle fibers in dermis
Solar lentigo	Sun-exposed skin, increase with age	Increased melanin	Appear normal to increased, no contiguity	Elongated rete, solar elastosis
Lentigo simplex	Early onset, not related to sun exposure	Increased melanin	Increased, in focal contiguity	Elongated rete
Lentiginosis profusa	Many lesions at birth or childhood	Increased melanin	Increased, in focal contiguity	Elongated rete, nevus nests in some lesions
Multiple lentiginosis syndromes (LEOPARD, LAMB)	Many lesions, dominant trait	Increased melanin	Increased, in focal contiguity	Elongated rete, nevus nests in some lesions
Speckled lentiginous nevus	Macule at birth, becomes speckled	Increased melanin	Increased, in focal contiguity	Elongated rete, nevus nests in speckled areas
Peutz-Jeghers lentigines	Perioral, dominant trait, GI polyps	Increased melanin (marked)	No increase by DOPA stain	

DOPA, 3,4-dihydroxy-L-phenylalanine; GI, gastrointestinal; LAMB, lentiginous nevi, atrial and/or mucocutaneous myxomas, myxoid neurofibromas, ephelides, blue nevi; LEOPARD, lentigines, electrocardiographic conduction defects, ocular hypertelorism, pulmonary stenosis, and abnormalities of the genitalia consisting of gonadal or ovarian hypoplasia, retardation of growth, and neural deafness.

Melanocytic Nevi

Common Melanocytic Nevus

Although the term "nevus" may refer to a variety of hamartomatous and/or neoplastic lesions in the skin, the unqualified term in common usage and in this chapter refers to a *melanocytic nevus*, which is generally considered to be a benign neoplastic proliferation of melanocytes, leading to a localized pigmented or nonpigmented lesion usually less than 5 mm in diameter. Nevi vary considerably in their clinical appearance. In addition to the pathologic variants, which will be discussed separately, five clinical types may be recognized: (a) flat lesions, (b) slightly elevated lesions, often with a raised center and a flat periphery, (c) papillomatous lesions, (d) dome-shaped lesions, and (e) pedunculated lesions. The first three types are always pigmented; the last two may or may not be pigmented. Any of the elevated lesions may be surrounded by a flat periphery, within which changes of melanocytic dysplasia may be seen histologically ("nevus with dysplasia"). Dome-shaped lesions often contain several coarse hairs. Although exceptions occur, one can predict to a certain degree from the clinical appearance of a nevus whether on histologic examination it will prove to be a junctional nevus (confined to the epidermis), a compound nevus (epidermal and dermal), or an intradermal nevus. Most small, flat lesions represent either a lentigo simplex or a junctional nevus; flat lesions or lesions with a flat periphery 5 mm or more in diameter with irregular indefinite borders and pigment variegation are clinically dysplastic nevi, although if these changes are severe, melanoma may need to be ruled out. Most slightly elevated lesions and some papillomatous lesions represent compound nevi (especially if they are pigmented); and most papillomatous lesions and nearly all dome-shaped and pedunculated lesions that are not pigmented represent intradermal nevi (100).

Melanocytic nevi are only rarely present at birth (see section Congenital Melanocytic Nevus). Most nevi appear in adolescence and early adulthood. In this age period, they may occur episodically and, rarely, as widespread eruptive nevi (101–103). New nevi arise occasionally in midlife and rarely in later life. Except for occasional cosmetic significance, nevi are important only in relation to melanoma, for which they are risk markers, simulants, and potential precursors (67,104,105).

A general concept of clinical importance for melanocytic nevi is that, unlike melanoma, which inexorably progresses over time, nevi enlarge to a point, stabilize, and then involute, becoming less frequent in the elderly than in younger age groups (64). This clinical attribute is directly related to the importance of heightened suspicion that is aroused when a previously stable nevus undergoes change in size or pigmentation.

Histopathology

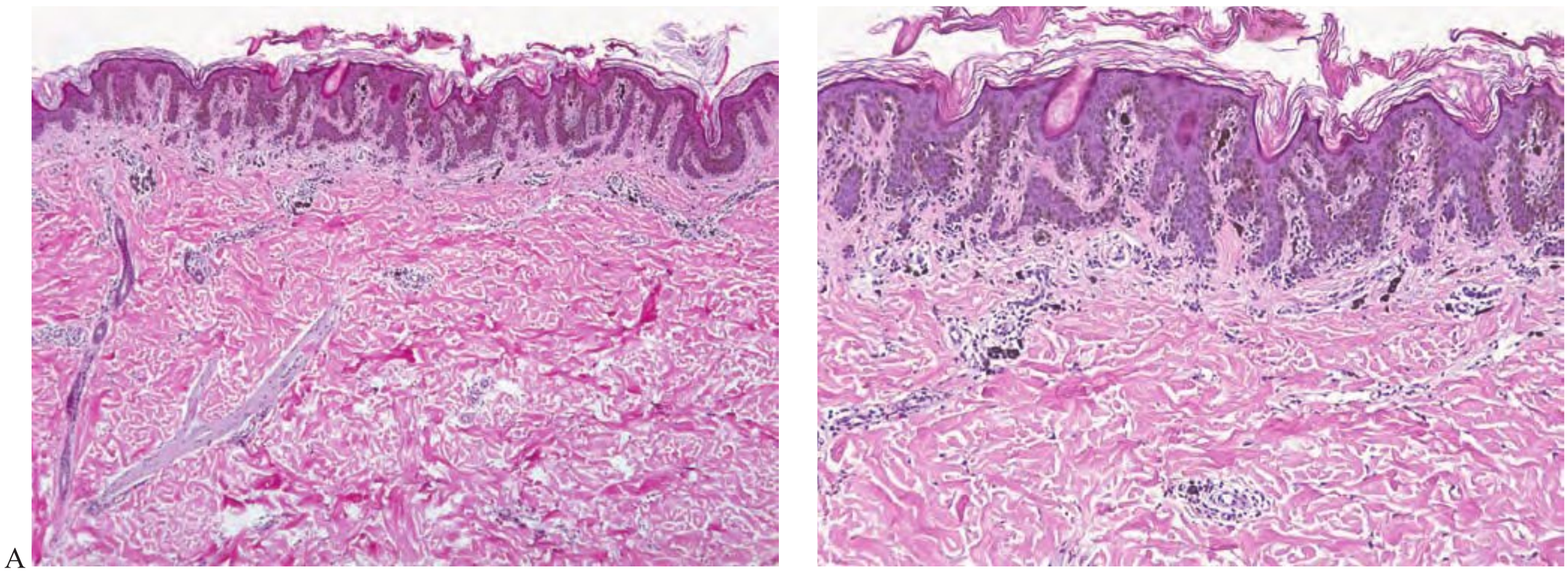
Melanocytic nevi are defined and recognized by the presence of nevus cells, which, even though they are melanocytes, differ from ordinary melanocytes by being arranged at least partially in clusters or "nests." Other defining characteristics of nevus cells include a tendency to rounded rather than dendritic cell shape and a propensity to retain pigment in their cytoplasm rather than to transfer it to neighboring keratinocytes (106). Nevus cells show considerable variation in their appearance and often are not pigmented, so that they are often recognizable as nevus cells more by their arrangement in clusters or nests than by their cellular features. As the result of a characteristic shrinkage artifact, nevus cell nests often appear partially separated from their surrounding stroma and, in some nevi such as the spindle and epithelioid cell variant, from surrounding epithelium.

Although a histologic subdivision of nevi into junctional, compound, and intradermal nevi is generally accepted, it should be realized that these are transitional stages in the life cycle of nevi, from junctional to compound to intradermal, and finally to involuting lesions.

Lentigo Simplex. Lentigo simplex, as described earlier, may be regarded as an early or evolving form of melanocytic nevus. Histologically, these are small (usually less than 2 mm) and are characterized by an increased number of nevoid melanocytes present in contiguity with one another near the tips and sides of elongated rete ridges. This pattern, characteristic of lentigines, is therefore described as lentiginous melanocytic proliferation. The lack of nests at the histologic level distinguishes the lentigo from a nevus, by definition. However, transitional forms between a simple lentigo and a lentiginous junctional nevus (a lentigo with a few nests) are commonly observed, and the two histologic entities are indistinguishable clinically, giving rise to the term nevoid lentigo (86) or jentigo (84). The former term has been used more or less synonymously with lentigo maligna (81,107), and therefore we prefer the term lentiginous junctional nevus for these very common lesions (Fig. 28-5) (69).

Junctional Nevus. In a junctional nevus, nevus cells may lie in well-circumscribed nests either entirely within the lower epidermis or bulging downward into the dermis but still in contact with the epidermis, perhaps in the process of dropping off to form a compound nevus. The nevus cells in these nests generally have a regular, rounded to cuboidal appearance, although they are occasionally spindle shaped. In addition, a varying number of diffusely arranged single nevus cells is seen in the lowermost epidermis, especially in the basal cell layer. In many lesions, single cells are about as common as nests, recapitulating the histology of a simple lentigo. Such lesions in our practice are termed lentiginous junctional nevi (Fig. 28-5). Varying amounts of melanin granules are seen in the nevus cells. Some of the nevus cells, on staining with silver, show dendritic processes containing melanin granules, making them indistinguishable from melanocytes, but in general the degree of dendritic differentiation is markedly reduced compared to melanocytes. The nested and single melanocytes are arranged mainly at the tips and sides of rete ridges; continuous proliferation of single cells between the rete, confluence of nests, or pagetoid extension of cells into the suprabasal epidermal layers may be architectural indicators of dysplasia or evolving *in situ* melanoma.

Although nevus cells only occasionally penetrate into the upper layers of the epidermis ("pagetoid extension"), aggregates



A B

FIGURE 28-5. A: Lentiginous junctional nevus. Most examples are less than 4 mm, usually about 2 to 3 mm, in diameter. A dermal component, if present in a lentiginous nevus, lies in the center of the lesion, and the epidermal component extends beyond its shoulder. B: In the epidermis, single cells and nests of nevus are arranged near the dermal–epidermal junction near the tips and sides of elongated rete ridges (a lentiginous pattern). There is minimal or no atypia. There is no continuous proliferation of melanocytes in the suprapapillary regions of the epidermis between the rete ridges. These architectural features are repeated but exaggerated in dysplastic nevi, which in addition exhibit mild to moderate random cytologic atypia and more conspicuous stromal reactions.

of melanin granules may be seen in the stratum corneum in deeply pigmented junctional nevi. Often, the rete ridges are elongated as in lentigo simplex (see section Lentigo Simplex and Related Lesions), and single cells, as well as nests of nevus cells, are seen at the bases of the rete ridges. Not infrequently, as in lentigo simplex, the upper dermis contains an infiltrate of melanophages and mononuclear cells. These lesions that combine features of lentigo simplex and junctional nevus are exceedingly common, and, as indicated, may be termed lentiginous junctional nevi. Lesions with these features but larger than 5 mm clinically or 4 to 5 mm in a histologic section often prove to have cytologic atypia and to be dysplastic nevi (see section Dysplastic Nevus).

In children, some junctional nevi may show considerable cellularity with some degree of cellular enlargement, pleomorphism, and pagetoid cells above the basal layer. They may also often show fine, dusty melanin particles and a dense inflammatory infiltrate (92,108). Some of these lesions may represent Spitz nevi or dysplastic nevi (see respective sections). Others may correlate with a tendency for ordinary junctional nevus cells to be enlarged, or epithelioid, in younger individuals. The small size of the lesion, the sharp lateral demarcation, the lack of severe or uniform atypia and of mitoses, and the fact that in children melanomas are very rare help in the distinction from melanoma. However, if the criteria mentioned are present, the diagnosis of melanoma should be considered, even in a child.

Compound Nevus. Clinically, a compound nevus is a pigmented papule (Fig. 28-6A) or a plaque. In most nondysplastic

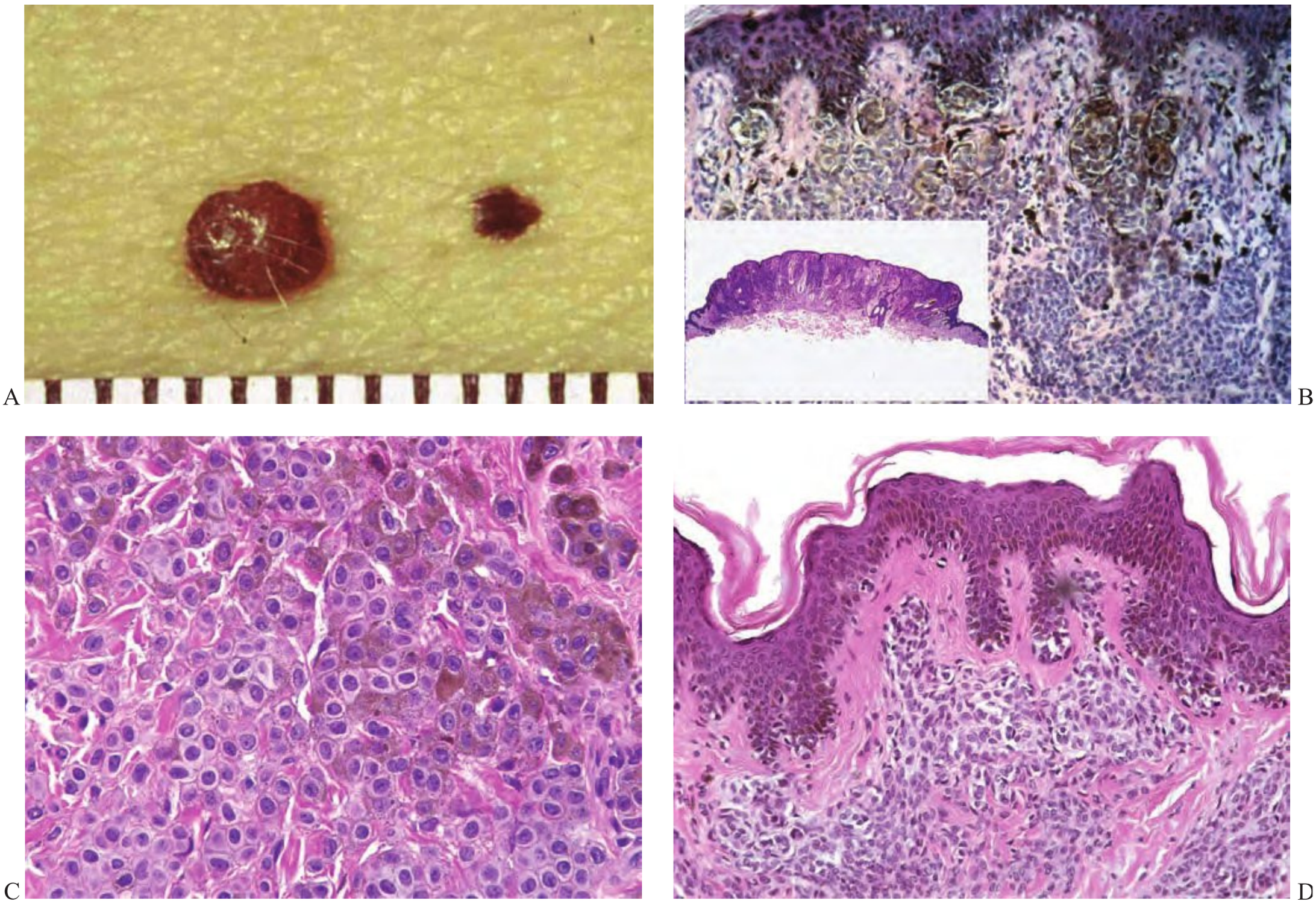


FIGURE 28-6. A: Compound nevi. Each lesion is a true papule without any adjacent macular component. The lesion on the right is a pigmented compound nevus. The lesion on the left has little pigment and clinically is a predominantly dermal nevus. B: Histologically, the lesion is a true papule without an adjacent junctional component (inset). Nests of nevus cells are present at the dermal–epidermal junction. It is believed that these nests become separated from the epidermis to lie in the dermis, piling on one another in an accretive pattern of growth and resulting in gradual elevation of the epidermis above its original position to form the papule. Pigment is present mostly in junctional and superficial dermal nevus cells. C: Dermal nevus with type A nevus cells. The type A cells have visible cytoplasm in contact with that of neighboring nevus cells. The nuclei are small, without atypia or prominent nucleoli. There are no mitoses. D: Lentiginous compound nevus. In this as in many nevi, nests are admixed with single cells in the junctional component, a lentiginous pattern. The cells in the dermis are small, lymphocyte-like type B cells. (continued)

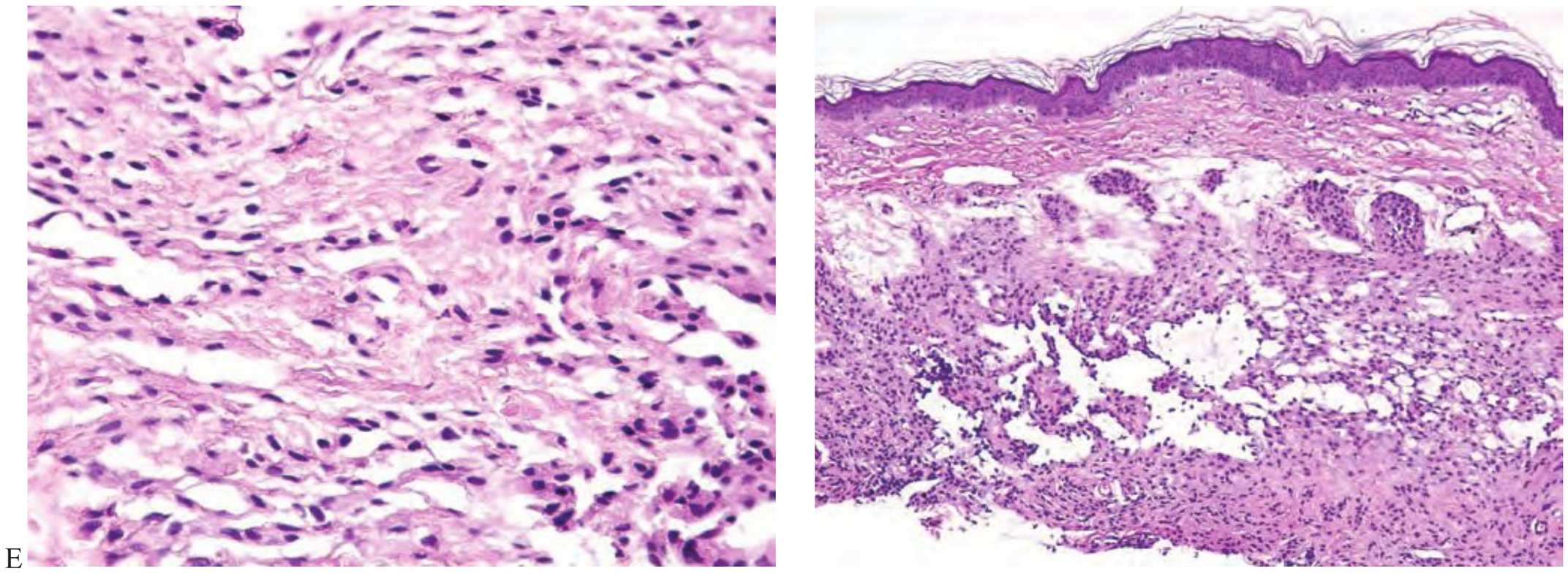


FIGURE 28-6. Continued. E: Type C dermal nevus cells at the base of a nevus. The cells at the base of a nevus tend to be spindled in shape and to have collagen between the individual cells. If they extend into the reticular dermis, they tend to disperse as individual cells among the superficial collagen fibers, a pattern that is also characteristic of Spitz nevi. F: Dermal nevus with pseudolymphatic spaces. The type B nevus cells at the top of the lesion have small nuclei and scant cytoplasm, reminiscent of lymphocytes. The spaces are a common artifact in dermal or compound nevi. They may simulate lymphatic invasion of a melanoma but are completely benign. The cells at the base of the lesion are predominantly type C cells. G: Neurotized dermal nevus cells at the base of a dermal nevus. The structures at the base of a neurotized dermal nevus may be reminiscent of nerve fibers or neural organs such as Wagner-Meissner corpuscles.

compound nevi, there is no adjacent macular component. Histologically, a compound nevus possesses features of both a junctional and an intradermal nevus. Nevus cell nests are present in the epidermis, as well as appearing to "drop off" from the epidermis into the superficial dermis and, in many lesions, the reticular dermis (Fig. 28-6B). This time-honored theory of *abtropfung* or dropping off of nevus cells proposed by Unna has been challenged by the finding that junctional nevi are at least as common in adults as in children (109). Nevus cells in the upper, middle, and lower dermis may present characteristic morphologic variations called types A, B, and C, respectively (42,110). Usually, the type A nevus cells in the upper dermis are round to cuboidal, show abundant cytoplasm containing varying amounts of melanin granules, and tend to form nests. Type A cells with especially abundant cytoplasm, as may occur in children and young adults, may be termed epithelioid cells (Fig. 28-6C). Melanophages are occasionally seen in the surrounding stroma. The cells in the middermis usually are type B cells; they are distinctly smaller than the type A cells, display less cytoplasm and less melanin, and generally lie in well-defined aggregates or cords. They may to some extent resemble lymphoid cells (Fig. 28-6D). Type C nevus cells in the lower dermis tend to resemble fibroblasts or Schwann cells because they are usually elongated and possess a spindle-shaped nucleus. They often lie in strands and only rarely contain melanin (Fig. 28-6E). Occasionally they form aggregates that resemble Meissner corpuscles. Occasional nevi show abnormal stratification within the deeper dermis of otherwise benign type A nevus cells, resulting in the designation of inverted type A nevus.

The decrease in cell size, melanization, and progression from nests to cords to more neuroid spindle cells with dermal descent seen in nevi is often referred to as maturation and is regarded as evidence of benignity because the size of the cells in a melanoma usually does not decrease with depth. The process of nevus cell maturation has alternatively been regarded as one of senescence or atrophy (111), perhaps driven by the tumor suppressor p16, which is activated in response to the effects of an activated oncogene such as BRAF or NRAS in a phenomenon termed oncogene-induced senescence (112). If dermal nevus cells are confined to the papillary dermis, they often retain a discrete or "pushing" border with the stroma. However, nevus cells that enter the reticular dermis tend to disperse among collagen fiber bundles as single cells or attenuated single

files of cells. This pattern of infiltration of the dermis differs from that in most melanomas, in which groups of cells tend to dissect and displace the collagen bundles in a more expansive pattern (113). Lesions in which nevus cells extend into the lower reticular dermis and the subcutaneous fat or are located within nerves, hair follicles, sweat ducts, and sebaceous glands may be termed congenital pattern nevi because they share morphologic features with congenital nevi but are not necessarily present at birth (114) (see section Congenital Melanocytic Nevus).

Intradermal Nevus. Intradermal nevi show essentially no junctional activity. The upper dermis contains nests and cords of nevus cells. Multinucleated nevus cells may be seen in which small nuclei lie either in a rosette-like arrangement or close together in the center of the cell. These nevus giant cells differ significantly in appearance from the irregularly and even bizarrely shaped giant cells that are seen frequently in Spitz nevus and occasionally also in melanoma. As a result of shrinkage during tissue processing, clefts may form between some nests of nevus cells and the surrounding epidermis, as well as stroma, the latter leaving a defect that simulates a lymphatic space and thus mimics lymphatic invasion (Fig. 28-6F) (115).

Whereas the nevus cell nests located in the upper dermis often contain a moderate amount of melanin (particularly type A cells), the type B and C nevus cells in the midportion and the lower dermis rarely contain melanin. Type C cells appear spindle shaped, are arranged in bundles, and are embedded in collagenous fibers having a loose, pale, wavy appearance similar to that of the fibers in a neurofibroma, resulting in a "neurotized nevus." Such formations have been referred to as neuroid tubes. In other areas, the nevus cells lie within concentrically arranged, loosely layered filamentous tissue, forming so-called nevic corpuscles that resemble Meissner's tactile bodies (Fig. 28-6G). Neurotized nevus cells express the marker S100A6 protein, a form of S100 found in Schwann cells, supporting the hypothesis that maturation in these lesions recapitulates some features of Schwann cell differentiation (116).

Occasional intradermal nevi are devoid of nevus cell nests in the upper dermis and contain only spindle-shaped nevus cells embedded in abundant, loosely arranged collagenous tissue. These nevi may be referred to as neural nevi. The differentiation from a solitary neurofibroma may be difficult in routinely stained sections, but distinction might be possible with an immunohistochemical technique using myelin basic protein, which is positive only in neurofibroma (117) (see Histogenesis). Neurofibromas also tend to contain small nerve twigs and axons that can be highlighted with glial fibrillary acidic protein staining (118), a feature not typical of neurotized nevi.

Some intradermal and, less commonly, compound nevi show hyperkeratosis and papillomatosis, which may be associated with a lacelike, downward growth of epidermal strands and with horn cysts. Such nevi resemble seborrheic keratoses in their epidermal architecture. In other instances, large hair follicles are observed. Rupture of a large hair follicle may manifest itself clinically in an increase in the size of the nevus associated with an inflammatory reaction, leading to clinical suspicion of a melanoma. Histologic examination in such instances shows a partially destroyed epidermal follicular lining with a pronounced inflammatory infiltrate containing foreign-body giant cells as a reaction to the presence of keratin in the dermis. Occasionally, intradermal nevi contain scattered large fat cells within the aggregates of nevus cells. This is likely to be a regressive phenomenon in which fat cells replace involuting nevus cells (119) or, alternatively, (and more likely) true adipocyte metaplasia within the stroma of the nevus.

Some intradermal nevi, including variants of spindle and epithelioid cell nevi, induce marked deposition of coarse, sometimes hyalinized collagen. Such nevi are described as sclerosing variants. This change occasionally may confound diagnosis but is not of biological significance.

In occasional otherwise typical dermal nevi (or in the dermal component of compound nevi), rare mitoses are found in the dermis. This phenomenon has been described in children (108) and in association with pregnancy (120). If there are no other indicators of malignancy, we report these cases as "nevi with mitoses" and generally recommend complete excision. The possibility of nevoid melanoma (see later section) should be seriously considered in such lesions (121).

Pathogenesis of Acquired Melanocytic Nevi

For many years, Masson's theory of the dual origin of nevus cells was widely accepted (42). He believed that the nevus cells in the upper dermis developed from epidermal melanocytes, whereas the nevus cells in the lower dermis developed from Schwann cells, as suggested by the frequent presence of nerve-like structures in the latter. The fact that both melanocytes and Schwann cells are derived from the neural crest seemed to support Masson's view, as did the presence of a nonspecific cholinesterase reaction in both deep nevus cells and Schwann cells and the absence of melanin in the deep nevus cells (122). However, in favor of a melanocytic origin of these deep dermal nevus cells was the presence of melanosomes with dopa-oxidase activity even in deeply situated nevus cells that had a neuroid appearance on light microscopy (123). An electron microscopic examination of neuroid structures in nevi revealed that these nevic corpuscles contained no Schwann cells or axons but were instead composed exclusively of cells that contain premelanosome-like dense bodies in their perikaryon (124). Furthermore, myelin basic protein has been found to be regularly present by immunoperoxidase in Schwann cells and absent in all types of melanocytic nevi (117). In addition, melanocyte-specific markers like Melan-A/MART-1, HMB-45, tyrosinase, and others are often positive in nevi but typically absent in neural cells and neurofibromas (125).

Another important point in favor of a single origin of the nevus cell is to be found in the life cycle of nevi. Although there are exceptions, most nevi appear in childhood, adolescence, and early adulthood, and, with advancing age, there is a progressive decrease in the number of nevi (126). The evolution and involution of nevi correlate with their histologic appearance. Junctional proliferation of nevus cells is present in almost every

nevus in children but decreases with age. Intradermal nevi, by contrast, are most unusual in the first decade of life, and their proportion increases progressively with age. The incidence of fibrosis, fatty infiltration/metaplasia, and neuroid changes increases with age. Thus, the formation of cylindrical neuroid structures represents the end stage of differentiation and not a source of origin of intradermal nevi (126,127).

Concerning the relationship between epidermal melanocytes and nevus cells, some authors believe that these two types of cells have a different embryologic genesis, with the nevus cell originating from a neural crest precursor cell referred to as a nevoblast (128). Most authors regard the two cell types as identical, however (129). It would seem that the morphologic features by which nevus cells differ from melanocytes, such as the absence of dendrites as seen by light microscopy, their arrangement in cell nests, their larger size, and their tendency to retain pigment, are secondary adjustments of the cells. Electron microscopy has shown that the fine structure of nevus cells is comparable to that of epidermal melanocytes (130) (EM 46, 47). Cultured nevus cells, whether derived from congenital or acquired lesions, have been found to be highly dendritic, as are epidermal melanocytes (129). In conclusion, it seems established that nevus cells differ from Schwann cells and are benign neoplastic variants of melanocytes.

The molecular pathology of nevi is beginning to be understood. In a recent study of the BRAF oncogene, which had previously been found to be mutated in a high percentage of metastatic melanomas (131), mutations resulting in the V599E amino acid substitution were found in 68% of melanoma metastases, 80% of primary melanomas, and, unexpectedly, 82% of nevi (132). Activating mutations of the oncogene NRAS (mutually exclusive with BRAF mutations) have also been described in melanoma-associated nevi and in congenital nevi (133–136). These data suggest that mutational activation of the RAS/RAF/MAPK mitogenic pathway in nevi is a critical step in the initiation of melanocytic neoplasia but alone is insufficient for melanoma tumorigenesis (132). High levels of the tumor suppressor gene product p16INK4 in benign nevi may represent the mechanism whereby the cell cycle remains regulated in nevi, even in the presence of activating oncogene mutations (112,137–139).

Balloon Cell Nevus

Balloon cell nevi are histologic curiosities that possess no clinical features by which they can be differentiated from other nevi. They are quite rare.

Histopathology. Balloon cells may be seen within the epidermis singly or in groups or may be absent from the epidermis. In the dermis, they lie arranged in lobules of varying size, often with an admixture of ordinary nevus cells and often with transitional forms between the ordinary and ballooned nevus cells (Fig. 28-7). The balloon cells may be multinucleated and are considerably larger than ordinary nevus cells. Their nuclei are small, round, and usually centrally placed. Their cytoplasm appears empty, finely granular, or vacuolated, often with a few small melanin granules. There may be melanophages that are solidly packed with pigment. Stains for lipids, glycogen, and acid or neutral mucopolysaccharides are negative in the balloon cells. Electron microscopic examination reveals in balloon cells numerous large vacuoles formed by enlargement and coalescence of degenerating melanosomes (140,141). Balloon cell nevus is differentiated from balloon cell melanoma by the usual criteria. The large adipocytes present in some intradermal nevi as a result of fatty infiltration or stromal metaplasia differ from balloon cells by routine histology by having a flattened nucleus located at the periphery of the cell. In the differentiation from clear cell hidradenoma and other clear cell tumors, the absence of periodic acid-Schiff–positive glycogen and keratin in balloon cell nevus might be helpful; balloon nevus cells also stain for S100 protein, and although eccrine neoplasms (and adipocytes) may also express this marker, they will also usually be positive for Melan-A/MART-1 and negative for keratin markers.

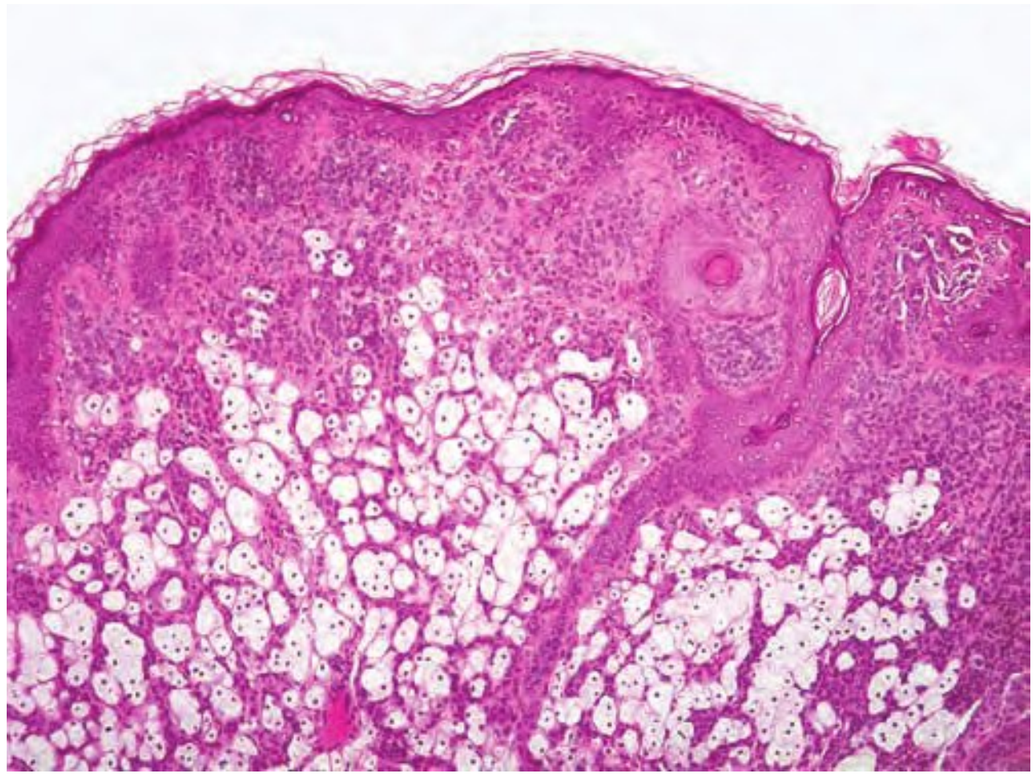


FIGURE 28-7. Balloon cell nevus. Large cells with pale cytoplasm are admixed with mature nevus cells. There is no high-grade atypia or mitotic activity.

Nevi of Special Sites

There is apparent variation in the morphology of common nevi by site. In a study of Australian schoolchildren, gender differences in nevus density on the back and lower limbs were similar to gender differences for melanoma, with back lesions favoring males and lower-extremity lesions favoring females. Small nevi (2 to 4 mm) were most dense on the arms, whereas large nevi (5 mm or greater) were most dense on the posterior trunk, where they were related to age, male sex, and freckling. The findings were considered to support the hypothesis of site-specific differences in nevus proliferative potential (142). Nevi in certain locations may exhibit features that are unusual in the vast majority of common nevi on the trunk, limbs, or face and scalp. These special-site nevi have been best defined in acral locations (palmar, plantar, and subungual nevi) and in genital

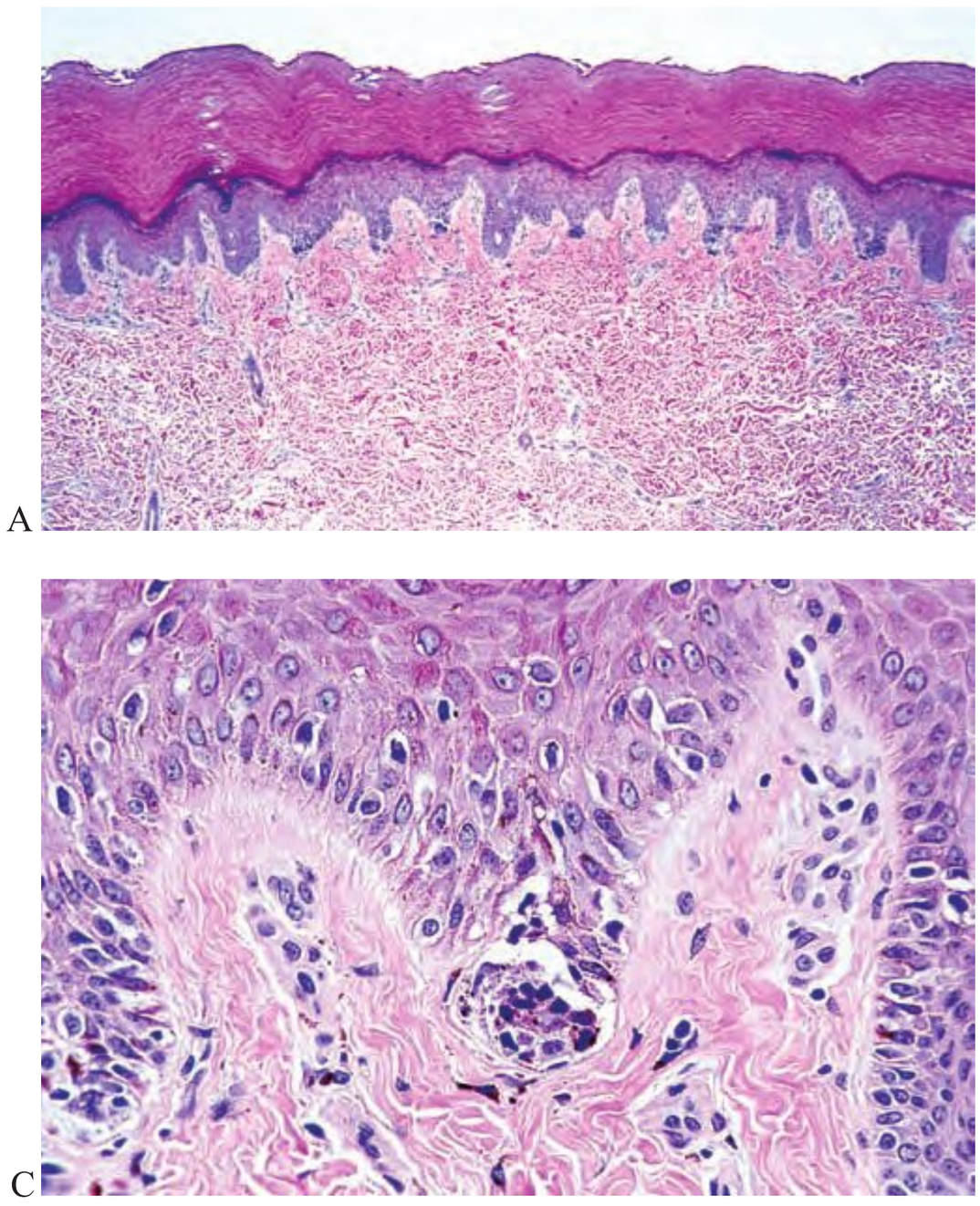
skin. Nevi in skin flexural areas (ear lobe, axilla, umbilicus, inguinal creases, pubis, scrotum, and perianal area) may also show unusual features, similar to those to be described for acral nevi (143). Recently, the skin of the ears, the skin of the breast, and the skin of the scalp in adolescents have been added to this seemingly ever-expanding list of "special" sites (144–147). In general, the "special" features of the nevi are seen in only a minority of the nevi from these sites; the other nevi are quite unremarkable.

Nevi of Acral Skin

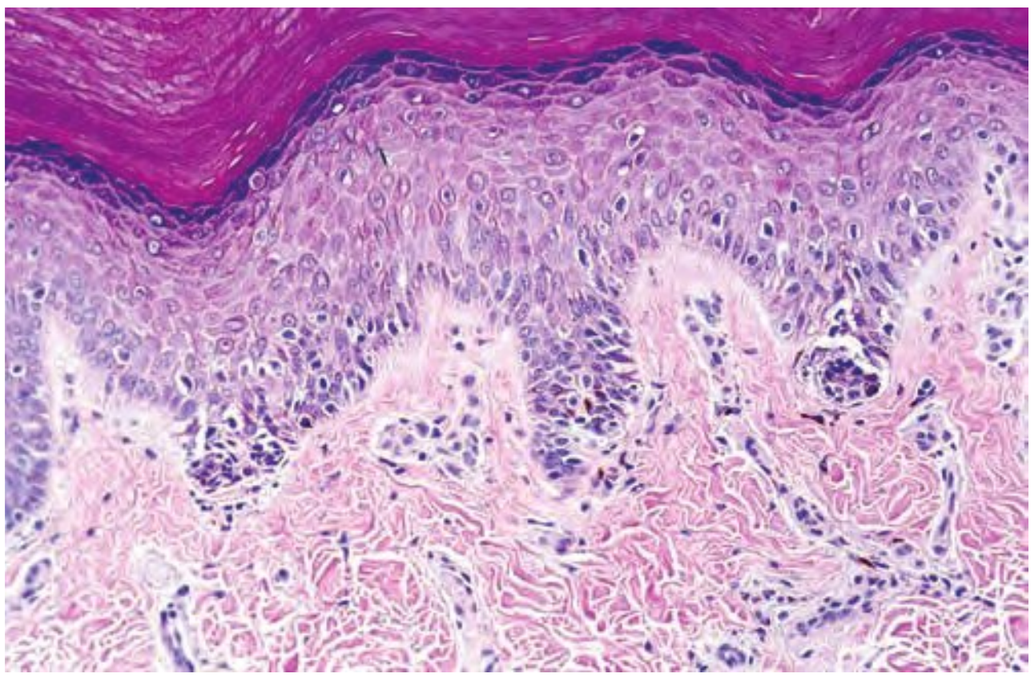
Melanocytic nevi are present on the skin of the palms or soles in as many as 4% to 9% of the population (148). Clinically, they are usually small, symmetric, well-circumscribed brown macules with a tendency to dark ridging along dermoglyphics that can be clinically striking and may impart a seemingly irregular border. They are usually stable, and are more often junctional than are nevi of the trunk.

Histopathology. Acral nevi tend to be more cellular than most common nevi, and the nevus cells may be arranged in predominantly lentiginous rather than nested patterns in the epidermis. Recently, pagetoid proliferation ("pagetoid melanocytosis") of lesional nevus cells in the epidermis above the basal layer was described in benign acral nevi (149–152). These features may perhaps account for recommendations in the older literature to remove acral nevi because of suspicion of melanoma. However, there is no evidence that these lesions, when devoid of true dysplasia, are common precursors or risk markers for acral melanomas.

Acral nevi may simulate and must be differentiated from melanoma, and this may be difficult especially in small biopsies. Clemente and colleagues studied a series of acral nevi and identified a subset that they termed acral-lentiginous nevi (150). The distinctive features of these nevi compared to other acral nonlentiginous nevi included several features also seen in acral-lentiginous melanomas: poor lateral circumscription, elongation of rete ridges, continuous junctional proliferation of melanocytes, the presence of scattered melanocytes within the upper epidermis, and the presence of junctional melanocytes with abundant pale cytoplasm and round to oval, sometimes hyperchromatic nuclei with prominent nucleoli. In lentiginous compound acral nevi, the nevus cells in the dermis, unlike melanoma cells, mature to the lesional base. There is no high-grade uniform cytologic atypia, no extensive and high-level pagetoid melanocytosis in the epidermis, and no mitoses (Fig. 28-8). There may be patchy lymphocytes and occasional melanophages in the dermis. Some of these features may suggest dysplastic nevus. However, the rete ridge pattern of keratinocytes in most acral nevi does not show the uniform elongation with occasional accentuation of anastomosing rete that characterizes dysplastic nevi, the complete array of stromal changes of dysplastic nevi are not observed in most acral nevi, and atypia of melanocytes, as a rule, is minimal or absent. In case of doubt, it may be appropriate to evaluate the patient's other nevi, especially if there is a family or personal history of melanoma. An acral-lentiginous lesion that extends to



A



B

C

FIGURE 28-8. A: Acral-lentiginous nevus. The lesion is small, quite well circumscribed, and entirely contained within the biopsy specimen. B: Acral-lentiginous nevus. Nests of nevoid to small epithelioid melanocytes predominate near the dermal—epidermal junction. They tend to be small, evenly spaced, and discreet. C: Acral-lentiginous nevus. Although a few lesional cells may be present above the junction in a pagetoid pattern, there is no severe uniform atypia or mitotic activity, and there is no continuous proliferation of single cells between the nests.

specimen borders should be evaluated carefully, and clinicopathologic correlation should be obtained to ensure that the specimen does not represent the periphery of a larger lesion. In such cases it may be judicious to recommend complete excision, to rule out additional pathology, and to preclude persistence or recurrence of the lesion. Finally, because a nevus is acral does not preclude the unusual possibility that it is also dysplastic, but this diagnosis must rely on the presence of cytologic and stromal criteria for dysplastic nevus in addition to those commonly encountered in nevi of acral sites.

Melanonychia Striata (Longitudinal Melanonychia)

Melanonychia striata refers to a pigmented band extending in the long axis of the nail. Such bands are common in blacks and Asians and therefore regarded as normal (153,154). However, the sudden appearance of melanonychia striata is cause for concern, particularly in whites, requiring a punch biopsy of the nail matrix (155). An exception is the melanonychia striata seen in the Laugier-Hunziker syndrome, which may affect one, several, or all fingernails in association with pigmented macules of the lips or the buccal mucosa. This type of melanonychia is always benign (153,156).

For carrying out the biopsy, longitudinal bilateral releasing incisions are made along the medial and lateral sides of the posterior nail fold. Next, the entire posterior nail fold is reflected proximally to expose and make visible the very end of the pigmented streak, which is usually within the matrix of the nail. Then the biopsy specimen is taken with a 3- or 4-mm punch through the nail plate and matrix down to the phalangeal bone (157,158).

Histopathology. Histologic examination in most instances shows merely basal cell layer hyperpigmentation without an obvious increase in the number of melanocytes. Such lesions have been termed melanotic macules (159) or nail matrix activation, referring to an increased production of melanin with a normal number of melanocytes (160). In a study of 18 cases, 10 were melanotic macules, 1 case was melanoma *in situ*, another showed keratinocytic atypia, and 3 were subungual hemorrhages (161). In other cases, a junctional nevus, a compound nevus of acral type as described earlier, or an acral-lentiginous melanoma, either *in situ* or invasive, may be found. The junctional or compound nevi tend to be of the lentiginous acral nevus pattern described earlier. Longitudinal melanonychia may also be associated with pigmented Bowen's disease (155). Longitudinal melanonychia in children is almost always benign: In a study of 40 cases in children younger than the age of 16 years, the histologic diagnosis was nevus in 19 cases (junctional in 17 cases and compound in 2), lentigo in 12 cases, and simple hyperpigmentation ("functional melanonychia") in 9. None of the patients in this series had melanoma (162). Subungual melanomas, although very rare, do occasionally occur in children (163).

Nevus of Genital Skin

Some clinically unremarkable nevi located on or near genital skin may present with histologic features that simulate some aspects of melanomas. The lesions have no clinical significance except the possibility of diagnostic error. They have been termed atypical melanocytic nevi of the genital type and are most often seen on the vulva of young (premenopausal) women, but they may also been seen on perineal skin (164–166). Similar lesions also occur uncommonly on the male genitalia (167). The lesions are often removed incidentally. They are typically symmetric papular lesions, usually less than 1 cm in diameter, and uniformly pigmented with discrete, well-circumscribed borders. The atypical features appear to represent a histologic curiosity seen in a minority of vulvar nevi. In a comparative histologic study of vulvar and common nevi most of the vulvar lesions were unremarkable (168). Vulvar nevi themselves are quite uncommon; in patients in a gynecology practice, the prevalence was only 2.3% (169). An interesting variant pattern of nevi has been described in association with lichen sclerosus et atrophicus, most commonly on skin of the vulva, perineum, or rarely elsewhere. These nevi had features in common with persistent ("recurrent") melanocytic nevi and can mimic malignant melanoma. This activated melanocytic phenotype seen in lichen sclerosus–associated melanocytic nevi suggests a stromal-induced change (165). The clinical differential diagnosis for atypical genital nevi also includes early genital lentigines, as described previously.

Histopathology. The scanning magnification impression is typically that of a small, well-circumscribed papular lesion composed of nevus cells arranged in clusters in the papillary dermis and arranged mainly in nests in the epidermis, where the cells do not extend beyond the shoulder of the dermal component, as typically occurs in compound dysplastic nevi (Fig. 28-9). The nevus cells may be large, with prominent nucleoli and abundant cytoplasm containing finely divided ("muddy") melanin pigment. The epidermal nests may vary considerably in size and shape, tending to become confluent. The nests tend to be variable in size, shape, and position, originating from the sides as well as the tips of rete, and often oriented parallel to the surface. The melanocytes within the nests are often dyshesive. Single cells and nests of nevus cells may occasionally be seen within the epithelia of skin adnexa. The epidermis occasionally is irregularly thickened, resulting in an asymmetric silhouette. Some of the features seen in atypical vulvar nevi may arouse a suspicion of melanoma. However, the lesions are comparatively small and well circumscribed, without significant junctional proliferation of atypical melanocytes beyond the major dermal component, as is seen in most mucosal melanomas. Moreover, there is little or no pagetoid spread of single or nested melanocytes into the epidermis, there is no necrosis and usually no ulcer, and, of importance, there is no mitotic activity in the dermis (168). Stromal patterns more characteristic of melanoma (diffuse fibroplasia) or dysplasia (concentric fibroplasia) are generally lacking in these lesions (166). The diagnosis of melanoma in vulvar skin should be made with caution (but is sometimes unavoidable) in a premenopausal woman. Occasional vulvar nevi do exhibit high-grade cytologic atypia, however, and although the biological behavior of such lesions in

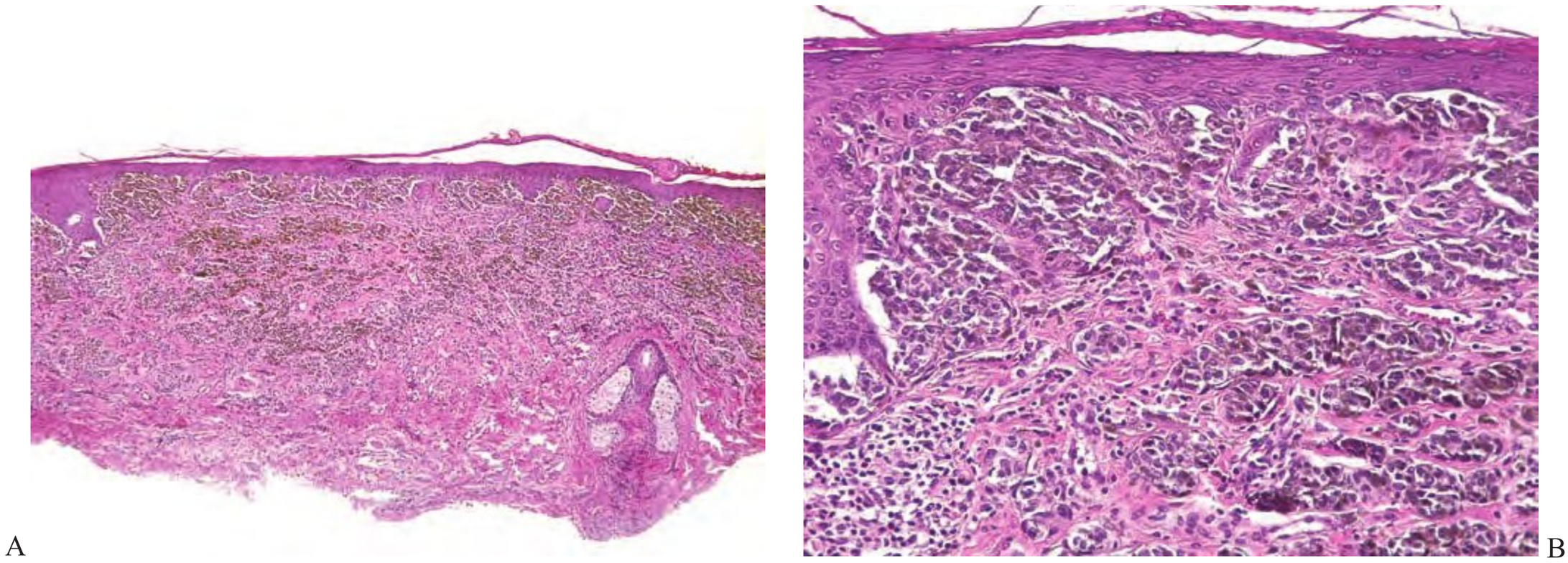


FIGURE 28-9. A: Nevus of genital skin. Nevi on genital skin may exhibit atypical features at high power but are usually relatively small and symmetric and thus benign in their appearance at scanning magnification and also clinically. B: Atypical features in genital nevi may include nests that tend to be large and confluent and to vary a good deal in size and shape and cells that tend to be large, with macronucleoli, and dyshesive from one another. Mitoses are rare or absent, and there is no adjacent in situ or microinvasive radial-growth-phase component.

young to middle-aged women has not been fully studied, it is prudent to excise such lesions modestly to prevent local persistence or recurrence in scar tissue.

In an apparently unrelated phenomenon, atypical nevi have been described in association with lichen sclerosus et atrophicus. These lesions resembled persistent or recurrent melanocytic nevi (so-called pseudomelanoma; see later section) (165).

Nevi of Flexural Sites

Based on histologic findings, it has been suggested that nevi in flexural sites may differ histologically from those at other sites, in general resembling the appearances of nevi of genital skin and potentially simulating melanoma. In a study of 40 melanocytic nevi of flexural sites (axilla, umbilicus, inguinal creases, pubis, scrotum, and perianal area), 22 of them had a nested and dyshesive pattern similar to the genital pattern nevi. This pattern was characterized by the confluence of enlarged nests with variation in size, shape, and position at the dermoepidermal junction and by the diminished cohesion of melanocytes. Nevi of breast skin may show similar features. These changes in flexural nevi, like those in other "special sites," should not be overinterpreted as indicative of melanoma (143); by the same token, authentic dysplastic nevi and melanomas may occur in these sites and should not be underdiagnosed (170).

Spitz Nevus

The Spitz nevus, named after Sophie Spitz, who first described it in 1948 (171), is known also as *benign juvenile melanoma* (a term that should be discouraged) and *spindle* and/or *epithelioid cell nevus*. The lesion was originally believed to occur largely in children, but it is now well recognized in young to early middle-aged adults (172,173). Rarely, it is present at birth (174). Because of a degree of unpredictability in the behavior of a subset of cases, particularly when lesions occur in adults, the term "Spitz tumor" has been suggested as preferable to "nevus," except in the most typical cases (175,176).

The lesion usually is solitary and is encountered most commonly on the lower extremities and face (177). In a recent comparative study, Spitz nevi were found to predominate on the thighs in persons younger than 40 years of age, whereas, in contrast, on the trunk melanomas were more frequent in persons 40 years of age or older (178). In most instances, the lesion consists of a dome-shaped, hairless, small pink nodule. Most Spitz nevi are small: in 95% of the patients, the size of the tumor is less than 1 cm, and in 75% it is 6 mm or less (179). The color is usually pink because of a scarcity of melanin and in some lesions associated vascularization of the stroma, and it is then often diagnosed clinically as a pyogenic granuloma, an angioma, or a dermal nevus. However, it may be tan and, in some cases, brown or even black. Ulceration is seen only rarely— in our experience, most commonly in lesions from young children. After an initial period of growth, most Spitz nevi are stable.

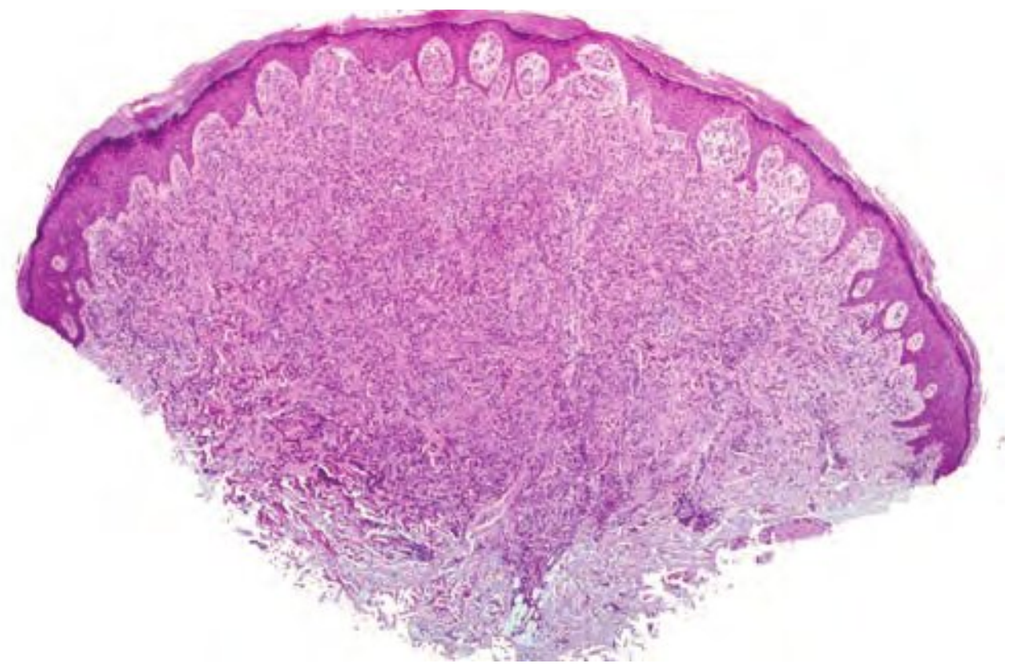
In rare instances, multiple tumors are encountered. These may be either agminated (grouped) in one area (180) or widely disseminated (181) (Fig. 28-10A). In a case of *agminated Spitz nevi*, a mosaic pattern of chromosomal translocation was demonstrated in lesional fibroblasts, suggesting a local event in embryogenesis (180).

Histopathology

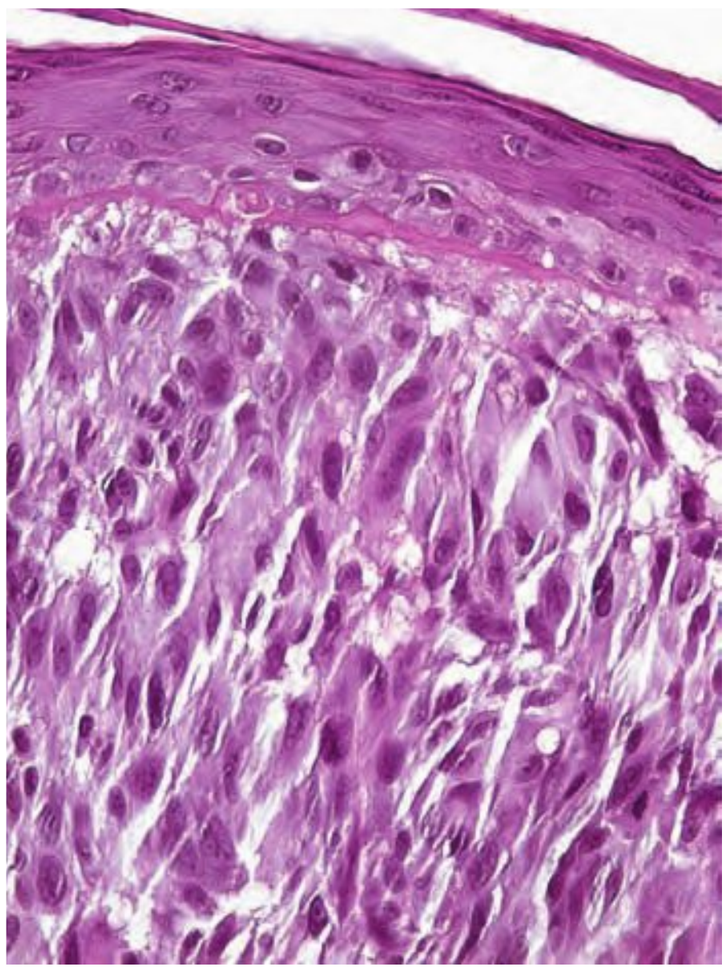
Spitz nevi/tumors are usually compound, but they can be intradermal or entirely junctional. Ackerman's term "nevus of



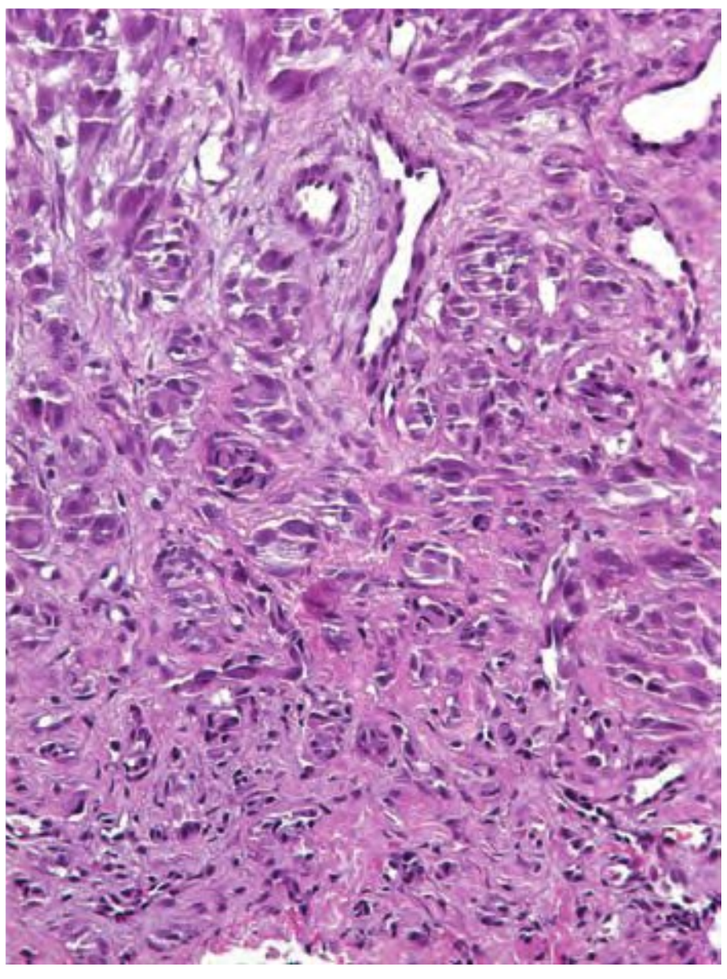
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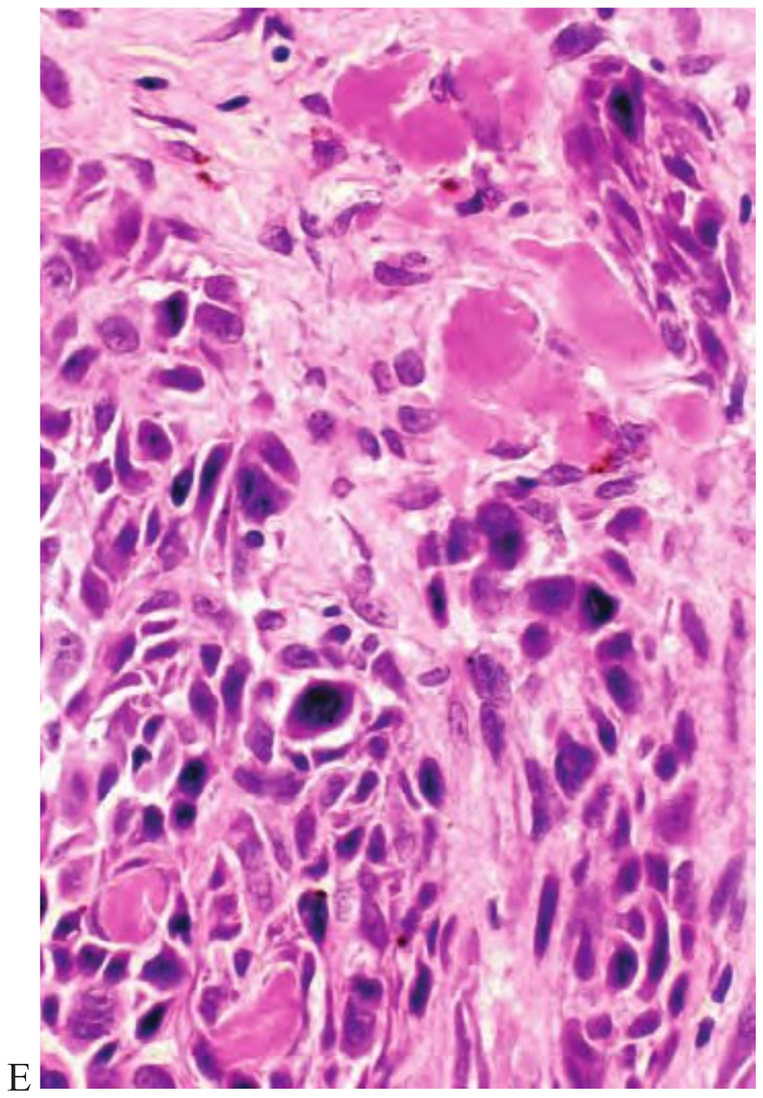


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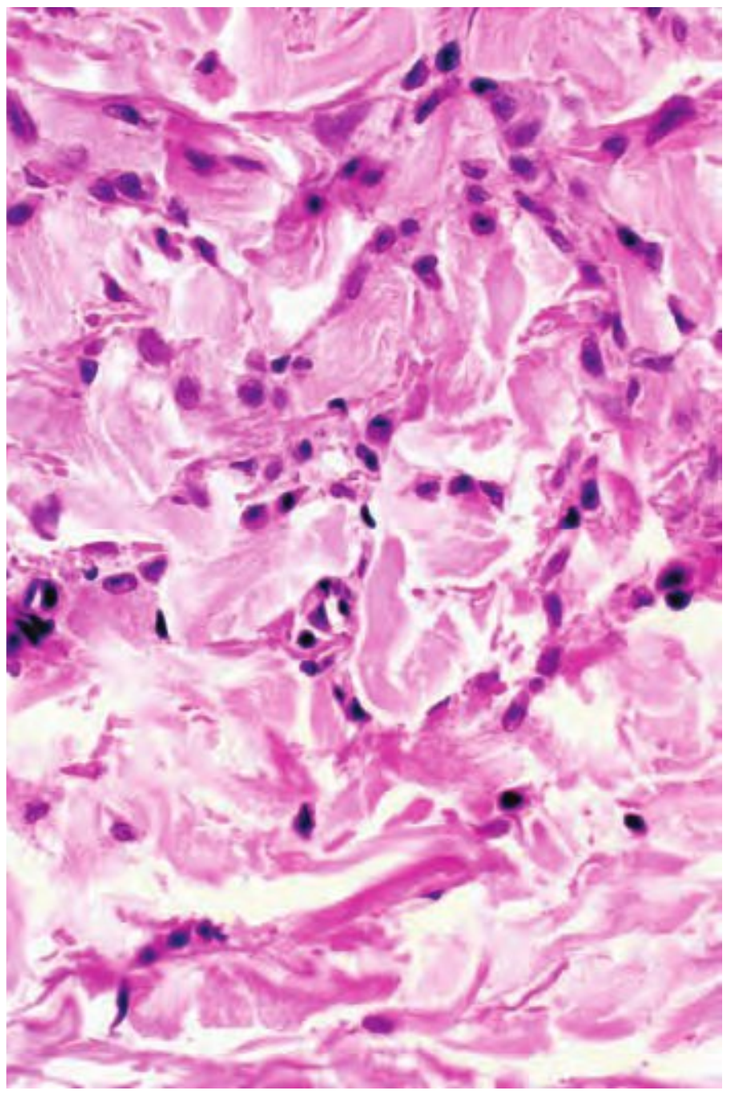


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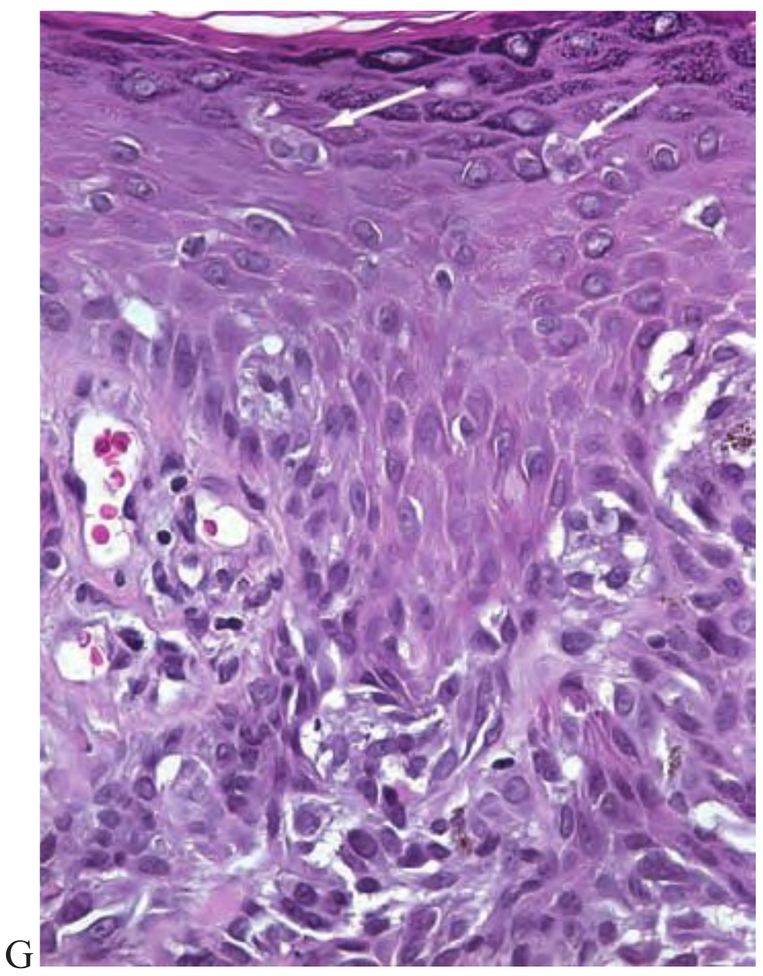
FIGURE 28-10. A: Agminated Spitz nevi. Most Spitz nevi are single lesions. In this example of agminated, or grouped, Spitz nevi, each individual lesion is a characteristic Spitz nevus—relatively small, symmetric, well-circumscribed tan papules. B: Most Spitz nevi are small, circumscribed, symmetric papules at scanning magnification and clinically. This lesion is somewhat larger than most examples. C: Spitz nevi are defined by the presence of large cells, with abundant amphophilic cytoplasm, which may be spindled or polygonal in shape (large spindle and/or epithelioid melanocytes). The nuclei in a given Spitz nevus are more homogeneous than in most melanomas, usually large but with open chromatin and smooth nuclear membranes, and with prominent nucleoli. D: Maturation from larger cells near the surface to smaller cells at the base is an important feature of Spitz nevi. (continued)



E



F



G

FIGURE 28-10. Continued. E: Spitz nevus with globoid eosinophilic bodies (Kamino bodies). Although not pathognomonic, these structures are highly characteristic of Spitz nevi. F: At the base of a Spitz nevus, the lesional cells become smaller and "dispersed" among the reticular dermis collagen fibers. This is the same lesion as in panels D & E. Note the diminution in size (maturation) of the lesional cells at the base. G: Pagetoid extension of some cells of a Spitz nevus into the epidermis, as seen here, is not diagnostic of a melanoma if other attributes of melanoma are not observed. This pagetoid melanocytosis is not uncommon at least focally in lesions of young children.

large spindle and/or epithelioid cells" reflects the characteristic cytologic appearances that provide the essential definition for the lesion (173). Because of the large size of the lesional cells often with considerable nuclear and cytoplasmic pleomorphism and the frequent presence of an inflammatory infiltrate, the histologic picture often resembles that of a nodular melanoma. There is no doubt that, before the recognition of Spitz nevi as an entity, many cases were diagnosed as melanoma. Even today, differentiation from a melanoma can often be very difficult and occasionally even impossible. Features that aid in the distinction may be summarized as architectural pattern and cytologic features (Fig. 28-10A–G).

In terms of their architectural pattern, Spitz nevi resemble common nevi. They are usually compound, but, as stated earlier, they can be intradermal or entirely junctional. They are small, symmetric, and well circumscribed. It is somewhat unusual for the intraepidermal component to extend beyond the dermal component, and such a finding should prompt consideration of associated dysplasia or melanoma (182). The epidermal component is arranged in nests often formed by spindle cells that tend to be oriented vertically and, though large, do not show significant variation in size and shape or tend to become confluent. The cytoarchitecture or spindle cells aligned in parallel within the junctional nests is character-

istic and forms the basis for the descriptive term by which the nests are considered to be "raining down." In Spitz nevi with junctional activity, there are often artifactual semilunar clefts separating nests of nevus cells at the epidermal–dermal junction from adjacent and overlying epidermal cells. Not so commonly seen in melanoma, this feature represents a useful diagnostic feature (182).

Although there may be diffuse junctional activity, permeation of the epidermis by tumor cells (pagetoid melanocytosis) is relatively slight. If present, it usually consists of single nevus cells or small groups of cells and is generally limited to the lower half of the epidermis (Fig. 28-10G) (173). In a few Spitz nevi, however, pagetoid migration of lesional cells into the epidermis may be quite marked, especially in young children. These pagetoid Spitz nevi appear clinically as a small (less than 0.4 cm) pigmented macule in young patients. Features favoring nevus over melanoma include small size, circumscription, symmetry, even distribution of cells, and lack of marked cytologic atypia (183). Pagetoid involvement of the suprabasal epidermis is not a common feature of Spitz nevi in adults; in such a case the diagnosis of melanoma should be considered (184). Occasionally, nests of lesional cells are seen in transit through the epidermis, described as transepidermal elimination of nevus cells (185,186).

The epidermis involved by Spitz nevi is often hyperplasic, with elongated rete ridges. Occasionally, this hyperplasia is sufficiently florid to be termed pseudoepitheliomatous, representing a possible source of confusion with squamous cell carcinoma, especially in a superficial biopsy (187). However, the epidermis may be thinned and even ulcerated, especially in very young children. A pattern termed consumption of the epidermis, defined as "thinning of the epidermis with attenuation of the basal and suprabasal layers and loss of rete ridges in areas of direct contact with neoplastic melanocytes," has been suggested as an additional criterion for differentiating melanoma from nevi. This feature is seen in many melanomas but is absent in most Spitz tumors (188). Found in fewer than half of the patients, diffuse edema, stromal hyalinization, and telangiectasia in the papillary dermis, if present, are of slight diagnostic importance. The edema may cause a loose arrangement of the nevus cell nests (182).

Important cytologic features of Spitz nevi include especially the presence of large spindle cells and epithelioid cells (Fig. 28-10C). Spindle cells or epithelioid cells may predominate, or the two types of cells may be intermingled ("large spindle and/or epithelioid cells") (173). Apart from the shape of their cell bodies, the spindle cells and the epithelioid cells in any given Spitz nevus resemble one another in nuclear and in cytoplasmic consistency, suggesting that they may represent dimorphic expression of a single cell type. The cells are large, with abundant amphophilic cytoplasm that may contain scant, finely divided melanin pigment, although in most of the cells, pigment is typically absent. The nuclei are large, with pale, delicate, and evenly dispersed chromatin, regular, smooth nuclear membranes, and prominent eosinophilic or amphophilic nucleoli. The size of the lesional cells, more than any other feature, sets the Spitz nevus apart from the common nevus (189) and also from most melanomas. Bizarre giant cells may be seen in both melanoma and Spitz nevi, the difference being that, in the latter, they usually have regular nuclei of similar size, whereas in melanoma the nuclei are usually more pleomorphic. Mitoses are absent in about half of the cases. This is helpful in ruling out melanoma in these lesions. Usually, there are only a few mitoses, but occasionally, they are quite numerous in the epidermal compartment. A dermal mitotic rate of greater than two mitoses per square millimeter, abnormal mitoses, or mitoses close to the base of the dermal component (within the lower half of the dermal component) are unusual in Spitz nevi (190) and may warrant a diagnosis of melanoma or a descriptive diagnosis of melanocytic tumor of uncertain potential. Atypical mitoses are uncommon, and if they are found, the lesion should be interpreted with great caution (182,190). The complete absence of mitoses in 50% of Spitz nevi is very helpful in ruling out melanoma in these cases.

Of special importance is maturation of the cells with increasing depth, so that they become smaller and look more like the cells of a common nevus (Fig. 28-10D–F) (182). Also important is the uniformity of the lesional cells from one side of the lesion to the other: At any given level of the lesion from the epidermis to its base, the lesional cells look the same. Although large superficially, the cells at the base of most Spitz nevi are small, and they tend to disperse as single cells or files of single cells among reticular dermis collagen bundles. Involvement of the reticular dermis is highly characteristic of Spitz nevi, and as they descend into this part of the dermis, some of the cells become separated from the apparent border of the lesion to form outlier cells (179) that can be revealed, for example, by a stain for S100 antigen. Other benign nevi also tend to infiltrate in this way if they involve the reticular dermis (191). Melanomas, in contrast, tend to form solid tongues or fascicles of tumor cells that separate and displace the collagen bundles in the reticular dermis without forming outlier cells.

A useful although not pathognomonic cytologic criterion for Spitz nevi is the presence within the epidermis of red globules resembling colloid bodies in 60% to 80% of cases. They may form larger bodies through coalescence. These "Kamino bodies" are most commonly seen in the basal layer above the tips of dermal papillae (Fig. 28-10E). Similar-appearing eosinophilic globules have been noted in the epidermis in only 2% of melanomas and 0.9% of ordinary nevi, in which they are, however, less conspicuous because they do not coalesce (192,193). Although often these bodies may resemble apoptotic cells, formal studies have found no evidence of active apoptosis and have related the eosinophilic material to hyalinized collagen or basement membrane–like material (194).

Melanin is in many instances completely or nearly absent in Spitz nevi. In a few cases, melanin is moderate or dense. Some of these pigmented Spitz nevi are better classified as pigmented spindle cell nevi, related lesions that are discussed in the next section. An inflammatory infiltrate is found in many Spitz nevi and may be quite heavy. Its distribution can be bandlike, mainly at the base, as in some melanomas. Often,

however, the infiltrate is patchy around blood vessels and is seen throughout the lesion (172,179,182).

On comparing Spitz nevi occurring in adults with those of children, it appears that pure epithelioid cell Spitz nevi are rare in adults. In addition, lesions in adults often are more pigmented than in children (195). Furthermore, desmoplastic Spitz nevi seem to occur predominantly in adults (173).

In some examples of Spitz nevi (and also in some nevi with smaller cells that may not meet criteria for Spitz nevi), diffuse fibrosis is present (196–198). These *desmoplastic Spitz nevi* generally show no junctional activity, nesting, or pigmentation. The nevus cells are predominantly spindle shaped and compressed by a desmoplastic stroma. However, they differ from a dermatofibroma by the presence of epithelioid and often also multinucleated cells. Desmoplastic melanoma almost always shows an associated lentiginous *in situ* component, in contrast to the rarity of junctional activity in desmoplastic Spitz nevi. Furthermore, desmoplastic melanomas are almost invariably negative (in their spindle cell component) for the HMB-45 and Melan-A (MART-1) melanocytic markers, which in contrast are usually positive in Spitz nevi (199,200).

Hyalinizing Spitz nevi are related lesions that present with spindle or epithelioid nevus cells embedded in a paucicellular hyalinized collagenous stroma. Some of these lesions have been mistaken histologically for metastatic carcinomas (201).

Angiomatoid Spitz nevi present histologically with large spindle and/or epithelioid nevus placed among "angiomatoid" densely arranged, small blood vessels lined by plump endothelial cells embedded in a collagenous stroma. The Spitz nevus cells may be quite inconspicuous among the vessels in some cases. There have been no reported cases of recurrence or metastases (202).

Histogenesis. On electron microscopic examination, Spitz nevi show in their upper portion melanocytes with numerous melanosomes; in their lower portion, the number of melanosomes in the melanocytes decreases. Melanization is incomplete in most melanosomes, and there is evidence of lysosomal degradation of melanosome complexes (203). The paucity of melanin in most Spitz nevi is thus explained. Biological marker studies have shed little or no light on the mechanisms whereby Spitz nevi appear to have the capacities for relatively rapid invasive and tumorigenic proliferation in the dermis but to lack the capacity for metastasis.

Diagnostic and Prognostic Markers. Morphometric and immunohistochemical studies have shown differences between Spitz nevi and melanomas, but none of these adjuncts to histologic diagnosis is in standard use. By immunohistochemistry, Spitz nevi react not only with differentiation markers for melanocytes such as S100 antigen, but also with HMB-45 and Melan-A/MART-1, the former a melanosomal antigen often expressed in proliferating melanocytic lesion (as well as melanoma), and the latter a more specific marker of melanocytic lineage (125,199,200). Spitz nevi tend to show a more orderly pattern of stratification of HMB-45 reactivity from superficial to deep compared to melanomas (199). A recent study demonstrated interesting differences in S100A6 protein expression between Spitz nevi and melanomas (204). Like nevi and unlike melanomas, Spitz nevi show a tendency toward diminution of nuclear size and/or DNA content (205,206), as well as for reactivity with certain antigens, from the superficial to the deep portions of the nevus (199). This stratification may be regarded as an expression of maturation/senescence that is diagnostically and no doubt also biologically important in the distinction between Spitz nevi and melanomas.

Nuclear size or volume assessed morphometrically has provided fairly good discrimination in some hands, especially when measured at the base of the tumor or when combined with a "maturation parameter," namely the ratio of nuclear area between the deep and superficial portions (207). Cell proliferation marker studies using PCNA or cyclin antibodies have in general shown Spitz nevi to be intermediate between common nevi and melanomas, but the specificity has been insufficient for diagnostic use (208–210). Perhaps of some potential practical utility is the absence of aneuploidy as judged by cytofluorometry (211,212) or DNA fluorescence *in situ* hybridization (FISH) (213,214), a feature that is specifically associated with Spitz nevi compared to melanomas in several studies. However, these methods have not been applied to a sufficiently large and well-characterized series of difficult cases for which they are most needed, but also for which their utility is likely to be most limited. In one such study, de Wit et al., using FISH, were able to identify only three of five lesions that had been originally diagnosed as Spitz nevi but later reclassified as melanoma because of the occurrence of metastasis (215). In another recent study, 5 of 22 Spitz nevi had an aneuploid cell population, so that the presence of aneuploidy cannot be considered diagnostic of melanoma (216).

In a recent study by Bastian et al. using FISH on tissue arrays, copy-number increases often associated with oncogenic mutations involving the HRAS gene on chromosome 11p were found in about 10% of cases (217). Tumors with 11p copy-number increases were larger, predominantly intradermal, and had marked desmoplasia, characteristic cytologic features, and an infiltrating growth pattern. HRAS activation by either mutation or copy-number increase alone could explain several of the histologic features that overlap with those of melanoma. It is speculated that HRAS activation in the absence of cooperating additional genetic alterations may drive the partially transformed melanocytes of these atypical Spitz nevi into senescence or a stable growth arrest (217), likely as a result of p16 activation in a process termed oncogene-induced senescence (218). There are no data to suggest that Spitz nevi with HRAS activation are at special risk for progression to melanoma; however, the biological potential of these lesions is not completely understood.

Differential Diagnosis. The distinction between Spitz nevi/tumors and benign nevi is usually trivial except for dysplastic nevi, which may be indicators of an individual at increased risk for melanoma. In cases of doubt in this regard, we add a note to the effect that the differential diagnosis may include a dysplastic

nevus and recommend that the patient be evaluated for other risk factors, such as multiple dysplastic nevi and a family or personal history of melanoma. Occasional examples of histiocytic tumors such as epithelioid histiocytomas or juvenile xanthogranulomas may be confused with epithelioid Spitz nevi or with melanomas, especially when foam cells or Touton giant cells are inconspicuous (219). It has been demonstrated that Melan-A and tyrosinase markers are sensitive and specific in making the diagnosis of a melanocytic lesion, whereas histiocytic markers such as CD68 and factor XIIIa are likely to be positive in the histiocytic lesions (see Chapter 26) (220–222).

The differential diagnosis with melanoma is of course of much greater importance. Differentiation of a Spitz nevus from a nodular melanoma can be difficult and even impossible in some cases because all of the changes seen in the Spitz nevus may also be observed in melanoma. This differential has been discussed extensively in previous sections. Crotty et al. considered that the presence of symmetry, Kamino bodies, and uniformity of cell nests or sheets from side to side favor a Spitz nevus, whereas the presence of abnormal mitoses, a dermal mitotic rate of greater than 2/mm^2, and mitotic figures within 0.25 mm of the deep border of the lesion favor a melanoma (190). We would add to this list the characteristic dispersion pattern of single cells at the base, which favors a Spitz or other benign nevus.

There are cases on record that were diagnosed as instances of Spitz nevus but later proved to be melanoma (215). Other cases, regarded by some as malignant Spitz nevi, have metastasized to regional lymph nodes but not beyond (223). These lesions, which are often large, ulcerated, deeply infiltrative, and mitotically active, can alternatively be signed out descriptively as melanocytic tumors of uncertain potential. Others regard these lesions as spitzoid melanomas, some considering that the prognosis for these tumors may be better than expected for an ordinary melanoma with similar microstaging attributes (175). The diagnosis of a Spitz nevus depends on an assessment of multiple morphologic features, which are summarized in Table 28-3. Given that so-called metastasizing Spitz nevi/tumors have been associated with long-term survival (224–228), it may be appropriate to regard the metastases as metastatic melanocytic tumors of uncertain potential rather than unqualified metastatic malignant melanoma. However, in our practice, such individuals would be offered a consideration of adjuvant protocols for metastatic melanoma.

TABLE 28-3 Spitz Nevus Versus Melanoma

Spitz nevus	Melanoma
Pattern features	
Usually <6 mm diameter	Usually >6 mm
Usually symmetric	Often but not always asymmetric
Single attenuated cells between reticular dermis collagen bundles at base	Nests and fascicles rather than single cells in the reticular dermis
Epidermal hyperplasia, hyperkeratosis, and hypergranulosis may be prominent	Epidermal reaction is often minimal
Usually little or no pagetoid spread of lesional cells into the epidermis	Usually obvious pagetoid spread into the epidermis
Epidermal component usually does not extend beyond the lateral border	Lateral extension (radial growth phase) is common except in nodular melanoma
Ovoid nests of lesional cells oriented perpendicular to the epidermis	Nests variable in size, shape, and orientation
Discontinuous junctional proliferation	May be continuous proliferation
Little or no pigment	Often heavily pigmented, or irregularly scattered pigmented cells within the lesion
Small uniform nests in the dermis at base	Larger variable nests at base
Cytologic features	
Nuclear chromatin is open, with prominent nucleoli	Nuclei may be hyperchromatic and clumped
Nuclear membranes are regular	Irregular nuclear membranes
Single and confluent eosinophilic globoid bodies in epidermis and superficial dermis	If present, globoid Kamino bodies are inconspicuous and usually single
Mitoses absent or low mitotic rate	Mitoses rarely absent, rate often high
Atypical mitoses rare or absent	Atypical mitoses common
Mitoses rare in lower third of lesion	Mitoses common in lower third of lesion
Cells uniform from side to side	Greater tendency to cellular variability
Cells mature with descent to base	Little or no maturation

Because of the difficulty of making an absolutely certain differentiation from melanoma, it is advisable as a precautionary measure that lesions diagnosed as Spitz tumors/nevi be excised completely, especially in persons at or beyond puberty, particularly because such lesions are usually small. Although the issue is debatable (229), exceptions to this general rule might include those lesions for which there are cosmetic or other contraindications to excision and for which the diagnosis of Spitz nevus is certain despite the partial nature of the biopsy (230). In addition, one should never exclude a diagnosis of melanoma based on age alone because melanomas may arise in children, although this is rare. Spatz et al. provided criteria for grading risk in Spitz tumors, considering metastasizing cases in childhood. These criteria included diagnosis at age greater than 10 years, diameter of the lesion greater than 10 mm, presence of ulceration, involvement of the subcutaneous fat (level V), and mitotic activity of at least 6/mm^2 (176). As noted earlier, it is not always possible to make an unequivocal distinction between a melanoma or a Spitz tumor/nevus, and in these doubtful cases we will often use the descriptive term "melanocytic tumor of uncertain potential" (MELTUMP) and provide a differential diagnosis that might in cases of extreme doubt include microstaging attributes that would apply if the lesion were interpreted as a melanoma (231).

Pigmented Spindle Cell Nevus

This tumor, first described by Richard Reed in 1973 (232), may be regarded as a variant of the Spitz nevus (167,173) or as a distinctive clinicopathologic entity (233). In our experience and that of others, most cases differ significantly from classical Spitz nevi, but some present with overlapping features, indicative of a close relationship between the two entities (234–236). Although this distinction has no clinical significance, in that each is a benign lesion, it is important to rule out melanoma, and this is facilitated by an understanding of the differences between these two common melanoma simulants.

The lesions are usually 3 to 6 mm in diameter, deeply pigmented, and either flat or slightly raised. Most patients are young adults, and the most common location is on the lower extremities. Pigmented spindle cell nevi are uncommon after the age of 35 years. A classic presentation is that of a newly evolved black plaque on the thigh of a young woman. Because of the heavy pigment and the history of sudden appearance, a diagnosis of melanoma is often suspected clinically. In contrast, Spitz nevi are usually submitted with a benign clinical diagnosis, such as an angioma or a dermal nevus. Like Spitz nevi, the lesions are generally stable after a relatively sudden appearance and a short-lived period of growth.

Histopathology. The pigmented spindle cell nevus is characterized by its relatively small size and its symmetry and by a proliferation of uniform, narrow, elongated, spindle-shaped, often heavily pigmented melanocytes at the dermal–epidermal junction (233–235,237). The nests of spindle cells are vertically oriented and tend to blend with adjacent keratinocytes rather than forming clefts as in Spitz nevi. Eosinophilic globules (Kamino bodies) may be present (Fig. 28-11) (238). The tumor cells often form bundles that are separated by elongated rete ridges. In the papillary dermis, the nevus cells lie in compact clusters, pushing the connective tissue aside. Numerous melanophages are characteristically diffusely present within the underlying papillary dermis. Involvement of the reticular dermis, common in Spitz nevi, is unusual in pigmented spindle cell nevus. Some lesions show upward epidermal extension of junctional nests of melanocytes. Single-cell upward invasion of the epidermis in a pagetoid pattern may be present but is usually not prominent (152,234). Features that may lead to a diagnosis qualified as atypical pigmented spindle cell nevus include architectural abnormalities including poor circumscription and pagetoid melanocytosis, prominent cytologic atypia, or a prominent epithelioid cell component (234). There may also be considerable overlap with dysplastic nevi (234). The significance of these atypical variants appears to lie in their greater chance of being misdiagnosed as melanoma because all reports of pigmented spindle cell nevi emphasize their benign behavior after excision.

Differential Diagnosis. The most important differential diagnosis is with melanoma of the superficial spreading type. In contrast to these melanomas, pigmented spindle cell nevi are smaller, symmetric, and show sharply demarcated lateral margins. The tumor cells appear strikingly uniform from side to side. If lesional cells of pigmented spindle cell nevi descend into the papillary dermis, they mature along nevus lines, in contrast to melanomas. Mitoses may be present in the epidermis in either lesion but are uncommon in the dermis in pigmented spindle cell nevi. Abnormal mitoses are exceedingly uncommon. Pagetoid melanocytosis is usually not prominent, and the spindle cell cytology differs from that of the epithelioid cells that predominate in most superficial spreading melanomas. Lentigo maligna melanomas may have spindle cells in their vertical-growth-phase component, but the epidermal component is usually composed of smaller, nevoid, albeit atypical, cells. Some pigmented spindle cell nevi may present overlapping features with dysplastic nevi but can usually be distinguished on the basis of their irregularly thickened epidermis, their vertically oriented nests, and the uniformity of cell type, the absence of cytologic dysplasia, and the absence of typical stromal alterations (e.g., lamellar fibrosis). In cases of extreme doubt, we may classify the lesions as superficial atypical melanocytic proliferation of uncertain significance (SAMPUS) and provide a differential diagnosis of melanoma *in situ* or dysplastic nevus. In the former case, a reexcision procedure is recommended, whereas in the latter case we recommend assessment of melanoma risk factors and perhaps follow-up, especially if the patients have other clinically atypical nevi or a family or personal history of melanoma (231). Some rare examples of lesions with larger expansile intradermal nodules may be difficult to distinguish from melanoma, and a descriptive diagnosis may be appropriate (MELTUMP; see later section).

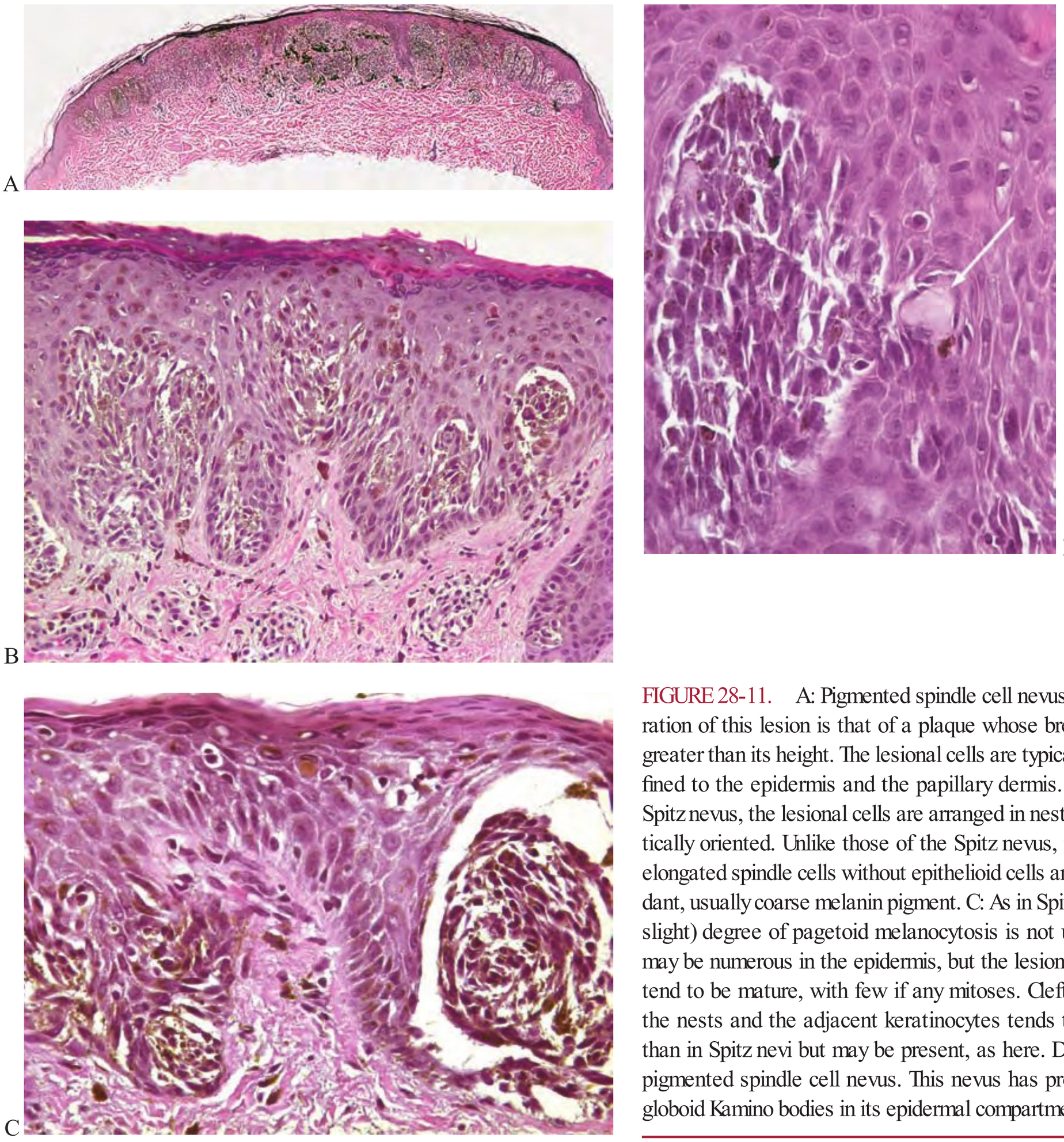


FIGURE 28-11. A: Pigmented spindle cell nevus. The typical configuration of this lesion is that of a plaque whose breadth is considerably greater than its height. The lesional cells are typically junctional or confined to the epidermis and the papillary dermis. B: As in the classic Spitz nevus, the lesional cells are arranged in nests that tend to be vertically oriented. Unlike those of the Spitz nevus, the cells are narrow, elongated spindle cells without epithelioid cells and they contain abundant, usually coarse melanin pigment. C: As in Spitz nevi, some (usually slight) degree of pagetoid melanocytosis is not unexpected. Mitoses may be numerous in the epidermis, but the lesional cells in the dermis tend to be mature, with few if any mitoses. Clefting artifact between the nests and the adjacent keratinocytes tends to be less prominent than in Spitz nevi but may be present, as here. D: Kamino bodies in a pigmented spindle cell nevus. This nevus has prominent eosinophilic globoid Kamino bodies in its epidermal compartment.

Congenital Melanocytic Nevus

A congenital melanocytic nevus may be defined as a lesion present at birth and containing nevus cells. Congenital nevi are found in about 1% to 2% of newborn infants (239,240), and thus, although such lesions are rare when compared to the total number of all noncongenital nevi, their occurrence is a relatively common clinical event. In many instances, congenital nevi are larger than acquired nevi, measuring more than 1.5 cm in diameter (241). However, only a few are of considerable size. Those measuring more than 20 cm in greatest diameter are referred to as *giant congenital melanocytic nevi* (Fig. 28-12A) (242). *Nongiant congenital melanocytic nevi* are usually slightly raised and often pigmented, and they may show a moderate growth of hair. They may be classified as "small" (less than 1.5 cm in diameter) or "intermediate" (greater than 1.5 cm and less than 20 cm, or amenable to local excision) (242,243). A number of variants have been described, such as the *cerebriform congenital nevus*, which presents as a skin-colored, convoluted mass (244); the *spotted grouped pigmented nevi*, showing closely set brown to black papules (245); the *congenital acral melanocytic nevus*, which consists of a blue-black patch on the sole or the distal portion of a finger clinically resembling an acral-lentiginous melanoma (246); and the *desmoplastic hairless hypopigmented nevus*, which presents clinically as a hard, ligneous, progressively hypopigmented and alopecic giant congenital nevus and is characterized histologically by intense dermal fibrosis, scarce nevus cells, and hypotrophic or absent hair follicles (247). Giant congenital melanocytic nevi often have the distribution of a garment ("garment nevi"). They usually are deeply pigmented and are covered with a moderate growth of hair. Often, there are many scattered satellite lesions of a similar appearance (248). These

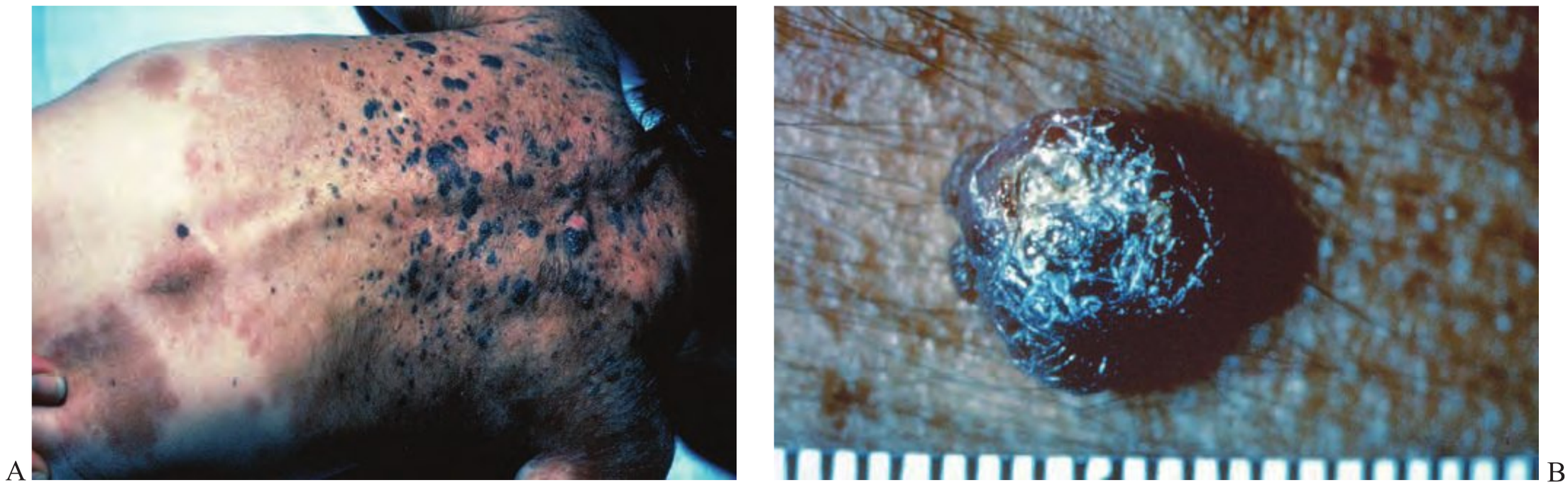


FIGURE 28-12. A: Giant congenital nevus (clinical). These lesions have also been called "garment nevi" because of their coverage of such large areas of skin. Focal areas of increased pigmentation, sometimes associated with palpable nodularity, are not uncommon in giant congenital nevi. Such foci should be followed carefully, and any lesions showing evidence of progressive changes should be excised to rule out melanoma. B: Melanoma in a giant congenital nevus. This nodule developed on the back of the patient illustrated in panel A at the age of 4 years. The patient died within about 2 years of metastatic melanoma.

satellite nevi are benign, in contrast to the satellite metastases that may be associated with melanomas. Leptomeningeal melanocytosis is occasionally found in cases in which the giant congenital nevus involves the neck and scalp. There may be not only epilepsy and mental retardation, but also a primary leptomeningeal melanoma (249). In one study, magnetic resonance findings of meningeal melanosis were identified in 14 of 43 asymptomatic children with giant congenital melanocytic nevi. These findings are consistent with an increased lifetime risk of central nervous system melanoma (250).

Incidence of Cutaneous Melanoma. The lifetime incidence of melanoma arising either in a giant congenital nevus or, as seen rarely, in one of the many smaller satellite nevi is estimated to lie between about 6% and 12% (251–267). Thus, the majority of patients with giant congenital nevi will never develop melanoma. In one study, increasing numbers of satellite lesions and larger lesional diameters were associated with melanoma and neurocutaneous melanosis (267). The melanoma may be present at birth, or it may arise in infancy or any time later in life (Fig. 28-12B). The mortality of such melanomas is substantial. In a cohort study in which 33 patents with giant congenital nevi were followed, 2 fatal melanomas developed, representing a relative risk approximately 1,000-fold greater than that in the general population (254), whereas in another study of 80 pediatric cases, 4 melanomas (3 of them fatal) occurred after an average follow-up of about 5 years (255). In follow-up data on 170 patients in the New York University Registry of Large Congenital Melanocytic Nevi, four melanomas had developed, including extracutaneous melanomas in the central nervous system and one retroperitoneal melanoma (254,265,267). In a review of the literature, approximately 70% of the melanomas that occurred in patients with giant congenital nevi developed before puberty (254). It is therefore generally agreed that it would be desirable for giant melanocytic nevi to be excised, if feasible. However, complete excision is often not possible, and melanomas may develop in extracutaneous sites. Thus, clinical surveillance is considered to be an acceptable alternative in such situations (258,265).

The incidence of melanoma in nongiant congenital nevi—those less than 20 cm in greatest diameter—is unknown, but it is probably greater than that in a comparable area of normal skin. It is likely that the risk is related to the lesion's size (252). The excision of all nongiant congenital nevi, where feasible, is advised by many (252,268) although not all authors (242,269). Most of the melanomas observed in these nongiant lesions occurred after puberty (253).

Histopathology

The histologic appearance of giant congenital nevi differs from that of acquired nevi in terms of their greater size and depth and in the involvement of skin appendages and sometimes even deeper tissues (e.g., galea aponeurotica and cranial nerve extension in scalp lesions) (Fig. 28-13). Nongiant congenital nevi may have the same histologic appearance as acquired nevi or may show features of congenital nevi (Fig. 28-14) (114,270,271). The features in nongiant congenital nevi are neither sensitive nor specific for truly congenital origin of a nevus: a recent histologic study with comparison with clinical data showed that 32 nevi with the histologic criteria of congenital nevi were actually acquired, and that 179 nevi present at birth did not fulfill these criteria. However, such studies are complicated by the possibility that some congenital nevi may be clinically covert at birth and thus regarded as acquired. In the case of deep and large (giant) congenital nevi, in contrast, the clinicopathologic correlation was 100% (272). Cytologically, the cells of congenital nevi are similar to those of acquired nevi. The nevus cells are typically positive for the melanocytic markers S100, HMB-45, and

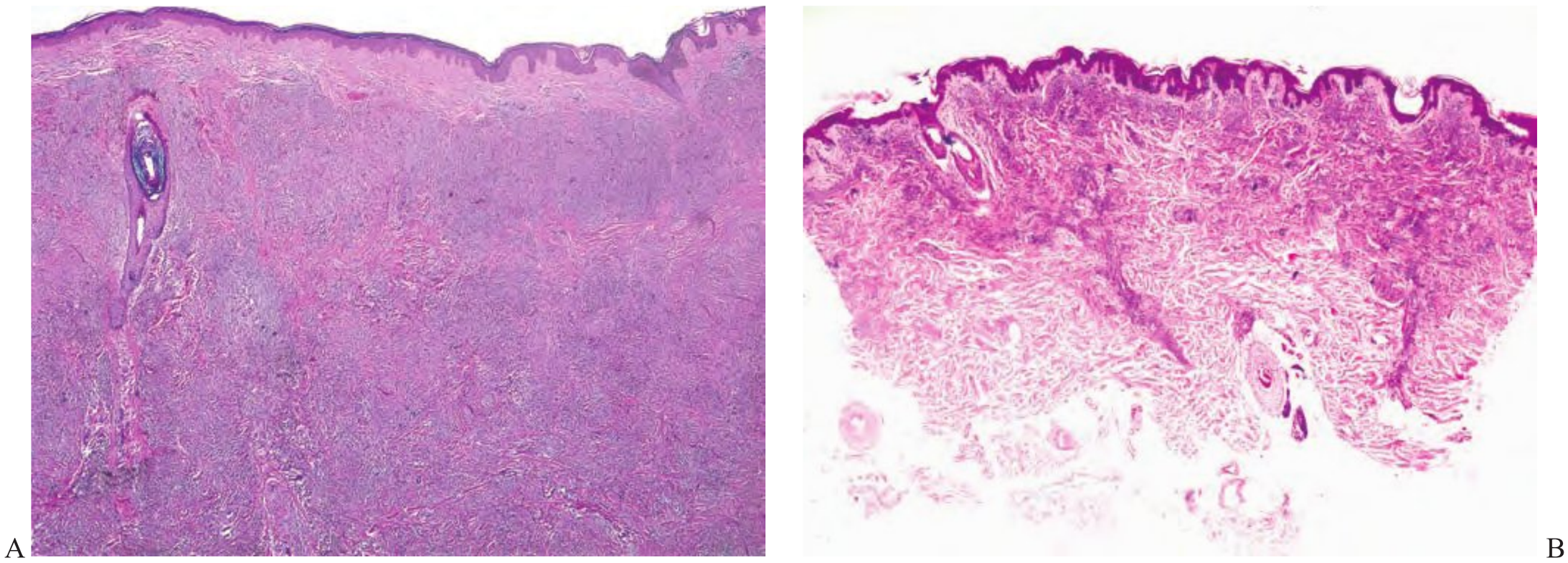


FIGURE 28-13. A: This nevus is very broad (many centimeters, extending well beyond the borders of the image) and deep, that is, the lesional cells extend from the epidermis through the reticular dermis and into the fat. B: In another giant congenital nevus, sheets of nevus cells are placed among reticular dermis collagen bundles. The dermal component of giant congenital nevi is often variably cellular, and in addition to nevic differentiation there may be evidence of schwannian or even heterotopic elements.

Melan-A, the last of which has the best combination of sensitivity and specificity (125).

Nongiant (Small and Intermediate) Congenital Melanocytic Nevi. At one time these were believed to be superficial at birth and to show deep involvement later (241). However, a serial study showed no change in pattern in follow-up biopsies (273). This and other studies have shown various patterns in the distribution of the nevus cells independent of the age of the patient. Thus, nongiant congenital nevi may be junctional, compound, or intradermal nevi, and their location in the dermis may be either superficial, which may include junctional involvement, or superficial and deep (273,274). They may differ from acquired nevi by one or more features: (a) presence of melanocytes, often in nests, around and within hair follicles, in sweat ducts and glands, in sebaceous glands, in or in intimate association with vessel walls, in arrector pili muscles, and in the perineurium of nerves; (b) extension of melanocytes between collagen bundles singly or in double rows; and (c) extension into the deepest reticular dermis and into the subcutis (Fig. 28-14) (241). However, many nongiant congenital nevi show none of these features. For example, some documented congenital nevi have been entirely junctional (273), whereas the likelihood of deep dermal involvement appears to increase with the size of the lesion (275) and is actually uncommon in lesions smaller than 3 cm (271). Conversely, the presence of most of the features mentioned has been documented in nevi that indubitably became clinically apparent after birth ("tardive" congenital nevi) (276). Thus, nevi with the constellation of

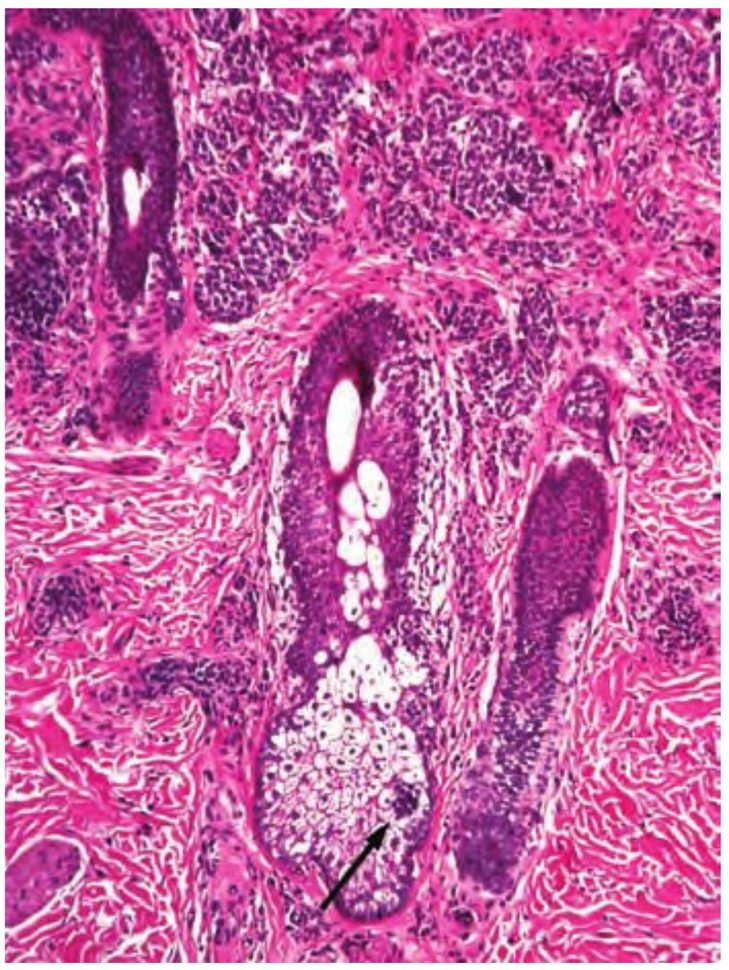


FIGURE 28-14. Compound nevus with congenital pattern features. Nevus cells extend around skin appendages and between fibers of the reticular dermis. The presence of nevus cells within skin appendages (as here in the sebaceous unit) is a quite specific feature indicating true congenital onset of a nevus. The extension of nevus cells into the upper reticular dermis and around skin appendages is quite characteristic of congenital nevi. However, acquired nevi may also exhibit this deep pattern, and, conversely, congenital nevi are not always deep.

features described may be characterized as nevi with congenital pattern features, but not all of these lesions are truly congenital in origin. It appears that most congenital nevi have mutation of NRAS, in contrast to most acquired nevi, which have mutated BRAF. The lesions appear to undergo oncogene-induced senescence, similar to acquired nevi (277). In another contrast, most of the "congenital pattern" nevi that are actually acquired have BRAF mutations, possibly related to sun exposure (278). It remains to be seen whether such nevi have any special significance as risk markers or potential precursors of melanoma (264).

Among the special forms of nongiant congenital nevi, the *cerebriform congenital nevus* usually presents as an intradermal nevus with neuroid changes simulating those seen in neurofibroma (244). Lesions called *spotted grouped pigmented nevi* also are intradermal nevi. They are either eccrine centered or follicle centered. If they are eccrine centered, each eccrine sweat duct is tightly enveloped by nevus cells, whereas hair follicles are involved only slightly (245). If they are follicle centered, nevus cell nests are found mainly around the hair follicles. In the *acral nevus of congenital origin*, a compound nevus is seen with considerable pigmentation in the upper dermis, and aggregates of nonpigmented nevus cells are seen around blood vessels and eccrine glands in the lower dermis (246). In a lesion called *desmoplastic hairless hypopigmented nevus*, there is intense dermal fibrosis, scarce nevus cells, and hypotrophic or absent hair follicles. Follow-up biopsies have documented the progressive nature of the fibrosis and nevus cell depletion (247).

In some congenital melanocytic nevi, changes are observed that may simulate a melanoma. In a recent study, features that could simulate malignant melanoma in a congenital nevus included (a) asymmetry and poor circumscription, (b) an increased number of single melanocytes, which predominated over nests of melanocytes in some high-power fields, (c) single melanocytes not equidistant from one another, (d) scattered single melanocytes present above the dermoepidermal junction, and (e) confluence of nests of melanocytes, all features in common with malignant melanoma (279). In our experience, such changes are generally slight in degree, and severe uniform cytologic atypia or frequent mitoses are not observed.

Giant Congenital Melanocytic Nevi. These are often are more complex than nongiant congenital nevi. Three patterns may be found within them: a compound or intradermal nevus, a neural nevus, and a blue nevus pattern (249). In most instances, the compound or intradermal nevus component predominates, whereas, in others, the neural nevus component predominates. In the latter case, formations such as neuroid tubes and nevic corpuscles are present. These areas may show considerable similarity to a neurofibroma. A component resembling a blue nevus or a cellular blue nevus is found in some of the giant pigmented nevi, usually as a minor component. In rare instances, however, the entire congenital lesion consists of a giant blue nevus, which, in one patient with a lesion of the scalp, was reported to extend to the dura (35) and in another had infiltrated the brain (36). Nevus cells may be present in lymph nodes draining skin containing a giant congenital nevus; this phenomenon should not be mistaken for involvement by a melanoma. In general, the nodal nevus cells lie in capsular or sinusoidal septal collagen, and the cells lack atypia (280).

Melanoma in Congenital Nevi. The pattern of occurrence of melanoma in giant congenital nevi was studied in a review of 34 patients who had primary cutaneous melanomas within their nevi; in 2 additional patients, melanoma developed at cutaneous sites other than within their nevi. All patients in whom melanoma developed within the nevi had nevi in axial locations; however, 91% of the nevi were axial. No melanoma was found that had arisen in any of the 26 nevi confined to the extremities. In addition, no melanoma was found that had arisen in thousands of satellite nevi (260). If a melanoma arises in a congenital nevus, it usually originates at the epidermal–dermal junction and the appearances are those of an ordinary form of melanoma, usually of the superficial spreading or nodular types (see section Classification of Melanoma). Most of the congenital nevi associated with such melanomas are small and superficial (281). Occasionally, however, a melanoma in a giant congenital nevus, in contrast with nearly all other cutaneous melanomas, arises deep in the dermis or subcutis (282–285).

Histologically, in our experience, some of the melanomas in giant congenital nevi have consisted largely of undifferentiated blastic cells resembling lymphoblasts and containing little or no melanin, whereas others are comprised or large epithelioid cells similar to those of many melanomas. Other patterns of malignancy that have been described in congenital nevi have included neoplasms with the appearance of a neurosarcoma (286), lesions that have been termed malignant blue nevus (287–289), neoplasms with heterologous mesenchymal elements including rhabdomyoblasts (290) and lipoblasts, undifferentiated spindle cell cancers, and well-differentiated neoplasms termed minimal deviation melanomas (289). It has been emphasized that peculiar differentiation is to be expected in neoplasms of giant congenital nevi, and that alarmingly cellular neoplasms may not behave aggressively (289). Thus, pathology does not always readily predict outcome. This is especially true in our experience when melanomas arise in the first few months of life.

Cytologic and architectural atypia may occasionally be seen in congenital nevi, and criteria for the distinction of these lesions from melanoma are similar to those discussed in the differential diagnosis of dysplastic nevi and superficial spreading melanomas in later sections. In an interesting study, abnormal DNA content was found to correlate with cytologic atypia in giant congenital nevi (291). It is possible that the presence of atypical foci could increase the risk of malignant transformation.

Melanomas in small congenital nevi are typically of the usual superficial spreading type. In a recent study, 40 of 190 cases of melanoma were associated with preexisting nevi; of these, 15 had congenital features with a largest diameter of 1.5 cm, that is, small congenital pattern nevi. These 15 cases were melanomas of the superficial type with a mean tumor thickness lower than that of melanomas not associated with nevi

(0.33 vs. 1.50). Thus, a relatively high percentage of small congenital pattern nevi was found to be associated with melanomas, indicating that they may be considered as potential melanoma precursors. Nevertheless, the risk of progression of any given lesion is very low (264).

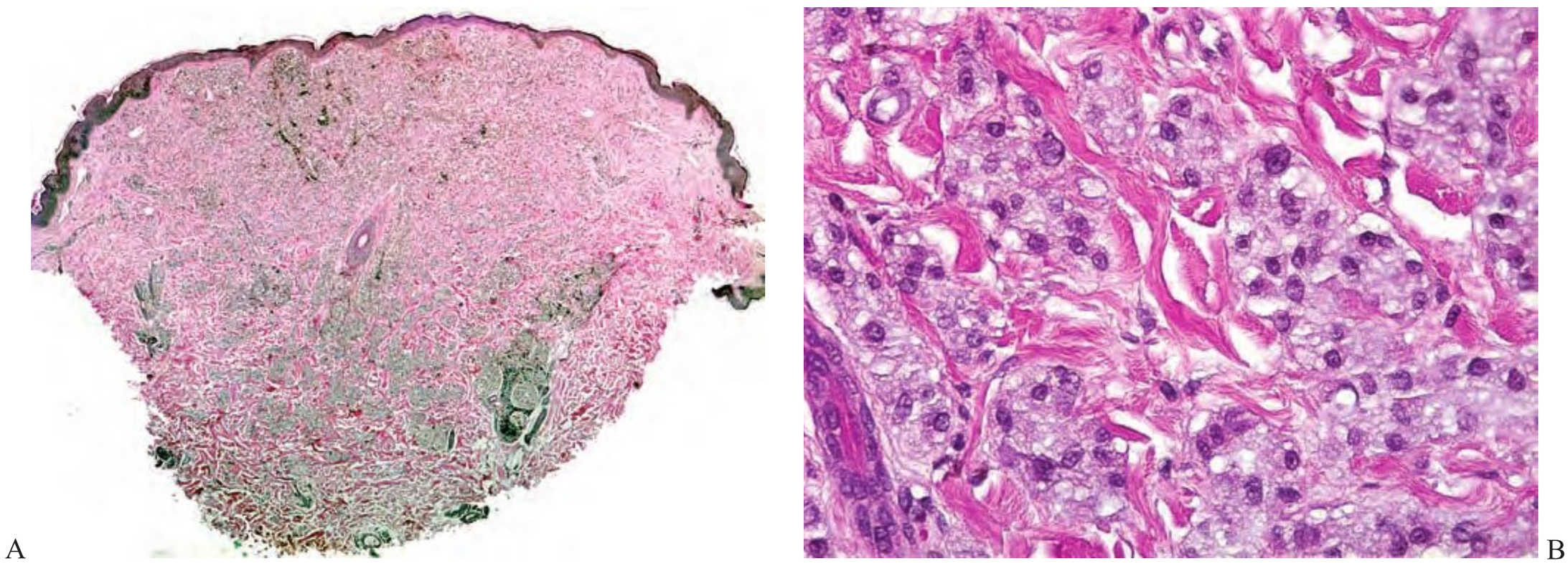
Proliferative Nodules in Congenital Nevi. Although melanomas may occur in the dermal component of congenital nevi, cellular proliferative nodules that occur in these nevi often do not behave in a clinically aggressive fashion (292). Such lesions may arise as one or more relatively small nodules that develop sometimes rapidly within a preexisting congenital nevus, particularly in infancy and early childhood. In a clinical pathologic study of a cohort of 26 cases, with a mean of 5-year follow-up on 16 patients, the lesions had an invariably benign clinical course. The features that are useful to differentiate cellular proliferative nodule from melanoma include (a) lack of high-grade uniform cellular atypia, (b) lack of necrosis within the nodule, (c) rarity of mitoses, (d) evidence of maturation in the form of blending or transitional forms between the cells in the nodule and the adjacent nevus cells, (e) lack of pagetoid spread into the overlying epidermis, and (f) no destructive expansile growth (293). If some of these features are present to a slight degree, the descriptive diagnosis of melanocytic tumor of uncertain potential may be appropriate (see later section). Cases of cellular nodules in congenital nevi demonstrate chromosome loss with patterns that differ from the findings in frank melanomas (294), and most of them have mutations of NRAS rather than BRAF, considered to be characteristic of lesions that develop in the absence of sun exposure (278).

Leptomeningeal Melanocytosis. There is a diffuse infiltration of the leptomeninges with pigmented melanocytes. In addition, the blood vessels entering the brain and spinal cord may be surrounded by melanocytes, and there may be areas of infiltration of the brain or spinal cord with melanocytes. Leptomeningeal melanoma can infiltrate the leptomeninx and form multiple nodules in the brain (295,296).

Deep Penetrating Nevus (Plexiform Spindle Cell Nevus)

This is a distinctive entity that has some features of combined nevus, blue nevus, and Spitz nevus (297,298). In the first report of 70 cases from a referral center, many cases had previously been misdiagnosed histologically as melanomas. Similar lesions have also been described as plexiform spindle cell nevi (41,299,300). Most of the lesions occurred in the second and third decades (range 3 to 63 years). The head, neck, and shoulder were the most frequent sites of involvement, with no occurrences on the hands or feet. The lesions ranged from 2 to 9 mm and were darkly pigmented papules and nodules, often diagnosed clinically as blue nevi or cellular blue nevi. In a mean follow-up of 7 years, none recurred or metastasized. Occasional recurrences, but no metastases, have since been described (301). On cross section, the lesions extended at least halfway into the dermis, with a smooth, dome-shaped elevation of the epidermis. It is possible that lesions termed nevi with focal atypical epithelioid component or clonal or combined nevi may represent a superficial variant (301). These distinctions are of little or no importance; the key distinction is from melanoma.

Histopathology. At scanning magnification, the lesions are circumscribed and pyramidal in shape, with a broad base abutting the epidermis and an apex extending into or toward the fat (Fig. 28-15). Nests of nevus cells at the dermal–epidermal junction are usually present. The dermal component is composed of loosely arranged nests or plexiform fascicles of large



A B

FIGURE 28-15. A: Deep penetrating nevus. At scanning magnification, the lesion is pyramidal, with its base applied to the epidermis and its apex in the reticular dermis. B: The lesional cells in the dermis are arranged in clusters. They may be heavily pigmented, and there may be scattered large, hyperchromatic, and pleomorphic nuclei, constituting random cytologic atypia. Mitoses are absent or very rare.

pigmented spindle and epithelioid cells interspersed with melanophages. There is a tendency to formation of narrow spindle cells at the periphery of the nests, reminiscent of sustentacular cell differentiation. In many cases there is an admixture of smaller, more conventional nevus cells. The lesional cell nests tend to surround skin appendages and to infiltrate the collagen at the periphery of the lesion. The cells do not tend to mature with descent into the dermis. Some lesions have a patchy mild lymphocytic infiltrate.

At higher magnification, nuclear pleomorphism may be striking in some lesions, with variation in size and shape, hyperchromasia, and nuclear pseudoinclusions. The atypia tends to be confined to randomly scattered cells rather than being uniform or present in a majority of the cells. Nucleoli are usually inconspicuous, but a few large eosinophilic nucleoli may be observed. Of importance, mitoses are absent or very rare, with no more than one or two in multiple sections of any given lesion. The cytoplasm is abundant and contains finely divided brown melanin pigment. The lesional cells react positively for S100 protein and HMB-45 antigen (300).

Differential Diagnosis. Deep penetrating nevi can be distinguished from *nodular melanoma* by architectural and cytologic features. Most bulky tumorigenic melanomas exhibit a more striking pattern of epidermal involvement, with spread of atypical cells into the epidermis and, often, with ulceration. Melanomas are likely to be more broad than deep, whereas deep penetrating nevi tend to be vertically oriented like Spitz nevi. Tumorigenic melanomas usually exhibit a more destructive pattern of infiltration, with displacement and compression of the stroma, and often with necrosis. Most also display marked nuclear atypia with frequent and often abnormal mitoses. A few nodular spindle cell melanomas have lower-grade nuclear atypia, and in these cases the presence of more than a few mitoses may be decisive. A study found rates of expression of the cell cycle proliferation marker PCNA to be somewhat higher in deep penetrating nevi than in ordinary banal nevi but considerably lower than in melanomas (302).

Benign lesions that may show some tendency to overlapping features with deep penetrating nevi include *common and cellular blue nevi*, as well as *spindle and epithelioid cell nevi*, and *clonal or combined nevi* (301). Although deep penetrating nevi can usually be distinguished from these benign lesions, the distinction from melanoma is of greatest importance. Neural involvement is not an indicator of malignancy in these lesions. Although most deep penetrating nevi will have a banal clinical course, sufficient numbers have not been studied to ensure this with certainty, and we generally recommend modest complete excision of such lesions. As with Spitz nevi, this approach also minimizes the possibility of local recurrence of a nevus variant with intrinsically unusual features in scar tissue, a situation at potential risk for overdiagnosis and overtreatment as outright melanoma.

Halo Nevus

A halo nevus, also known as Sutton's nevus or nevus depigmentosa centrifugum, represents a pigmented nevus surrounded by a depigmented zone or halo (Fig. 28-16A). The nevus may be of almost any of the types described in the preceding sections, and a similar halo reaction may be seen rarely in relation to primary or metastatic melanoma (303). In the common type of halo nevus, which is characterized histologically by an inflammatory infiltrate and is therefore referred to as inflammatory halo nevus, the central nevus only rarely shows erythema or crusting; however, it undergoes involution in most instances, a process that extends over a period of several months. The area of depigmentation shows no clinical signs of inflammation and, even though it may persist for many months and even years, it ultimately repigments in most cases. Halo nevi tend to progress through several clinical stages. The classic early lesion is a brown nevus with a surrounding, usually symmetric rim of vitiligo-like depigmentation. The central nevus may then lose its pigment and appear pink with a surrounding halo; the central papule may then disappear, leading to a circular area of macular depigmentation, or the depigmented area may repigment, leaving no trace of its prior existence. In unusual lesions, darkening of the central nevus rather than lightening has been described (304). Most persons with halo nevi are children or young adults, and the back is the most common site. Not infrequently, halo nevi are multiple, occurring either simultaneously or successively.

Besides the more common inflammatory halo nevus with histologically apparent inflammation, there also are cases of non-inflammatory halo nevi in which histologic examination shows no inflammatory infiltrate (305). In such instances, the nevus does not involute. In addition, there is the so-called halo nevus phenomenon, also referred to as halo nevus without halo. In these instances, the nevus shows histologic signs of inflammation analogous to a halo nevus but without presenting a halo clinically (306). Such nevi may or may not involute. An association with Turner's syndrome has been recently described (307).

Halo dermatitis around a melanocytic nevus refers to a temporary inflammatory reaction surrounding a nevus (Meyerson's eczematous nevus) (308). There is a papular compound nevus that becomes surrounded by an eczematous halo. Histologically, the epidermis adjacent to the nevus is spongiotic. An analogous phenomenon of "nevocentric" erythema multiforme has also been described in which cytotoxic/interface alterations predominate (309). Similar changes may be seen around atypical or dysplastic nevi (310).

Histopathology. An inflammatory halo nevus in its early stage shows nests of nevus cells embedded in a dense inflammatory infiltrate, in the upper dermis, and at the epidermal–dermal junction (Fig. 28-16B–D). Later, scattered nevus cells tend to predominate over nests. Even when melanin is still present in the nevus cells, these cells often show evidence of damage to their nucleus and cytoplasm, and some frankly apoptotic nevus cells are commonly observed. Some cells, especially superficially, may have enlarged ovoid nucleoli, changes that may be regarded as a form of "reactive atypia." High-grade nuclear atypia is not observed. Of importance, the lesional cells tend to show evidence of maturation, becoming smaller

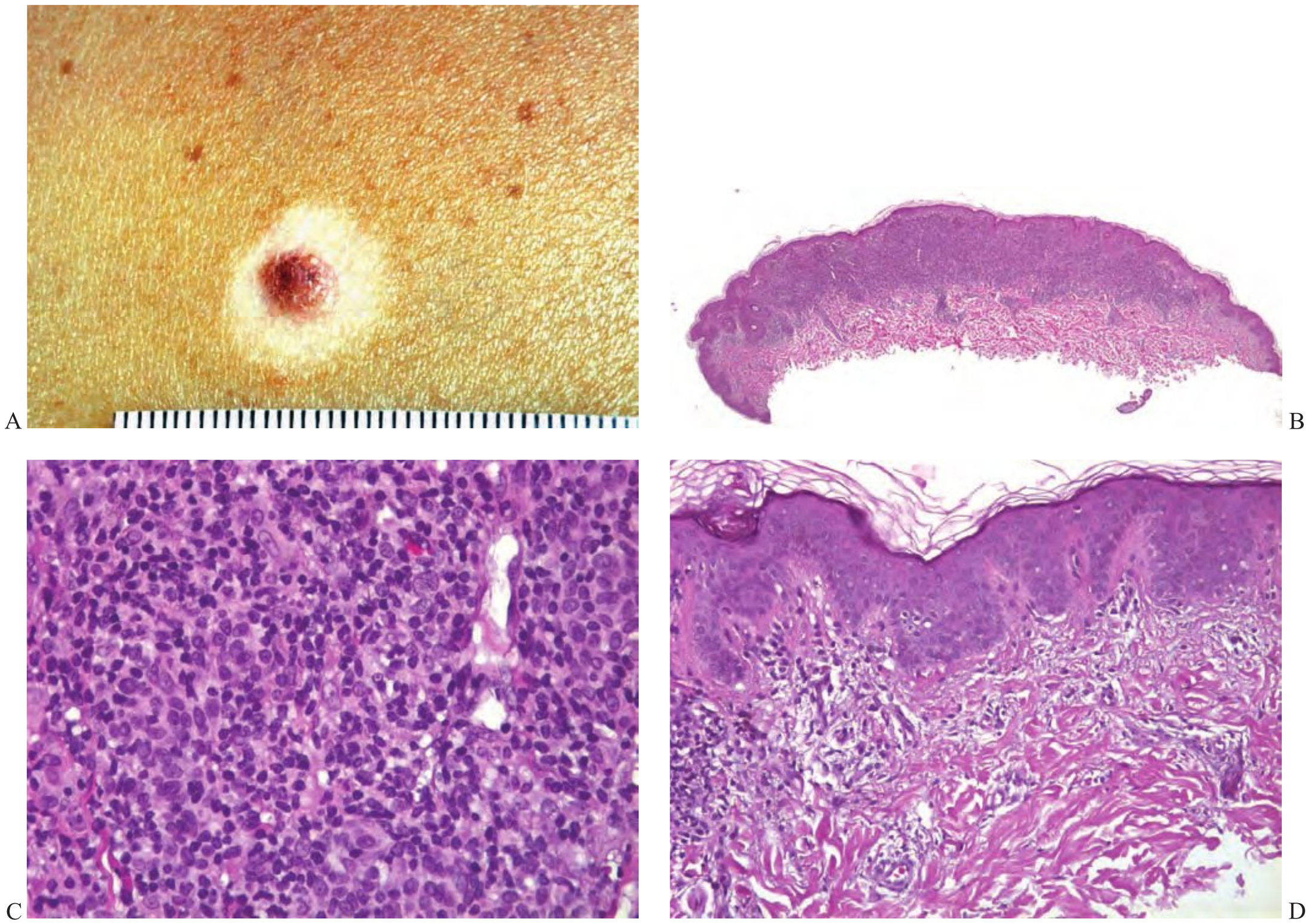


FIGURE 28-16. A: Halo nevus clinical. The halo develops around a preexisting unremarkable compound nevus. B: Halo nevus. A dense infiltrative lymphocytic response blurs the silhouette of the lesional nevus cells in the dermis at scanning magnification. C: Halo nevus. Small lymphocytes are diffusely placed among the dermal nevus cells, which may appear swollen and slightly atypical (reactive atypia). Severe or uniform atypia or mitotic activity should suggest the possibility of melanoma. D: Halo nevus. At the periphery of the nevus, the halo is a region where pigment and melanocytes are reduced or absent, and there may be a subtle lymphocytic infiltrate at the dermal–epidermal junction, as here.

with descent from superficial to deep within the lesion. Nevus cell mitoses are rare, and if present should prompt consideration of the possibility of melanoma. In this regard, it may be difficult to differentiate nevus cell mitoses from those attributable to the reactive mononuclear cells, a problem we have found to be lessened by use of a combined (dual) Mib-1 (Ki-67) and Melan-A/MART-1 stain. Most of the cells in the dense inflammatory infiltrate are lymphocytes. However, some of them are macrophages, in which varying amounts of melanin are contained. As the infiltrate invades the nevus cell nests, it often is difficult to distinguish between the lymphoid cells of the infiltrate and the type B nevus cells in the middermis because they, too, may have the appearance of lymphoid cells. Immunohistochemical studies using S100 or a more specific marker such as Melan-A may be very helpful in identifying the nevus cells in the infiltrate (311). The infiltrate tends to extend upward into the lower portion of the epidermis. In most instances, the infiltrate is characterized by dense cellular packing without vasodilation or intercellular edema and by sharp demarcation along its lower border.

At a later stage, only a few and finally no distinct nevus cells can be identified. Gradually, after all nevus cells have disappeared, the inflammatory infiltrate subsides. Despite the clinical evidence of regression and the inflammatory infiltrate, which consists predominantly of T cells (312), fibrosis is not a prominent feature (313).

In both the inflammatory and the noninflammatory halo nevus, the epidermis of the halo first shows a reduction in the amount of melanin on staining with silver and fewer DOPA-positive melanocytes than are seen in the normal epidermis. Ultimately, there is complete absence of melanin and also a negative DOPA reaction. Especially in early lesions, lymphocytes

may be seen rosetting around damaged melanocytes in the halo.

Histogenesis. Immunohistochemical staining for S100 protein helps in the identification of nevus cells within the inflammatory infiltrate because their number may be small and it may be difficult to differentiate them from the lymphocytes of the infiltrate (311). However, Langerhans cells and some histiocytes also react with S100 protein, and therefore a more specific marker such as Melan-A is preferable. Electron microscopic study reveals that nevus cells and melanocytes within reach of the infiltrate are damaged and ultimately disappear. In the nevus, many nevus cells appear vacuolated and contain only few melanosomes, but large aggregates of melanosomes are seen within macrophages (314,315).

In the depigmenting halo, the melanocytes show various kinds of degeneration, such as vacuolization and coagulation of the cytoplasm and autophagocytosis of melanosomes (316). It has been suggested that an initial noncellular stage of inhibition of both the melanocytes and the nevus cells may be responsible for the development of the depigmented halo, preceding the appearance of a dermal lymphomacrophagic infiltrate that ultimately leads to the destruction of the nevus (314). Both in halo nevi and in vitiligo, the depigmentation takes place through disappearance of the melanocytes. However, despite occasional patients who present with both lesions, halo nevus is likely not a form of vitiligo (317). The abundance of potential antigen-presenting cells and lymphocytes (including $CD8^+$ T cells) in the regressing nevus at the site of depigmentation suggests that these cells participate in the destruction of nevus cells and melanocytes in the halo phenomenon (318). In an interesting study of the lymphoid elements infiltrating halo nevi, oligoclonal expansion of T cells was observed in all patients, and in one patient, T cells using the same T-cell receptor b-chain were observed in distinct halo nevi, demonstrating a local expansion of common clones that are most likely activated by shared antigens within the nevi (319).

Differential Diagnosis. It can be difficult to differentiate early lesions of inflammatory halo nevus from a melanoma; both types of lesions may have a dense cellular infiltrate in the dermis, and, in halo nevi, the nevus cell nests, as a result of having been invaded by the cellular infiltrate, may appear atypical, which we consider to be reactive. The danger of misinterpretation is greatest in halo nevi without a halo, the so-called halo nevus phenomenon. However, the inflammatory infiltrate in halo nevi is more pronounced than in melanoma and extends diffusely through the lesion rather than being concentrated at the periphery as in most examples of tumorigenic melanoma. The diagnosis of melanoma rather than halo nevus is likely in a complex lesion that has an adjacent *in situ* or microinvasive component. Whether or not such an adjacent component is present, attributes of the nodule itself that should prompt consideration of melanoma include larger size, asymmetry, increased cellularity, lack of lesional cell maturation, uniform high-grade nuclear atypia, and mitotic activity.

If no identifiable nevus cells are present, the diagnosis of halo nevus may be suggested by the presence of melanophages in the dense cellular infiltrate and by the absence of melanin in the epidermis on staining with silver. However, one should also consider the possibility of a regressed squamous lesion or melanoma.

Recurrent Nevus (Pseudomelanoma)

Recurrence of a nevus may show clinical hyperpigmentation that on biopsy may show histologic changes suggestive of melanoma (320–324). Recurrence may follow incomplete removal of a nevus, particularly by a shave biopsy or electrodessication, or the nevus may apparently have been completely excised. A similar phenomenon has been described in relation to Spitz tumors (325). The term persistent nevus is sometimes used because it is considered that the clinical recurrence must have arisen from nevus cells that were not removed by the prior procedure. However, we have also considered the possibility that the "recurrent" pigmentation might be the result of a reactive hyperplasia and nevoid transformation of melanocytes in the epidermis above the healing biopsy site as a consequence of melanocyte growth factors known to be elaborated by scar tissue (e.g., c-kit ligand or fibroblast growth factors). In any event, at a clinical level, recurrence of apparently completely excised nevi is common. In a prospective follow-up study, 28% of all nevi and 41% of hairy nevi were reported to have recurred within 12 months after shave excision (326). The pigmentation in recurrent nevi is confined to the region of the scar and typically presents within a few weeks of the surgical procedure (320). After this rapid appearance, the pigment is stable. In contrast, recurrent melanoma does not respect the border of the scar and extends over time into the adjacent skin. Paradoxically, recurrent melanoma occurs more slowly, over months or years, but progresses inexorably.

Histopathology. Although most recurrent nevi are not cytologically atypical, in a few instances they contain atypical melanocytes, both singly and in nests, arranged mainly along the epidermal–dermal junction, but occasionally also extending into the upper dermis and also into the epidermis in a pagetoid pattern (Fig. 28-17) (152). The junctional nests are often composed of pigmented epithelioid melanocytes forming irregular nests, possibly as a result of their growth within an atrophic epidermal layer that interfaces with scar tissue. Deep remnants of the nevus may be seen in the reticular dermis beneath the scar (324). A lymphocytic infiltrate with melanophages may be seen in the upper dermis. The fibrosis of the scar may mimic and be mistaken for regressive fibrosis in a melanoma, especially in a superficial shave biopsy, where the bases of the scar cannot be visualized. Nevus cells in the dermis tend to show evidence of maturation, and the Ki-67 proliferation rate is low (327). Distinction from melanoma may be difficult without a pertinent history. However, the presence of scarlike fibrosis in the upper dermis where fibroblasts/myofibroblasts and collagen bundles lie parallel to the epidermal layer and of remnants of a melanocytic nevus beneath the zone of fibrosis, as well as the

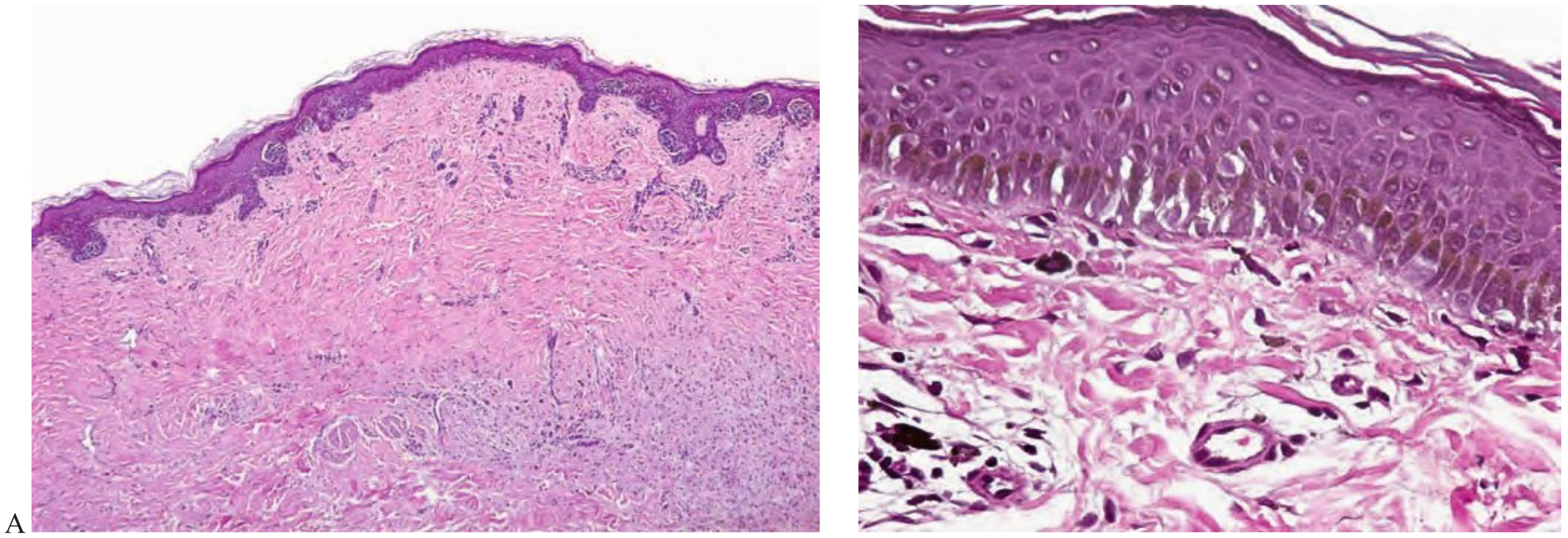


FIGURE 28-17. A: Recurrent and persistent melanocytic nevus. Recurrent pigmentation may occur after complete excision of a nevus or in the scar of a partial removal, as in this example, where the pathology of the recurrent nevus is seen only above the scar, and residual dermal nevus cells of the persistent original nevus are present to the right of the scar and beneath it. B: The cells of the recurrent nevus in the epidermis are variably enlarged, and they may be arranged with single cells predominating in foci and extending up into the epidermis in a pagetoid pattern, which is usually, as here, relatively subtle. Severe uniform atypia with extensive pagetoid proliferation should suggest the possibility of recurrent melanoma. The prior biopsy should be reviewed, if possible.

sharp lateral demarcation of the melanocytic proliferation devoid of lateral extension beyond the scar, usually make a correct diagnosis possible. As is true clinically, the recurrent nevus is confined to the epidermis above the scar, whereas recurrent melanoma may extend into the adjacent epidermis. However, persistent nevus, after a partial biopsy, may also involve skin adjacent to a scar. In this instance, ordinary criteria for the distinction between melanomas and nevi apply, as discussed later. In any problematic case in which the diagnosis is in doubt, the original biopsy should be obtained for review. This is particularly important in view of the possibility that genuinely dysplastic primary lesions, after initial biopsy, may also exhibit recurrent nevus–type changes.

Histogenesis. The nevus cells in some recurrent lesions may originate from residual nevus cells located either at the periphery of the lesion or along the outer root sheath of hairs. Recurrences that follow complete excision may be due to activation of melanocytes, possibly related to a subclinical field of melanocytes with a lowered threshold for nevus cell transformation that surrounded the original lesion. The confinement of these reactive changes to the regenerating epidermis above the biopsy scar suggests that the process may be related to growth factors involved in wound healing. Some of these, such as fibroblast growth factors and c-kit ligand, are well known to be trophic for melanocytes *in vitro* (328).

It is important to note that although previous biopsy is the most common cause of the recurrent nevus phenomenon, trauma to a lesion, potentially unrecognized by the patient, may also produce similar changes. Accordingly, whenever traumatic scar formation is noted in the dermal component of a nevus with overlying abnormalities of intraepidermal melanocytic proliferation, this possibility should be considered.

Dysplastic Nevus

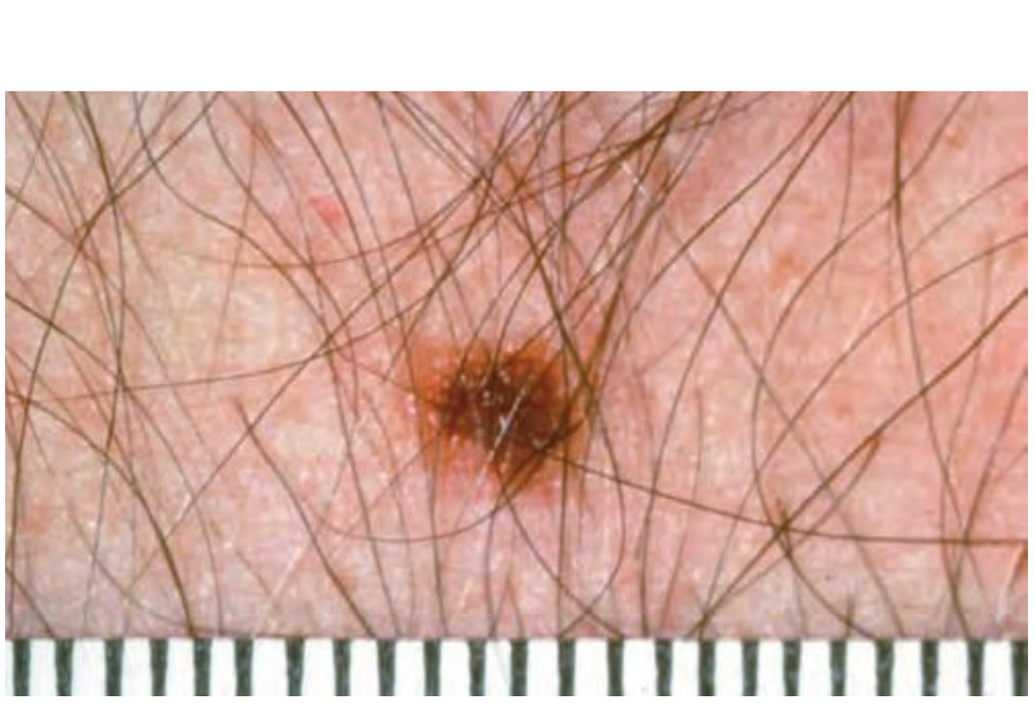
Dysplastic nevi were first described under the designations of B-K mole syndrome or atypical mole syndrome as multiple lesions occurring in patients with one or several melanomas and in some of their relatives (329,330). It soon became apparent that multiple moles, in addition to their familial occurrence, can also occur as a sporadic phenomenon in patients with a melanoma. This was referred to as the dysplastic nevus syndrome (331). Subsequently, cases of multiple dysplastic nevi without melanoma were reported (332). This was followed by the recognition that dysplastic nevi frequently occur as solitary lesions and are quite common, being found in 5% to 20% of various populations, depending on the criteria used (333). Although the nature and number of moles appear to be under genetic control (334), dysplastic nevi do not constitute a single-gene–related genetic syndrome, and in today's usage, it is more appropriate simply to characterize individuals as having dysplastic nevi, with some estimate of their number and degree of clinical atypia, rather than as having a particular form of dysplastic nevus syndrome.

Dysplastic nevi, clinically and histologically, can be placed into a continuum extending from a common nevus to a superficial spreading melanoma (335). They may be located anywhere on the body but are found most commonly on the trunk. A suitable rigorous definition of a clinically dysplastic nevus includes (a) the presence of a macular component either as the entire lesion or surrounding a papular center; (b) large

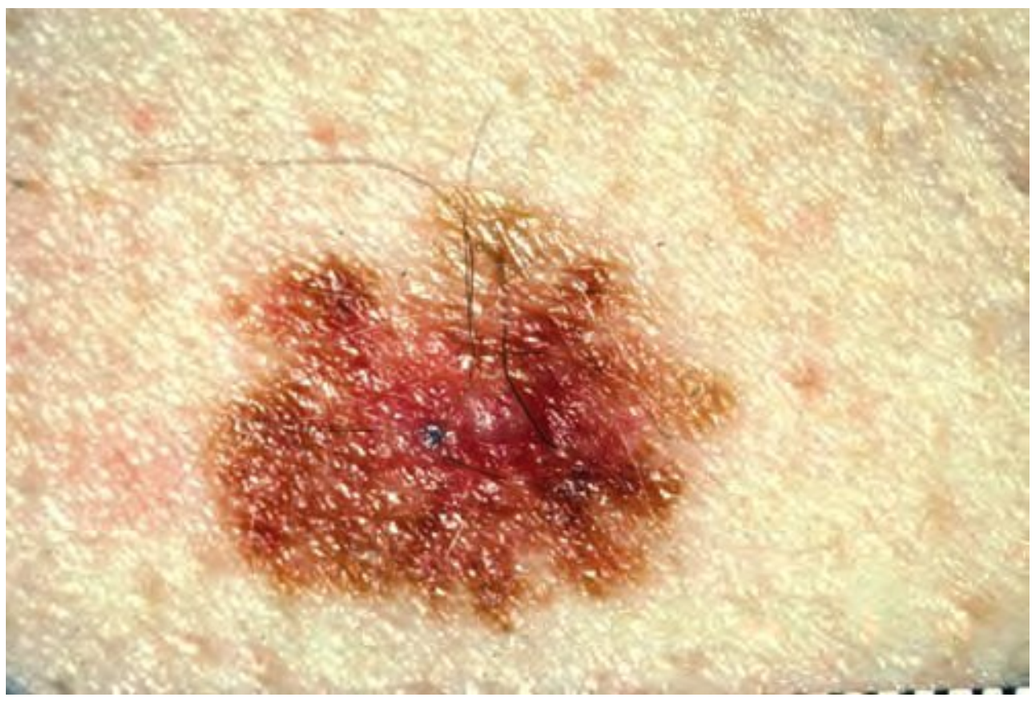
size, 5 mm or more; (c) irregular or ill-defined "fuzzy" border; and (d) irregular pigmentation within the lesion (Fig. 28-18A, B) (67,336). When defined in this manner, clinically recognized dysplastic nevi are a central risk factor for cutaneous melanoma; in a large case–control study, 1 clinically dysplastic nevus was associated with a 2-fold risk for melanoma, whereas 10 or more conferred a 12-fold increased risk (67). A recent meta-analysis of 46 studies concluded that a large number of common nevi was confirmed as an important risk factor with a substantially increased relative risk of 6.9 associated with the presence of 101 to 120 compared to less than 15 nevi, whereas only 5 (vs. 0) atypical (dysplastic) nevi were associated with a comparable relative risk of 6.4 (337).

Histopathology. When dysplastic nevi were first described in association with melanoma, it was considered that dysplastic nevi by definition always contained cytologically atypical melanocytes (333). Later, it was argued by some that an abnormal pattern of lentiginous melanocytic growth was a sufficient criterion without requiring atypia (338). It was even stated that "most compound nevi that are confined to the epidermis and the papillary dermis are dysplastic nevi" (338). Subsequently, the term Clark's nevus was coined to encompass all nevi with lentiginous junctional components (either alone or adjacent to a dermal component), irrespective of lesional size or of the presence or absence of cytologic atypia (339). This definition would include the very common small lentiginous junctional and compound nevi. Thus, the term Clark's nevus is not synonymous with the term dysplastic nevus. Because of controversy regarding its use and definition, use of the term dysplastic nevus was discouraged by a National Institutes of Health (NIH) panel, which proposed the synonymous term "nevus with architectural disorder and melanocytic atypia" (340). This clumsy term is used by a minority of dermatopathologists, with a majority favoring the dysplastic nevus nomenclature (341). Specificity in distinguishing dysplastic from nondysplastic nevi is likely to be increased by the inclusion of size and cytologic atypia as criteria, as was done in the original reports. In our practice, small lesions or lesions with architectural features of dysplastic nevi but without cytologic atypia may be reported as compound nevi or as lentiginous compound nevi, or the NIH descriptive terminology may be used. Criteria for assessing melanocytic dysplasia may be summarized in two categories: architectural features and cytologic features (333). These features are closely but not perfectly correlated (Fig. 28-18) (342).

In the architectural pattern of melanocytic dysplasia, the lesions are either entirely junctional, or there is a prominent junctional component that is symmetrically distributed at the shoulders or junctional edges that extend laterally beyond a central dermal component (Fig. 28-18C). At higher magnification, nested and lentiginous proliferation of nevus cells in the epidermis is the dominant feature in the junctional component. There is elongation of the rete ridges and an increase in the number of junctional melanocytes, arranged in nests with long axes tending to lie in parallel to the epidermal surface. These nests tend to lie near the tips and sides of elongated rete ridges and to form bridges via apparent fusion of nests between adjacent rete (Fig. 28-18D). There may be scattered single cells in lentiginous array as well, but these do not predominate, and there is no continuous proliferation of single cells between the rete. The melanocytes in the junctional nests are frequently spindle shaped, but they may be large and epithelioid and show abundant cytoplasm with fine, dusty (finely divided)

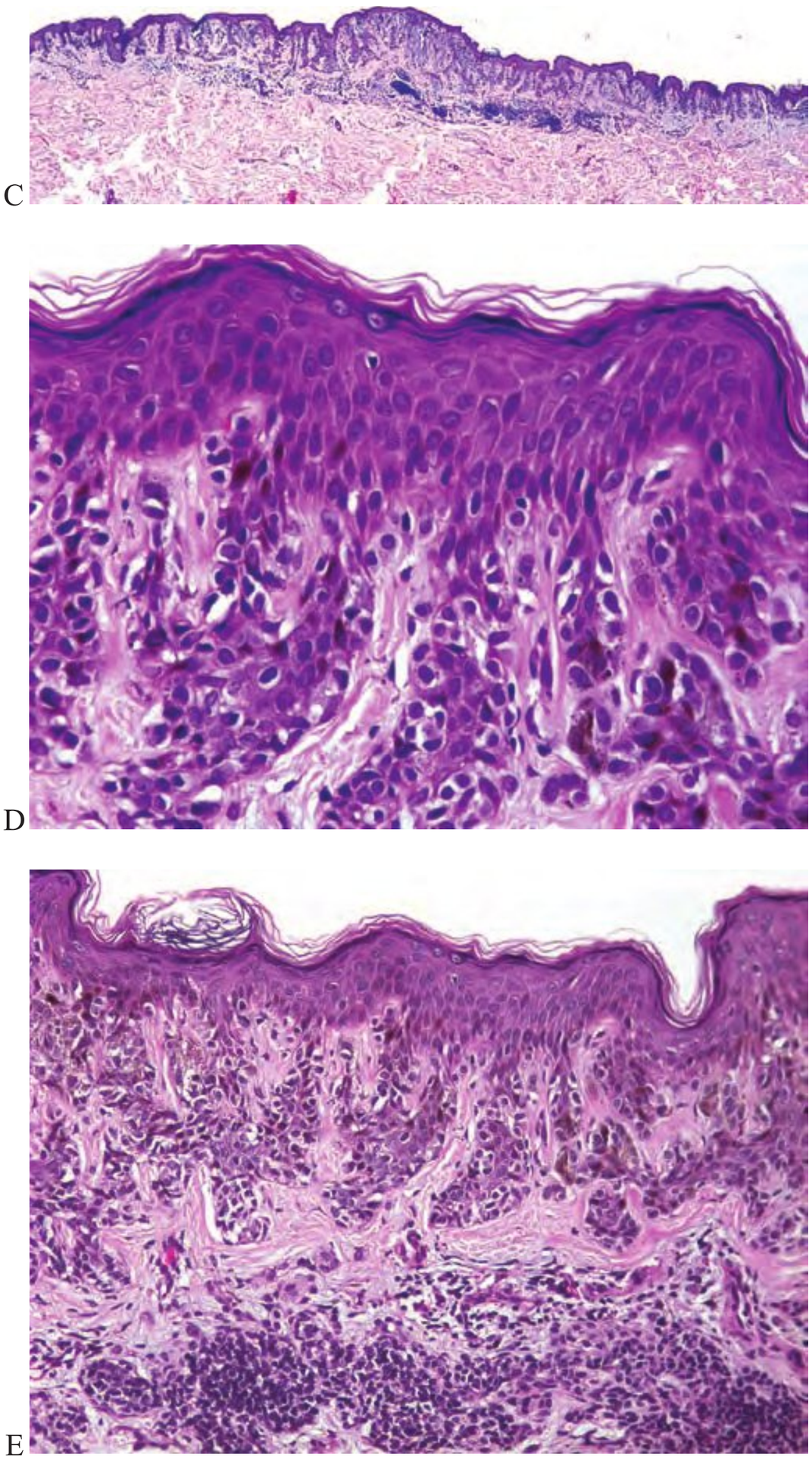


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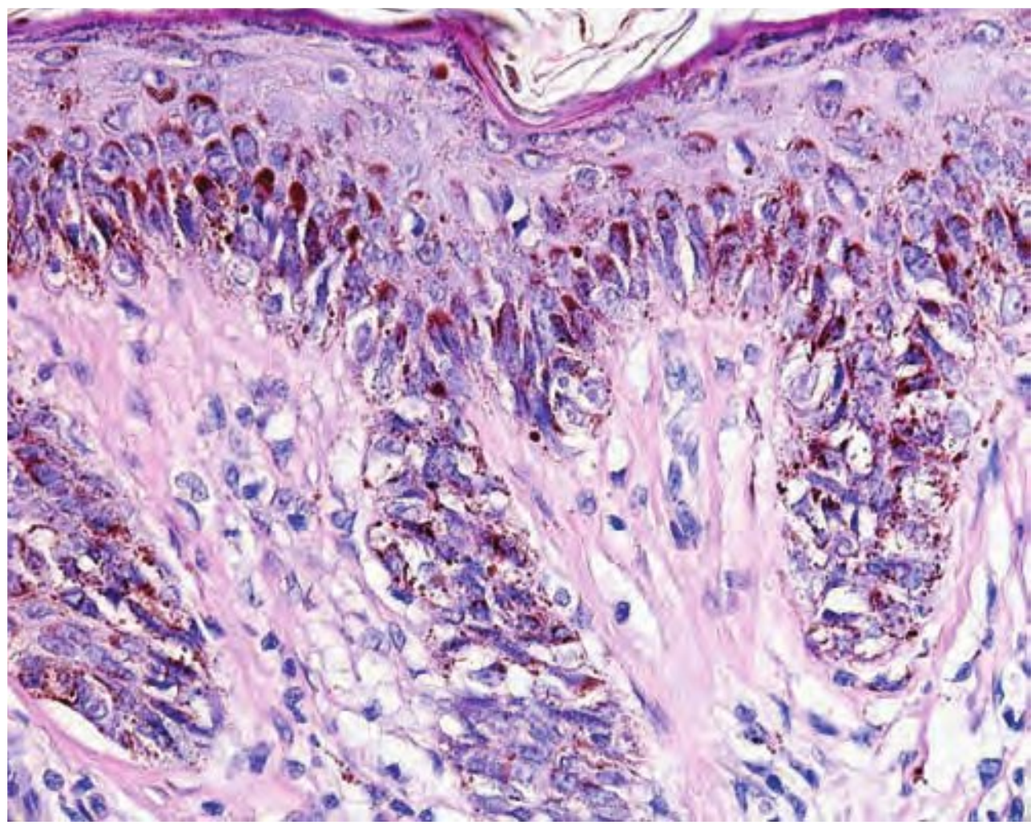
FIGURE 28-18. A: Junctional dysplastic nevus. A lesion that meets minimal clinical criteria. The diameter is almost exactly 5 mm, the lesion is entirely flat, there is mild pigmentary variegation, and the border is ill defined or "fuzzy." B: Compound dysplastic nevus. This lesion is relatively broad and quite irregular in outline, with variegated shades of tan and brown pigmentation. There is a papular compound portion near the center, and the periphery is flat, with an ill-defined "fuzzy" border in some areas but a more discrete border in others. This morphology overlaps with that of a radial-growth-phase melanoma of the superficial spreading type, and a lesion such as this should be considered carefully for excision to rule out a possible melanoma. (continued)



C

D

E



F

FIGURE 28-18. Continued. C: At scanning magnification, the lesions are broad and symmetric. If a dermal component is present, as here in the center of the lesion, the epidermal component (which is always present) extends beyond its shoulder. D: In the junctional compartment of the nevus (the shoulder just mentioned), the epidermal rete ridges are elongated but delicate, and there are nests of lesional cells that tend to be oriented parallel to the surface and to bridge between adjacent elongated rete. The lesional cell nuclei tend to be moderately enlarged compared to most banal type A nevus cells, and a minority of them have slightly irregular nuclei that are either hyperchromatic or have prominent nucleoli (random mild to moderate cytologic atypia). E: In the center of the nevus, there are orderly dermal nevus cells that are usually confined to the papillary dermis or may enter the upper reticular dermis. The junctional component in such a lesion tends to resemble that at the shoulder. F: Severe melanocytic dysplasia with changes suggestive of evolving melanoma in situ. There is a tendency to confluence and lack of definition of nests and to continuous extension of the proliferation in the suprapapillary plates between the rete. Cytologic atypia in the form of nuclear irregularity and the presence of nucleoli, though moderate in degree, is relatively uniform.

melanin granules. If the lesion is compound, nests of melanocytes in the papillary dermis show a uniform appearance and evidence of maturation with descent into the dermis, as seen in an ordinary compound nevus. In these compound dysplastic nevi, the intraepidermal component extends by definition beyond the lateral border of the dermal component, forming a shoulder to the lesion histologically and a "target-like" or "fried-egg" pattern clinically. Pagetoid extension of melanocytes into the epidermis is absent or slight and limited to the lowermost layers. A lymphoid inflammatory infiltrate, usually only of a mild or moderate degree and intermingled with melanophages, is present in the dermis beneath areas of junctional activity. The papillary dermis is also characteristically fibrotic, and typically lamellae of collagen encircle affected rete (concentric fibroplasia) and/or form stacked layers within dermal papillae (lamellar fibroplasia). The nevus cells in the dermis are mature, usually of the type B variety (Fig. 28-18E). They are often in continuity with similar cells in the papillary dermis, or in some cases they may enter the upper reticular dermis (compound dysplastic nevus with congenital features) (343). Most dysplastic nevi are clinically stable (344), so that they are not active in the sense of continuing growth.

Cytologically, in addition to the lentiginous melanocytic hyperplasia, melanocytic nuclear atypia is required for the diagnosis. This atypia is characterized by irregularly shaped, large, hyperchromatic nuclei in some melanocytes. Most atypical melanocytes lie singly or in small groups, and the atypia involves only a minority of the lesional cells ("random" cytologic atypia) (Fig. 28-18D). Focal extension of atypical-appearing melanocytes into the lower spinous layer may be seen, but if this is prominent, the possibility that transformation into melanoma *in situ* may have occurred

TABLE 28-4 Criteria for Dysplastic Nevus Grading

Atypia	None	Mild	Moderate	Severe	Melanoma
Lateral circumscription	+++	++	+	+	+/−
Symmetry	+++	+++	+++	+/−	+/−
Junctional extension	+/−	+++	+++	+++	++++
Rete ridge distortion	+/−	+/−	++	+++	++++
Concentric fibrosis	+/−	+	++	++	+/−
Diffuse fibrosis	+/−	+/−	+/−	+/−	+++
Lymphocytes	+/−	+	++	+++	++++
Upward migration	+/−	+/−	+/−	+/−	++++
Suprapapillary plates involved	−	−	−	+/−	++++
Nuclear size	+	+	++	++	+++
Nucleoli	−	+/−	+/−	+++	++++
Chromatin clumping	−	−	+/−	++	++++
Dermal mitoses	−	−	−	−	+++

Based on Arumi-Uria M, McNutt NS, Finnerty B. Grading of atypia in nevi: correlation with melanoma risk. Mod Pathol 2003;16:764–771.

should be seriously considered. A borderline lesion may be a severely dysplastic nevus or an early superficial spreading melanoma that is still *in situ* or microinvasive. Because such early melanomas are curable after simple excision (345), this distinction does not carry the implication of increased mortality, as long as the lesion is entirely removed. For lesions with severe dysplasia in which the differential diagnosis includes the possibility of early melanoma, conservative reexcision is recommended for lesions that have been minimally or incompletely excised.

Melanocytic dysplasia appears to be a quantitative trait, and several authors have produced guidelines for grading dysplasia. McNutt and his colleagues recently published a detailed schema for grading lesions from nevi without atypia to melanoma. This schema has been correlated with biology, in that patients with more atypia in their nevus biopsies are more likely to have had a primary melanoma. Table 28-4, adapted from Arumi-Uria et al. (346), presents key grading features in schematic form. The critically important criteria for distinguishing between nevi and melanoma are given in more detail in Table 28-5. The features of severe dysplasia in this study included nests predominating over single cells in the epidermis, only rare upward migration of cells in the center and not at the periphery of the lesion, and a dermal component that tended to be abundant, with more crowding of the dermal nests. Cytologically, the nuclei are usually larger than those of keratinocytes, and there was often an admixture of cells that include large, bizarre, hyperchromatic nuclei. Confluent ("uniform") atypia was not observed. Nucleoli were often prominent. The grading for each lesion was based on a combination of these architectural and cytologic features (346). Similar criteria for grading of dysplastic nevi have been published and illustrated by others (343,347–349). In general, in our opinion, lesions that show significant overlap with criteria for melanoma such as those listed here should be graded as severe dysplasia, with an indication, if appropriate, that evolving melanoma *in situ* cannot be ruled out (Fig. 28-18F). In cases of extreme doubt, a descriptive diagnosis such as superficial atypical melanocytic proliferation of uncertain significance may be used, with a differential diagnosis and often with a recommendation for therapy (231). Such lesions should be managed by complete excision, with, at a minimum, a clear margin of normal skin around the scar and any residual lesion. If melanoma *in situ* cannot be ruled out, current guidelines recommend consideration of excision with a 5-mm margin.

The diagnosis of melanocytic dysplasia has been found to be reproducible by two international multidisciplinary groups that used agreed-on criteria (350,351). In another study, including participants whose published criteria differed in their requirements for atypia and for a size criterion, it was concluded that the participating pathologists used different diagnostic criteria, but that their usage was consistent (352). It has been suggested that histologic criteria may be more specific when applied to larger lesions, and that cytologic atypia may play a key role in the identification and significance of these lesions. Slight melanocytic atypia may be subtle and poorly reproducible and also may be of modest clinical significance. On the other hand, the diagnosis of higher-grade dysplasia (severe dysplasia) is likely to be both more reproducible and of substantially greater biological significance (336,353). In our practice, for purposes of management of the lesion itself, we tend to distinguish between mild to moderate lesions and lesions that at least focally show severe dysplasia (e.g., moderate to severe, or severe). Severe dysplasia shares sufficient characteristics with melanoma (Table 28-4) to suggest that it should be managed as a lesion with potential for local recurrence, with complete excision and clear margins. Via such an approach, dysplastic nevi may essentially be segregated into low-grade and

TABLE 28-5 Dysplastic Nevus Versus Radial-Growth-Phase Melanoma

Dysplastic nevus	Radial-growth-phase melanoma
Pattern features	
May be <6 mm in diameter, not often >10 mm	Usually 6 mm, often >>10 mm
Somewhat symmetric	Often highly asymmetric
Often symmetrically arranged about shoulders of a mature dermal nevus	If dermal nevus is present, it is likely to be asymmetrically placed
Uniformly elongated narrow, delicate rete ridges	Irregularly thickened epidermis, often with effaced rete ridges
No alteration of stratum corneum	May be hyperkeratotic
Nests predominate over single cells in the epidermis	Single cells predominate, except in late lesions
Little or no pagetoid spread of lesional cells into epidermis	Usually obvious pagetoid spread into epidermis, extending to stratum corneum
Patchy lymphocytic infiltrate in papillary dermis	Brisk, bandlike infiltrate
No regression	Regression common
Last lesional cells at the lateral border are often in a nest	Last cells are often single and may be above the basal zone
Cytologic features	
Scattered atypical epithelioid cells with dusty melanin pigment, nucleoli, anisokaryosis ("random atypia")	Epithelioid cells with dusty pigment, nucleoli, anisokaryosis predominate ("uniform atypia")
Most cells are not atypical	Most cells are atypical
No mitoses in epidermis or dermis	Intraepidermal mitoses in about one third of cases; no mitoses in dermis
Cells in dermis, if any, are smaller than those in epidermis	Cells in dermis are similar to those in epidermis

high-grade lesions, providing a less complicated approach to diagnosis and therapy. On the other hand, in Shors et al.'s recent case–control study (354), reviewed in more detail in the next section, any dysplasia beyond mild was associated with increased melanoma risk, suggesting that patients with moderate or severe dysplasia, but perhaps not mild dysplasia (in the absence of other risk factors), should be offered follow-up. Further refinement of criteria for dysplastic nevus diagnosis will likely occur in the near future as a result of these studies.

Pathobiology. After the early descriptions of dysplastic nevi as markers of high risk for melanoma in hereditary melanoma kindreds, it was widely assumed that identification of individuals in the community at high risk for melanoma required biopsy of a nevus to rule out dysplasia. Subsequent studies have shown that risk is best assessed by the clinical evaluation of the patients' entire cutaneous phenotype. The total number of nevi and the number of large nevi (355), light skin color, and high freckle density (356) are all risk factors for development of melanoma, but the strongest risk factor is the presence and number of dysplastic nevi (67). Family history of melanoma is another significant risk factor (345,357), as is a personal history of prior melanoma (358). In members of hereditary melanoma kindreds, the lifetime risk for melanoma approaches 100% in members who have clinically dysplastic nevi, corresponding to approximately 100-fold relative risk compared to the general population (358–360). In people without a family history of melanoma, the relative risk as determined in multiple cohort and case–control studies from different geographic regions is of the order of 3- to 10-fold, depending on the number of dysplastic (clinically atypical) nevi on their skin (67,337,355,361–383). These data are based on clinical evaluation of nevi, which does not necessarily correlate well with histologic atypia (384). Even when a biopsy can be obtained, usually only one or two nevi are sampled, whereas clinical examination considers the whole phenotype.

Nevertheless, it is clear that histologic atypia in dysplastic nevi is associated with melanoma risk. In one study, histologically verified clinically dysplastic nevi were associated with a relative risk of 4.6 for melanoma (363). In a multiobserver study in which biopsies had been taken from 24 melanoma cases and 21 random controls, four of six observers (who had each used different criteria) found an increased prevalence of histologic dysplasia ranging up to a 3.5-fold increase in cases compared to controls (352). An interesting study Sagebiel et al. found that the degree of dysplasia in a nevus biopsy correlated with increasing age of the patient, with frank melanomas occupying the oldest age category (343). More recently, as discussed earlier (Table 28-4), Arumi-Uria et al., in a very large single-institution study, demonstrated a clear relationship between the degree of atypia in clinically atypical (dysplastic) nevi submitted for biopsy and the chance that a patient has had a melanoma, demonstrating that the risk of melanoma is greater for persons who tend to nevi with high-grade histologic atypia (346). Finally, this vexed question seems to have been settled in a case–control study carried out by Shors et al., who studied nevi from 80 melanoma cases and spouse controls and found that dysplastic nevi with moderate to severe histologic dysplasia were a risk factor for melanoma, with an adjusted

risk ratio of 3.99 (354). In future work, this group will have the opportunity to identify the criteria that best fit with risk, providing an evidence-based approach to refining the histological diagnosis of a dysplastic nevus.

Although melanomas in patients with dysplastic nevi may arise within a preexisting dysplastic nevus, the majority arise *de novo*. Histologic changes of an associated dysplastic nevus are seen at the periphery of melanomas in approximately 20% to 30% of cases (105,281,385–388), supporting the view that at least some cutaneous melanomas have their origin in a dysplastic nevus. Even so, most dysplastic nevi are clinically stable (344) and will never evolve into melanomas. This paradox is explained by the fact that dysplastic nevi are vastly more common than melanomas in the general population and provides a rationale against indiscriminate excision of clinically stable dysplastic nevi for prophylaxis of melanoma.

In keeping with their role as potential precursors and as simulants of melanoma, dysplastic nevi tend to occupy an intermediate position between nevi and melanomas in laboratory studies. In cell cycle proliferation marker studies, the reactivity of dysplastic nevi is intermediate although closer to that of common nevi than of melanoma (389,390). Electron microscopic studies of dysplastic nevi have shown abnormal spherical and partially melanized melanosomes similar to those seen in superficial spreading melanomas (391,392). Although most *in situ* hybridization or immunohistochemical studies have shown reactivity similar to common nevi, dysplastic nevi have reacted in an intermediate manner with some markers (393–395), whereas the reactivity with others has been more akin to that of melanomas (396) or nevi (397). Interesting studies have shown that the amount of red pheomelanin is greater in dysplastic nevi than in common nevi or normal skin (398). Because pheomelanin may be a generator of toxic free radicals after UV irradiation, this attribute may increase the risk of genetic mutations in these lesions that may contribute to continued tumor progression (399). Genetic changes in nevi and dysplastic nevi are beginning to be cataloged. For example, loss of heterozygosity at the 9p locus (which contains the p16/CDKN2A tumor suppressor gene) was found in 64% of dysplastic nevi and 50% of benign nevi, although homozygous deletion of p16 was found in 29% of dysplastic nevi but never in benign nevi (400). Recent studies have demonstrated aberrations in DNA repair pathways in dysplastic nevi (401) and microsatellite instability in melanomas and nevi, including dysplastic nevi (402,403). These findings are consistent with DNA repair deficiency in patients with dysplastic nevi and tend to correlate with patient groups ordered according to increasing melanoma risk (403).

Differential Diagnosis and Management. The major importance of biopsy in an individual with dysplastic nevi is to rule out the possibility of melanoma in a problematic lesion. Key features in making this distinction are reviewed in Table 28-5. Lesions in which some features of dysplasia are observed but not judged to be diagnostic may be reported as lentiginous (junctional or compound) nevi or nevus with architectural disorder with an interpretive note. Such a note may indicate that additional evaluation of the patient could be appropriate to assess melanoma risk, and that periodic surveillance could be appropriate, especially if there are other clinically atypical (dysplastic) nevi or a family or personal history of melanoma (404).

In conclusion, in patients with dysplastic nevi, periodic surveillance of the patient and evaluation of first-degree relatives may be indicated for early diagnosis of melanoma. This is especially so if the clinically dysplastic lesions are numerous and/or markedly atypical and in individuals who have a personal or family history of melanoma. There is evidence that surveillance and/or education of individuals at increased risk for melanoma can result in the diagnosis of melanomas in their early, curable stages (405). The major role of biopsy and of histologic examination of nevi in such individuals is to rule out melanoma in a clinically suspicious or changing lesion. However, histologic atypia also correlates with a patient's risk of developing a melanoma. Atypia is heterogeneous in these lesions (in contrast to the uniform atypia that characterizes most melanomas), and so complete excision biopsy is recommended (which can include shave or punch excisions, as long as the entire lesion is included in the specimen) (406). Lesions whose biopsy shows severe dysplasia or changes suggestive of evolving melanoma *in situ* (see Table 28-5) should be considered for conservative reexcision if their margins are close or involved (404).

MALIGNANT MELANOMA

Most malignant melanomas arise in the epidermis and these may be *in situ* (entirely within the epidermis) or invasive (extending from the epidermis into the dermis). Occasional invasive melanomas are entirely dermal at presentation. Invasive melanoma may be *tumorigenic* ("*vertical growth phase*") or *nontumorigenic* ("*radial growth phase*"). Melanoma *in situ* and nontumorigenic invasive melanoma can be divided into (a) lentigo maligna, (b) superficial spreading, (c) acral-lentiginous, and (d) mucosal lentiginous types. Tumorigenic melanoma may arise in relation to a preexisting nontumorigenic component of any of the foregoing types, in which case it is named accordingly. Alternatively, tumorigenic melanoma may arise *de novo*, without evidence of an adjacent *in situ* or microinvasive component at the time of detection, in which case it is termed (e) "nodular melanoma." However, some but all of these lesions probably arise initially via a nontumorigenic intraepidermal component that fails to develop or persist as the tumorigenic component evolves. Important variants of tumorigenic melanoma include (f) desmoplastic melanoma and (g) neurotropic melanoma. Other unusual forms of tumorigenic melanoma are discussed later.

All major types of melanoma originate almost invariably from melanocytes at the epidermal–dermal junction. Although the lesions are commonly associated with a preexisting nevus,

TABLE 28-6 Classification of Melanoma

Radial growth phase (RGP)
Nontumorigenic melanoma
  In situ or microinvasive
    Superficial spreading melanoma (SSM): 67% of all melanomas (410)
    Lentigo maligna melanoma (LMM): 9% (410)
    Acral-lentiginous melanoma (ALM): 4% (410)
    Unclassified radial growth phase (URGP): 5% (410)
Vertical growth phase (VGP)
Tumorigenic melanoma
  No RGP compartment
    Nodular melanoma (NM): 10% of all melanomas (410)
  RGP compartment present (may be SSM, LMM, ALM, URGP): 90% (410)
    Usual vertical growth phase: 96% (414)
    Desmoplastic: 3%, most are also neurotropic (414)
    Neurotropic, not desmoplastic: 1% (414)
Other variants (nevoid/ minimal deviation, balloon cell, amelanotic, spindle cell, malignant blue nevus, melanoma in congenital nevus, clear cell sarcoma, malignant melanocytic schwannoma, etc.): low frequency, no definitive frequency estimates exist

Based on 1996 and 2006 World Health Organization classifications (412,413).

more than half of them arise either *de novo* or have completely supplanted the precursor nevus at the time of presentation. The majority of cutaneous melanomas are believed to be caused by sunlight exposure, either intermittent (sunburn episodes) in the more common superficial spreading melanomas or chronic in the lentigo maligna melanomas. The cause of acral and mucosal melanomas is unknown.

Classification of Melanoma

There are two major categories of melanoma, which represent sequential stages or phases of stepwise tumor progression (407). In the nontumorigenic radial or horizontal growth phase, the neoplastic melanocytes (melanoma cells) are confined to the epidermis (melanoma *in situ*) or to the epidermis and papillary dermis without evidence of proliferation in the dermis and without formation of an expansile tumor mass. These lesions may be confined to the epidermis (*in situ* melanoma), or there may be a few cells in the dermis (microinvasive melanoma). This phase may be followed after varying lengths of time by the focal appearance of the mitogenic and/or tumorigenic vertical growth phase, or a phase of dermal invasion with capacity for not only cell survival, but also proliferation in the dermis and usually with expansile tumor formation. Thus, a fully evolved melanoma may have two major lesional compartments: the nontumorigenic, *in situ* or microinvasive radial growth phase, placed within which there may be a contiguous tumorigenic vertical-growth-phase compartment. In addition, dermal and/or epidermal compartments of an associated nevus may be recognized in some melanomas. Variants of each of the major compartments have been described and are listed in Table 28-6 (407–411).

About 5% to 10% of melanomas in different series fall into "unclassified" or "other" categories (410,411). The fact that categorization of an individual case is occasionally difficult does not mean that classification of melanoma, after accounting for tumor thickness and site, is unnecessary, as has been stated (415). Even though in the tumorigenic stage the prognosis is similar for all four types of melanoma, depending largely on the depth of invasion, the duration of the *in situ* phase preceding lentigo maligna melanoma is, on the average, longer than that of superficial spreading melanoma (416). Furthermore, there are differences in the apparent etiology of the various forms of melanoma and in their molecular biology (417,418). In a recent important study, attributes traditionally used in the classification of melanomas into the aforementioned clinicopathologic subtypes correlated strongly with the mutation status of the tumors studied. An algorithm involving an initial separation based on melanoma cell nesting and scatter, followed by consideration of cell size and age, predicted BRAF mutation with an error estimate of 13%, demonstrating that parameters routinely available and traditionally used by practicing pathologists allow good prediction of BRAF mutation status. It was concluded that this "strong association between genetic alterations and morphological findings further supports the existence of biologically distinct melanoma types, and the use of genetic factors to develop and clarify improved clinically applicable classification systems" (419). Finally, the separate description of the morphologic variants has nosologic and pedagogic value, facilitating accurate diagnosis by enabling the recognition of the variant patterns.

Morphology of Tumorigenic and Nontumorigenic Melanoma

In their nontumorigenic stage, melanomas tend to expand more or less inexorably along the radii of an imperfect circle as viewed clinically. The clinically derived term "radial" growth has no intuitive histologic meaning, and the histologic term "horizontal growth phase" has been suggested as an alternative. The major clinical diagnostic criteria have been summarized as the ABCD criteria (420), which include lesional *asymmetry* (one half of a lesion does not match the other in shape or in color distribution), lesional *border* irregularity (lesions tend to have an indented coastline like the map of a small island), lesional *color* variegation (the surface is multicolored and may include shades of tan, brown, blue-black, gray-white, and other variations), and lesional *diameter* generally greater than 6 mm (although some melanomas are smaller) (Fig. 28-19). These criteria, although useful, are imperfect; recent guidelines have emphasized the value of the "ugly duckling" sign of the changing or different-looking mole in the practice of skin self-examination (421). In view of this, the letter E could be added to the criteria to indicate the "evolving" nature of a changing melanocytic lesion.

Histologically, most of the lesional cells in nontumorigenic melanomas are located in the epidermis. Microinvasion is here defined as the presence of a few lesional cells in the papillary dermis, without tumorigenic proliferation, which is defined later. Microinvasive lesions are not specifically distinguishable from *in situ* melanomas on clinical grounds. It has been questioned whether microinvasive or *in situ*, nontumorigenic melanomas lack competence for metastasis; in a database of 624 clinical stage I invasive melanoma cases followed 10 years or more, the 8-year survival rate from 161 microinvasive or *in situ* (pure radial growth phase) melanomas was 100 ± 1%. In the same database, the patients with lesions having only radial growth phase were 4.3 years younger than those additionally having vertical growth phase, consistent with the hypothesis that the radial growth phase is antecedent and relatively indolent (345,422).

Clinically, the tumorigenic vertical growth phase is qualitatively different from the plaquelike radial growth phase. The tumor appears as an expanding papule within a previously indolent plaque lesion and grows in three dimensions in a balloon-like fashion to form a nodule (Fig. 28-19B). Typically, the ABCD criteria do not apply to the tumor nodule itself, which is commonly symmetric with smooth borders. The color is often


A


B

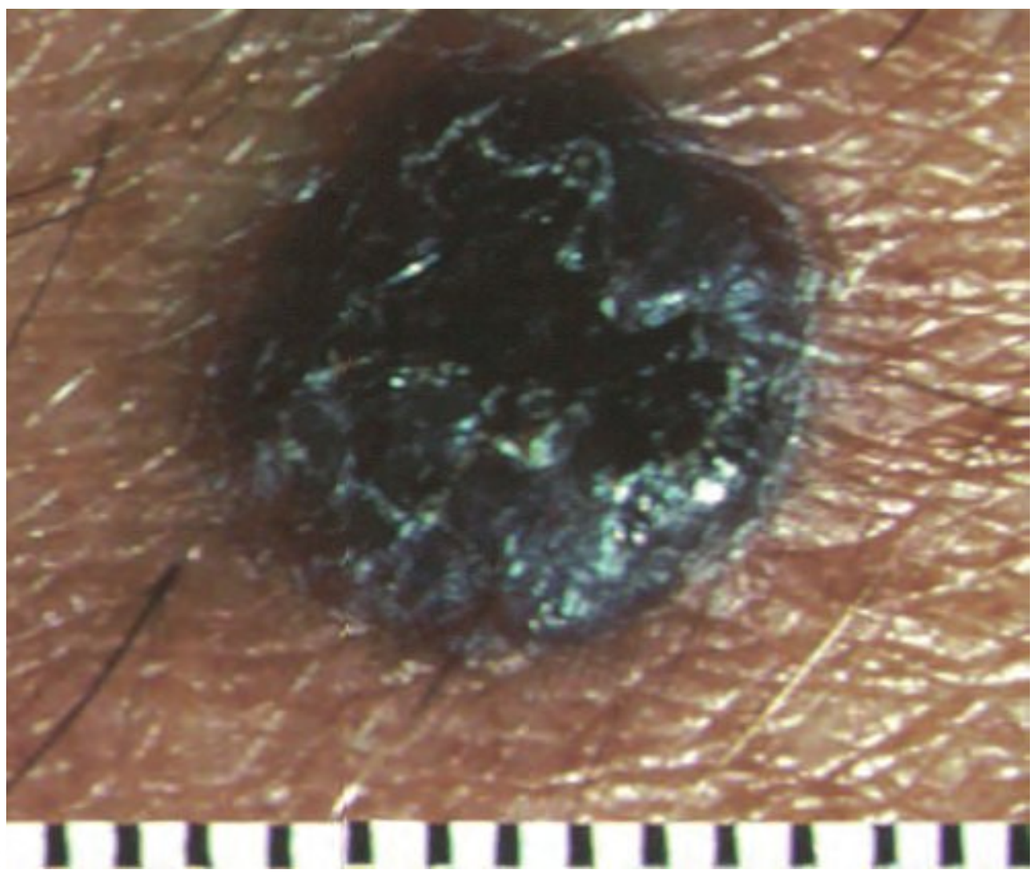

C

FIGURE 28-19. A: Superficial spreading melanoma, nontumorigenic, radial growth phase only (microinvasive), with focal regression. The lesion is large, asymmetric, with irregular border, and variegated colors including reddish-brown and focal areas of blue-black, as well as a focal grayish area of partial radial-growth-phase regression (near the middle of the lesion). This morphology could overlap with that of the severely dysplastic nevus in Fig. 28-18B. Each of these lesions is sufficiently atypical that it should be considered for excision for pathologic diagnosis. B: Acral-lentiginous melanoma, tumorigenic, with extensive radial growth phase, partial regression of the radial growth phase, and a bulky ulcerated tumorigenic vertical-growth-phase nodule. C: Nodular melanoma. The tumorigenic vertical-growth-phase nodule, lacking an adjacent radial growth phase by definition, is relatively small, symmetric, and uniform in color. The focally ulcerated surface may lead to presenting symptoms of bleeding and oozing, which are signs of a relatively advanced melanoma.

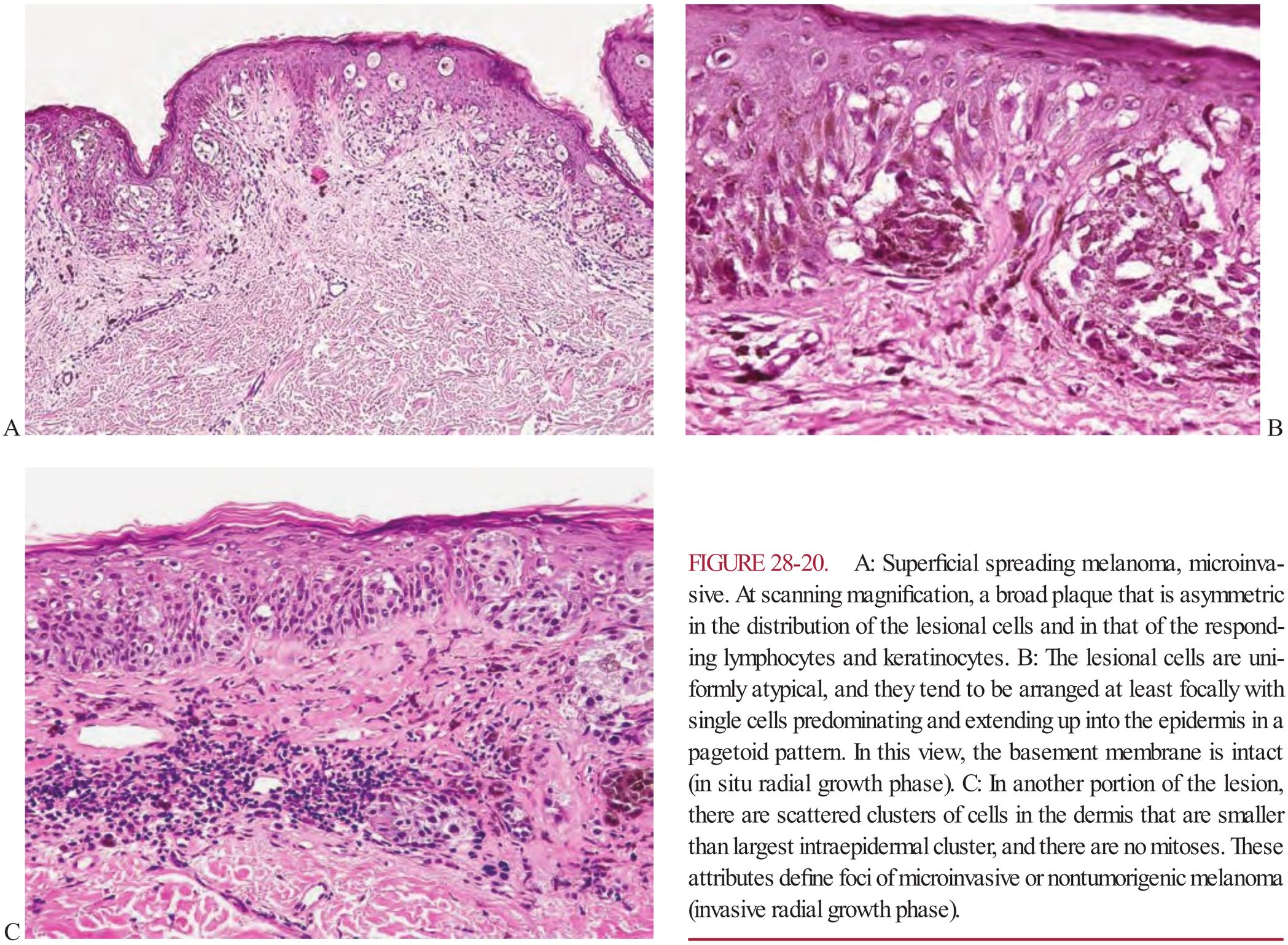


FIGURE 28-20. A: Superficial spreading melanoma, microinvasive. At scanning magnification, a broad plaque that is asymmetric in the distribution of the lesional cells and in that of the responding lymphocytes and keratinocytes. B: The lesional cells are uniformly atypical, and they tend to be arranged at least focally with single cells predominating and extending up into the epidermis in a pagetoid pattern. In this view, the basement membrane is intact (in situ radial growth phase). C: In another portion of the lesion, there are scattered clusters of cells in the dermis that are smaller than largest intraepidermal cluster, and there are no mitoses. These attributes define foci of microinvasive or nontumorigenic melanoma (invasive radial growth phase).

quite uniform and may be pink rather than blue-black, and the diameter of the tumor nodule itself is often less than 6 mm, even in a quite high-risk lesion. For these reasons, clinical diagnosis of melanoma may be subtle in a nodular melanoma that lacks an adjacent nontumorigenic compartment (Fig. 28-19C).

The major histologic feature that distinguishes a tumorigenic melanoma is the capacity for proliferation of melanoma cells in the extracellular matrix of the dermis to form an expansile mass. In contrast, nontumorigenic melanoma cells may proliferate inexorably in the epidermal compartment and may invade the dermis but do not proliferate there (Fig. 28-20). The lack of metastatic capacity in nontumorigenic melanomas may be explained by considering that cell proliferation in the extracellular matrix of a distant site is essential to the development of a metastasis. Thus, it is likely that a tumor that cannot proliferate in the matrix at its local site of origin would not do so in a metastatic site either. Operational definitions for tumorigenic and nontumorigenic melanoma and for radial and vertical growth phase are as follows (422,423):

Tumorigenic melanoma. A mass of melanoma cells is present in the dermis, defined as at least one cluster (nest) in the dermis that is larger than the largest intraepidermal cluster (indicative of a tumor with capacity for expansile growth in the dermis) (Fig. 28-21).

Nontumorigenic melanoma. No mass of melanoma cells is present in the dermis (there is no cluster larger than the largest intraepidermal cluster) (Fig. 28-20C).

Vertical growth phase (VGP). A lesion is classified as vertical growth phase if it is tumorigenic or if there are any dermal mitoses even in the absence of architectural criteria for tumorigenic growth. The presence of any mitoses in the dermal component of the melanoma is indicative of a tumor with capacity for expansile growth in the dermis and defines the concept of typical vertical growth phase even in the absence of a frank tumor mass (Fig. 28-21).

Radial growth phase *(RGP).* A lesion is classified as radial growth phase only ("pure" RGP, or "radial growth phase confined") if it is nontumorigenic and there are no dermal mitoses. Alternatively, the radial growth phase may be present as a compartment of a complex primary melanoma in which the foregoing histologic criteria apply only to that portion of the melanoma adjacent to the VGP (Fig. 28-21). "Pure" RGP melanoma may be defined as the absence of VGP in a primary melanoma (Fig. 28-20).

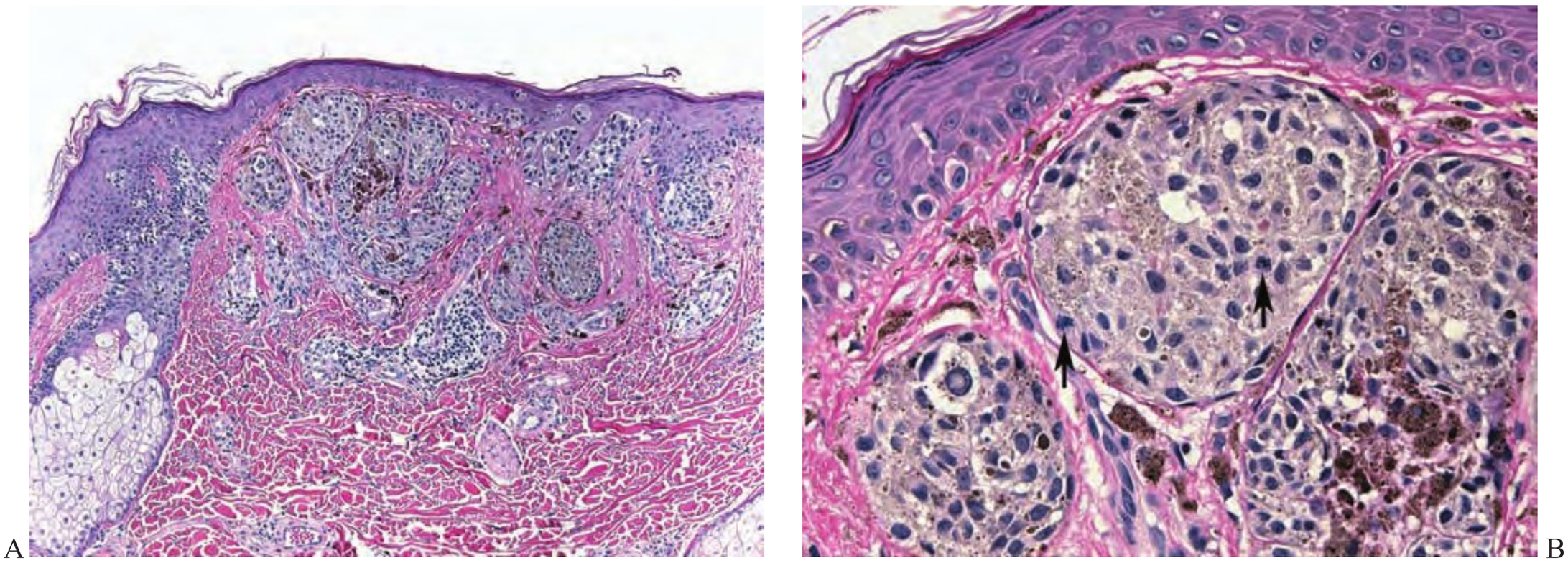


FIGURE 28-21. A: Melanoma with early tumorigenic vertical growth phase. This lesion is Clark level II because the papillary dermis is expanded but not quite filled by the proliferation. The Breslow thickness is approximately 0.5 mm. Several of the clusters of cells in the dermis are slightly larger than the largest clusters in the epidermis, indicative of tumorigenic proliferation in the dermis. The cells in the epidermis are smaller than those in the dermis and they extend laterally as a predominantly in situ radial-growth-phase compartment in the primary melanoma. B: At high magnification, there is uniform atypia, and there are scattered lesional cell mitoses in the early vertical growth phase. The melanin pigment is finely divided or "dusty."

In rare instances, a mass is formed in the dermal component of a melanoma by the accretive piling up of clusters of cells in the absence of any single cluster of cells that is larger than the largest intraepidermal cluster (Fig. 28-22). Reed et al. described these lesions as "variant vertical growth phase" or "accretive vertical growth phase" (232). These lesions are nontumorigenic. However, if any mitoses are present in such a lesion, it would meet the criteria for vertical growth phase defined earlier. The prognostic significance of variant vertical growth phase is uncertain. Most examples are thin, with a good prognosis as judged by prognostic models. In our experience, rare instances of metastasis have been associated with the presence of variant vertical growth phase; the overall metastatic rate is exceedingly low, comparable with that associated with other nontumorigenic melanomas.

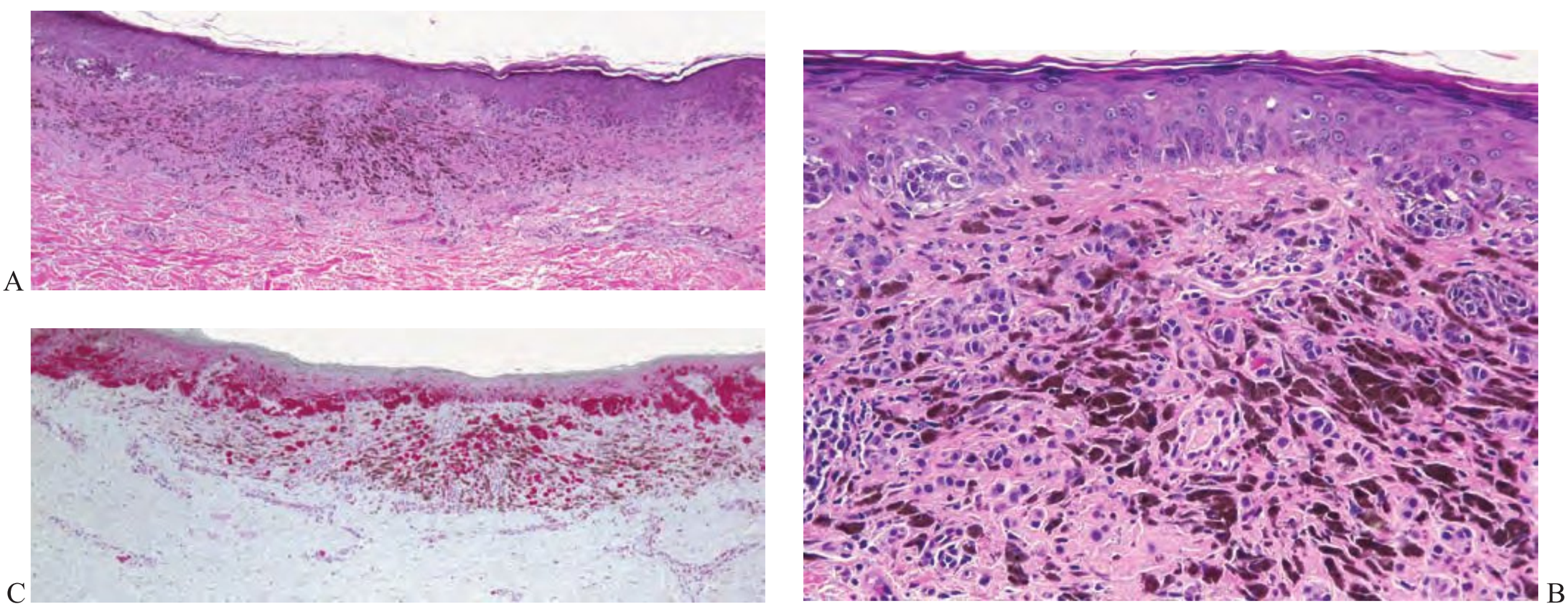


FIGURE 28-22. A: Melanoma with variant vertical growth phase ("accretive VGP"). There is a region in the center of the lesion where the papillary dermis is expanded by a small mass. B: The mass appears to have been formed by the accretive growth of numerous small nests, none of which is larger than the largest intraepidermal nest. C: A Melan-A stain graphically demonstrates the smaller nests in the dermis and the larger nests in the epidermis.

In a study conducted by the Pathology Panel of the Cancer Research Campaign in the United Kingdom, the level of agreement for recognition of vertical growth phase was "good" as judged by formal kappa analysis and was improved after discussion of standardized criteria among members of the reviewing panel (424). Subsequently, two additional studies confirmed this finding (425,426).

Molecular Pathology of Melanoma. Knowledge of the molecular pathology of melanoma has expanded dramatically since the discovery in 2001 of a high frequency of mutation of the oncogene BRAF in primary and metastatic melanomas (131). In a one study, mutations resulting in the activating V599E amino acid substitution were found in 68% of melanoma metastases, 80% of primary melanomas, and, unexpectedly, 82% of nevi (132). Activating mutations of the oncogene NRAS have also been described in melanomas and in tumor-associated and congenital nevi (133–135). Lesions that have mutated NRAS tend not to have mutated BRAF and vice versa (427). These data suggest that mutational activation of the RAS/RAF/MAPK mitogenic pathway in nevi is a critical step in the initiation of melanocytic neoplasia but alone is insufficient for melanoma tumorigenesis (132). The CDKN2A tumor suppressor gene product p16 is highly expressed in nevi (428,429), presumably restraining the proliferative pressure in these lesions despite the activating oncogene mutations, in a phenomenon termed "oncogene-induced senescence" (277). Loss of this suppressor in melanomas, in the context of activated mitogenic signaling pathways, may represent an important mechanism of progression (137).

The Nontumorigenic Compartment of Primary Malignant Melanoma (Radial Growth Phase)

The following sections describe the morphology of the nontumorigenic compartments of the different forms of melanoma. Next, we discuss the morphology of the tumorigenic vertical growth phase, which tends to be similar among the different forms. Typically, about 90% of all melanomas have a nontumorigenic compartment, and about half of these also have a tumorigenic focus; about 10% of melanomas, termed nodular melanomas, have a tumorigenic but no *in situ* or invasive radial-growth-phase compartment.

Two major patterns of nontumorigenic melanoma can be distinguished: pagetoid and lentiginous. The *lentiginous* pattern recapitulates the pattern of focally contiguous proliferation of nevus cells in the simplest melanocytic neoplasm, lentigo simplex. However, there is more uniform and complete contiguous basal replacement, and thus the proliferation is continuous, at least in part, between adjacent rete ridges. *Pagetoid* spread, graphically described as "buckshot scatter" of melanocytes within the epidermis, is the best-known pattern of melanomas. However, many melanomas, including many of the lentiginous ones, are entirely or partly lacking in pagetoid proliferation. In many melanomas, as in nevi, nests of melanocytes are present at the dermal–epidermal junction. These tend to differ from those in nevi in being more variable in size, shape, and orientation and in their more irregular spacing along the junction (430).

Not all superficial melanocytic proliferations can be reliably and reproducibly distinguished as either a superficial melanoma or as a nevus. In such cases, we provide a descriptive designation, such as superficial atypical melanocytic proliferation of uncertain significance, with a differential diagnosis. For example, a problematic lesion with dysplastic features and a small focus of pagetoid extension of slightly atypical melanocytes into the epidermis may be signed out as "junctional nevus with severe dysplasia and focal changes suggestive of evolving melanoma *in situ*." Because the differential diagnosis in these lesions includes melanoma *in situ*, which could locally persist, recur, and grow inexorably, although without metastatic potential at the time of diagnosis, we recommend a reexcision procedure for such lesions. The dimensions of such a procedure could follow guidelines for melanoma *in situ*, or at a minimum should be discussed with the patient and include a margin of normal tissue around the scar and any residual lesion.

Superficial Spreading Melanoma

Superficial spreading melanoma, also referred to as pagetoid melanoma (409), is the most frequent form of melanoma (about 70% of all cases), and may therefore be regarded as the "common" or "prototypic" form of melanoma. These lesions were described in the past as "atypical melanocytic hyperplasia" (431) or "precancerous melanosis," a term that dates to one of the earliest descriptions of melanoma by Dubreuilh in 1912 (432). The lesions, which occur in a relatively young to middle-aged patient population, may occur on exposed skin but are more commonly found on intermittently exposed skin and are rare on unexposed skin. In contrast to lentigo maligna, superficial spreading melanoma is believed to be associated with acute intermittent rather than chronic continuous sun exposure, which is often recreational rather than occupational (433). The most frequently involved sites are the upper back, especially in men, and the lower legs, especially in women. The lesions are slightly or definitely elevated, with a palpable border and an irregular outline. There is often variation in color that includes not only tan, brown, and black, but also pink, blue, and gray. White areas may be seen at sites of spontaneous regression (Fig. 28-19A). Microinvasion may be clinically unapparent, but the onset of tumorigenic vertical growth is indicated by the development of a papule followed by nodularity and sometimes also ulceration, the latter usually a late feature. In rare instances the lesion has a verrucous surface, in which case differentiation from a seborrheic keratosis may be difficult (434). In its early stage of development, superficial spreading melanoma may be indistinguishable clinically from a dysplastic nevus. Although dermoscopy can improve clinical diagnostic specificity (435), histologic examination remains the gold standard and is necessary for accurate diagnosis (435,436).

Histopathology. Architectural pattern features of importance in the diagnosis include the large diameter of the lesions, poor circumscription (the last cells at the edge of the lesion tending to be small, single, and scattered), and asymmetry (one half of the lesion does not mirror the other half) (430). The epidermis is irregularly thickened and thinned, in contrast to the uniformly elongated rete ridge pattern of a dysplastic nevus (Fig. 28-20A). Rather uniformly rounded, large melanocytes are scattered in a pagetoid pattern throughout the epidermis. The large cells lie predominantly in nests in the lower epidermis and singly in the upper epidermis. The nests tend to vary a good deal in size and shape and to become confluent. Dermal melanophages and a dermal infiltrate are regularly present. The lymphocytic infiltrate may be patchy and perivascular as in a dysplastic nevus but is typically dense and bandlike, especially in invasive lesions.

Cytologically, the lesional cells are rather uniform and have abundant cytoplasm containing varying amounts of melanin that often consists of small, "dusty" granules. They are almost entirely devoid of readily visible dendrites. The nuclei tend to be large and hyperchromatic, with irregular nuclear membranes and irregularly clumped chromatin (Fig. 28-20B). This uniform cytologic atypia is of considerable diagnostic importance and contrasts with the random cytologic atypia of dysplastic nevi.

When the lesion is *in situ*, the basement membrane is intact (as in the field seen in Fig. 28-20B) and there are no lesional cells in the dermis. In an invasive but nontumorigenic lesion (invasive radial growth phase or microinvasive melanoma), cells similar to those in the epidermis are present in the dermis in the form of small nests, with no nests larger than those in the epidermis, and with no dermal mitoses (Fig. 28-20C). When tumorigenic vertical growth phase is present, there is at least one, or often more than one, cluster of cells in the dermis that is larger than the largest intraepidermal nest, and/or there may be lesional cell mitoses in the dermis (Fig. 28-21A, B).

Histogenesis. On electron microscopic examination, melanosomes are present in great numbers in the large pagetoid tumor cells. Their shape is largely spheroid, rather than ellipsoid as in normal melanocytes and in the tumor cells of lentigo maligna (437). They often also show other abnormalities, such as absence of cross-linkages of the filaments within the melanosomes. Melanization within the melanosomes is variable but often incomplete (438). This accounts for the finely divided "dusty" character of the pigment in the cells of many melanomas. As already mentioned, it is likely that most superficial spreading melanomas have mutually exclusive activating mutations of the oncogene BRAF or NRAS. In a recent genotype–phenotype study, melanomas that had prominent nesting and pagetoid scatter of melanocytes—criteria similar to those for superficial spreading melanoma—were more likely than other melanomas to be associated with BRAF or NRAS mutations (419). These evolving genetic data will lead to refinement of the clinicopathologic melanoma classification system in the near future.

Differential Diagnosis. A junctional nevus differs from superficial spreading melanoma in radial growth phase by a lack of atypia in the tumor cells, particularly in their nuclei, by a lack of pagetoid upward extension of tumor cells, by the absence of a significant inflammatory infiltrate in the upper dermis, and often but not always by a sharper lateral demarcation. Salient features in the important distinction from junctional melanocytic dysplasia have been reviewed (Table 28-5), and include, at scanning magnification, larger size, asymmetry, an irregularly thickened and thinned epidermis, and a bandlike lymphocytic infiltrate in superficial spreading melanoma. At higher power, indicators of melanoma include the presence of high-level and extensive pagetoid melanocytosis (large neoplastic cells scattered among benign keratinocytes), high-grade and/or uniform cytologic atypia, and lesional cell mitoses (the latter present in about one third of cases). A junctional Spitz nevus, especially the uncommon pagetoid Spitz nevus, may simulate superficial spreading melanoma quite closely. Distinguishing features include generally smaller size, the presence of large spindle and/or epithelioid cells, the presence of Kamino bodies, and the lack of "consumption" or thinning of the epidermis above the lesion, as previously discussed (see section Spitz Nevus). The so-called nevi of special sites, including flexural sites, ears, scalp, and breast, may also simulate this form of melanoma in particular, and these should be seriously considered when a biopsy from one of these sites is examined (see also page 715). Caution should be exercised when what at first appears as melanoma *in situ* is restricted to the epidermis that overlies a surgical or traumatic scar because this must be differentiated from the recurrent nevus phenomenon [see section Recurrent Nevus (Pseudomelanoma)]. Helpful features include the precise spatial restriction of the atypical intraepidermal focus to the zone overlying (but not extending horizontally beyond) the scar, the presence of residual nevus cells, and the absence of true uniform cytologic atypia. Whenever possible, it is important to also review the initial biopsy in such cases. The differential diagnostic distinction from lentiginous melanomas is of less consequence because the management is the same. In lentigo maligna, the epidermis is atrophic and pagetoid melanocytosis is less prominent, and contiguous replacement of the basal cell layer by atypical melanocytes is the dominant pattern. Problematic cases can be reported as malignant melanoma (*in situ* or microinvasive, etc.) without designation as to type.

When tumorigenic vertical growth phase is present, it does not differ appreciably from that in any other form of melanoma, except for the adjacent radial growth phase (Fig. 28-23). Classification of such complex tumorigenic primary melanomas is based on the morphology of the radial growth phase.

Among the nonmelanocytic neoplasms that must be differentiated from a superficial spreading melanoma *in situ* are *Paget's disease* and pagetoid examples of *Bowen's disease* (*squamous cell carcinoma in situ*). Paget's disease (discussed in detail in Chapter 30) usually shows remnants of compressed basal cells beneath the tumor cells, whereas in superficial spreading melanoma the lesional cells extend to the basement membrane. In Paget's disease, the tumor cells may stain positively for carcinoembryonic

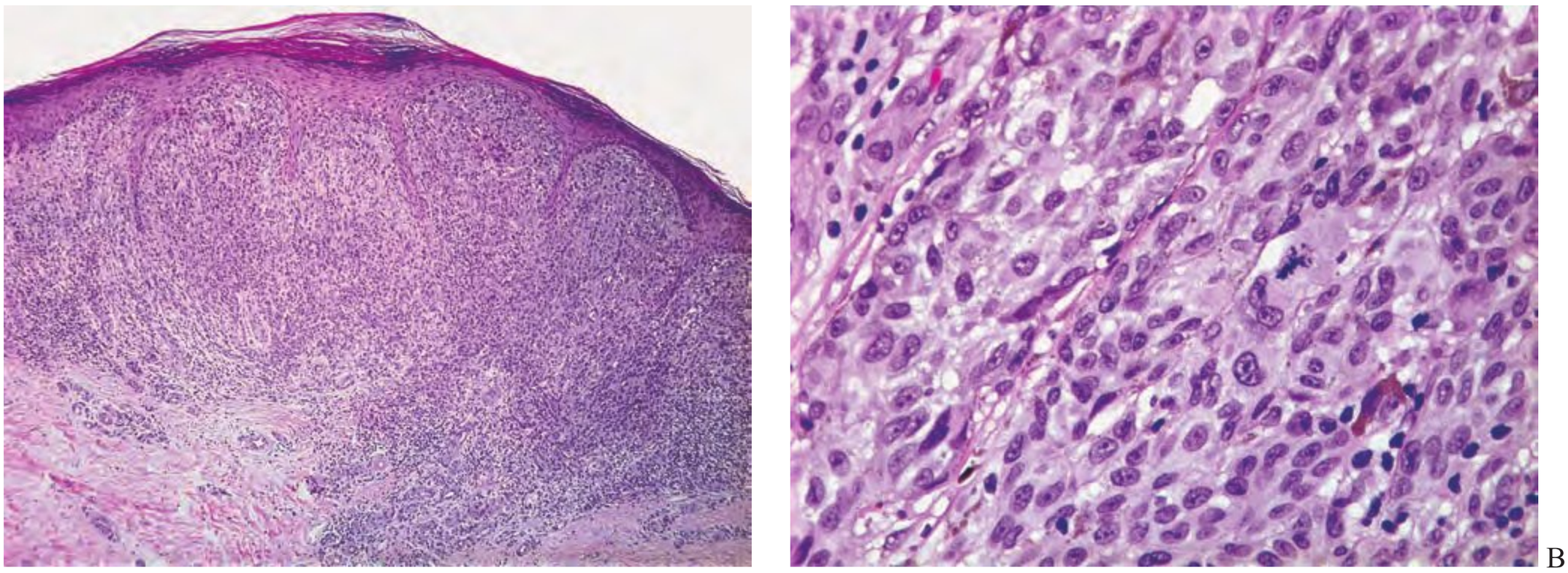


FIGURE 28-23. A: Malignant melanoma, tumorigenic. At scanning magnification, there is a bulky ulcerated tumor nodule, which is eccentrically placed in contiguity with a broad plaque, the nontumorigenic radial-growth-phase compartment (not shown, to the right of the image field). B: The tumorigenic nodule is composed of uniformly atypical, mitotically active, fully malignant melanocytes (melanoma cells).

antigen and keratin and are negative for HMB-45 and Melan-A. S100 reactivity, although unusual, may occasionally be observed in Paget's disease. Pagetoid Bowen's disease (discussed in Chapter 29) shows, as a rule, a well-preserved basal cell layer, except in areas in which dermal invasion has taken place, and immunohistochemically the atypical cells stain positively with antikeratin antibodies (e.g., AE1/AE3) (439). They do not stain with S100 or with Melan-A or HMB-45. It should be noted that the cells of Paget's disease and of Bowen's disease may contain melanin pigment because of transfer from reactive melanocytes in the adjacent skin.

A final pitfall in evaluating nonmelanocytic mimics of intraepidermal melanoma involves the variable tendency of keratinocytes within the uppermost epidermal layers to exhibit perinuclear retraction presumably due to cytoplasmic glycogenation combined with tissue processing. Some body sites (e.g., areola and along the milk line) may be particularly prone to this change, perhaps in part the result of so-called "clear cells of Toker." These cells may produce the false appearance of true pagetoid spread in an otherwise benign or dysplastic melanocytic lesion, thus inciting consideration of a diagnosis of superficial spreading melanoma. However, keratinocytes so altered are recognizable at high magnification as cells with nuclei surrounded by clear spaces (retraction clefts) that themselves are bordered by a rim of cytoplasm and joined by desmosomes, in contrast to pagetoid melanoma cells, which lack desmosomes and whose nuclei are directly enveloped by relatively clear cytoplasm that may be surrounded by a thin, clear mantle of retraction that separates the cell from adjacent keratinocytes.

Lentigo Maligna Melanoma

Lentigo maligna, previously referred to as *melanosis circumscripta preblastomatosa of Dubreuilh* and also as *melanotic freckle of Hutchinson* [or *Hutchinson's melanotic freckle* (*HMF*), a term used currently in Australia for this condition], accounts for about 10% of melanomas and typically occurs on the chronically exposed cutaneous surfaces of the elderly, most commonly on the face, and occasionally on the back, the forearms, or the lower legs (440). The term "lentigo maligna" may be regarded as synonymous with "lentigo maligna melanoma *in situ*" for most purposes. It is controversial whether lentigo maligna should be regarded as a form of melanoma *in situ* in all cases or whether some cases should be regarded as precursor lesions (lentigo maligna) of *in situ* melanoma (melanoma *in situ*, lentigo maligna type) (441). In any case, these lesions, like other melanomas *in situ*, do not metastasize after complete excision, although they may persist and recur if not adequately excised. The lesion evolves slowly over many years, starting as an unevenly pigmented macule that gradually extends peripherally and may attain a diameter of several centimeters. It has an irregular border and, as long as it remains *in situ* or microinvasive, shows no induration. While extending in some areas, it may show spontaneous regression in others, resulting in irregular depigmented areas. The color varies from light brown to brown with minute dark-brown or black flecks. Fine reticulated lines are usually also present and help in distinguishing the lesions from actinic lentigines. In contrast to superficial spreading melanoma, the border is usually impalpable and indistinct. For this reason, the accurate clinical delineation of the border of a lentigo maligna melanoma can be problematic, and this not uncommonly results in unexpected positive or close margins in resection specimens. Occasionally, a lesion of lentigo maligna lacks melanin pigmentation (442–444). The clinical appearance then resembles that of a solar keratosis or Bowen's disease or of an inflammatory patch, such as lupus.

It has been suggested that the risk of progression from lentigo maligna to invasive lentigo maligna melanoma may be about 5% (445), although some cases may progress rapidly (446). After adjustment for tumor thickness and other factors, lentigo maligna melanoma (LMM) has the same prognosis as other forms of melanoma (447). However, its demographics and associations differ from those of the most common form of melanoma, superficial spreading melanoma (SSM). For example, patients with LMM have fewer nevi but more actinic keratoses than patients with SSM, consistent with a hypothesis of chronic sun exposure in the etiology of LMM (448). In addition, especially in older individuals, lesions that lack nesting and pagetoid scatter of melanocytes—criteria similar to those described for lentigo maligna melanoma—are less likely to be associated with BRAF or NRAS mutations than when these attributes are present, as in SSMs (419). In contrast, the oncogene KIT has been found to be mutated in 28% of melanomas on chronically sun-damaged skin (449). These evolving genetic data will lead to refinement of the clinicopathologic melanoma classification system in the near future.

Histopathology

Architectural Features. In its earliest stage, lentigo maligna may show at its periphery only hyperpigmentation with slight melanocytic proliferation, mainly in the basal cell layer. Toward the center of the lesion, there is a more pronounced increase in the concentration of basal melanocytes and some irregularity in their arrangement. Until there is contiguous proliferation of lesional melanocytes, these changes are not specific and may overlap with those of actinic lentigines. The epidermis is frequently flattened, in contrast to SSM, in which it is irregularly thickened and thinned, or actinic lentigines, in which there is elongation of the rete. This feature, although of diagnostic importance, is less prominent than in superficial spreading melanoma (Fig. 28-24). Noteworthy is the tendency of the basal layer of follicular infundibula to also be involved by the lentiginous proliferation of atypical melanocytes in lentigo maligna.

Some nesting of melanocytes in the basal layer may be seen, but this is not usually pronounced until invasion of the dermis is developing (450). The atypical melanocytes within the nests usually retain their spindled shape, and they often "hang down" like rain droplets from the interface (410). Except in areas of nesting, the melanocytes tend to retain their dendritic processes. If the melanocytes are heavily melanized, some dendrites may be visible even in sections stained with hematoxylin-eosin; otherwise, staining with silver demonstrates the dendrites.

The upper dermis, which almost always shows severe elastotic solar degeneration, contains numerous melanophages and a rather pronounced, often bandlike, inflammatory infiltrate. Invasion may be demonstrable in these areas of dermal inflammation. Because invasion in a lentigo maligna melanoma (as in other melanomas) is a focal process, one should ensure that the specimen is adequately grossed and sectioned in order not to miss such areas. The presence or absence

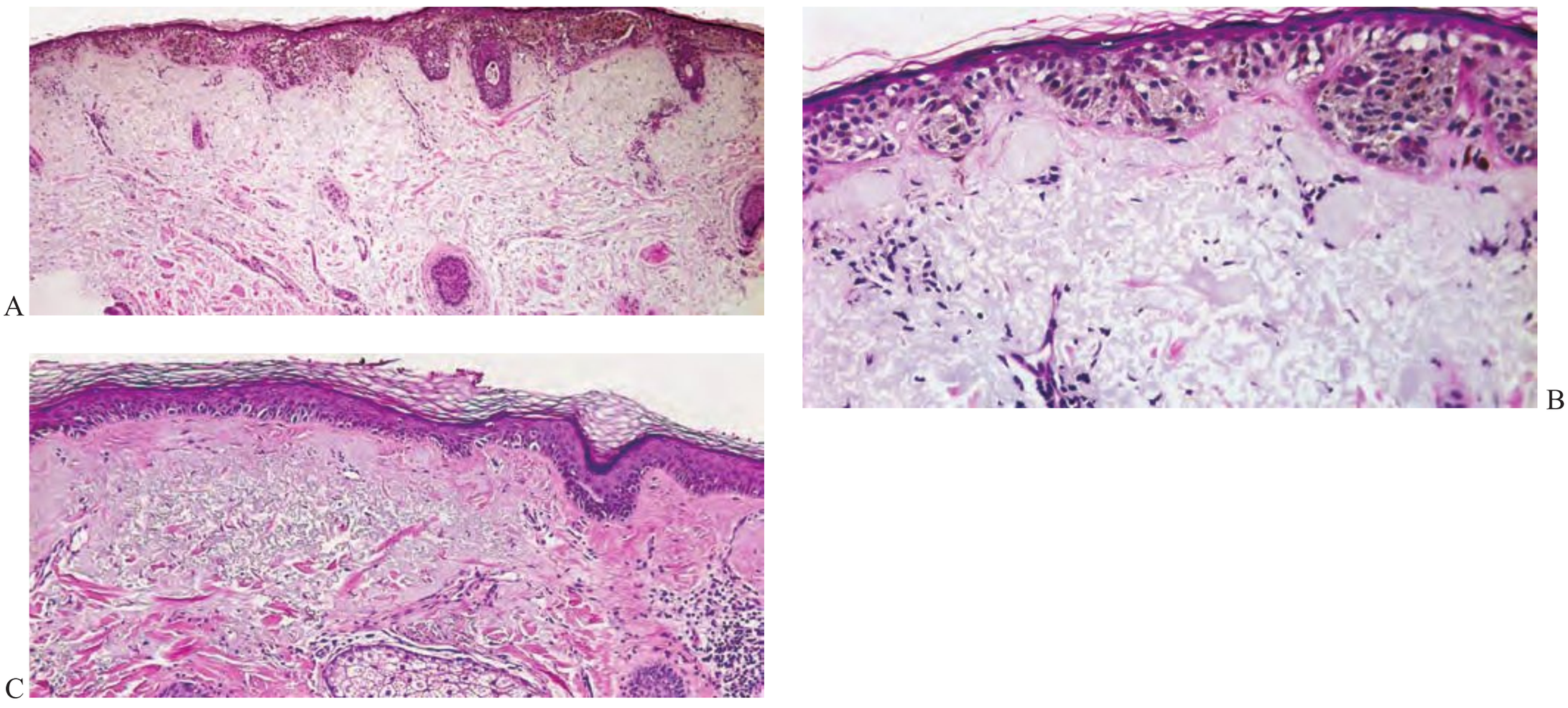


FIGURE 28-24. A: Lentigo maligna melanoma in situ. At low magnification, the lesions are broad and asymmetric in the distribution of lesional and host responding cells. B: The epidermis is atrophic, and there is usually severe actinic elastosis in the dermis. C: As in superficial spreading melanoma, the lesional cells exhibit moderate to severe uniform cytologic atypia. There is usually some evidence of pagetoid proliferation in lentigo maligna melanoma, especially near areas of invasion. However, especially at the periphery of the lesion, this is much less prominent, and the lesional cells are smaller than in superficial spreading melanoma.

of tumorigenic vertical growth phase is recognized using criteria already presented. The possibility of a desmoplastic vertical-growth-phase component (see later section) should be kept in mind because this may be a subtle finding. In case of doubt, an S100 stain can be crucial in demonstrating the lesion.

Cytologic Features. In fully evolved lesions of lentigo maligna, the lesional melanocytes in the epidermis show a marked increase in concentration, so that they come to lie in contiguity with one another, and their number in some areas exceeds that of the basal keratinocytes. Many of them are elongated and spindle shaped. Their nuclei appear atypical, being enlarged, hyperchromatic, and pleomorphic. However, the chromatin pattern is often not as open or "vesicular" as that seen in the more epithelioid cells of superficial spreading melanoma in its radial phase of growth. Frequently, atypical melanocytes extend along the basal cell layer of hair follicles, often for a considerable distance, frequently extending to the base of a shave biopsy specimen. Usually, the proliferating melanocytes contain moderate melanin, and melanin is present also in keratinocytes. There is usually some upward pagetoid extension of atypical melanocytes.

In summary, the properties of contiguous proliferation and uniform cytologic atypia in a broad, poorly circumscribed lesion are clearly of major importance in the diagnosis of *in situ* or microinvasive lentigo maligna melanoma. These features are shared with superficial spreading melanoma, whereas focal pagetoid melanocytosis, although often present, is less prominent. It should also be remembered that some individuals with chronic sun damage may show diffuse, clinically covert, noncontiguous lentiginous proliferation of somewhat atypical melanocytes within the epidermal basal cell layer, and thus correlation with clinical appearance may be critical to determining the biological significance of low-grade atypical melanocytic hyperplasias. Mitotic figures are uncommonly present in the epidermal compartment of lentigo maligna melanoma; if present in the dermis, they are indicative of vertical growth phase. When tumorigenic vertical growth supervenes, it is often of the spindle cell type, including the desmoplastic and neurotropic variants.

Pathogenesis. As an explanation for the somewhat distinctive behavior of lentigo maligna, the theory has been offered that it is derived from spindle-shaped junctional melanocytes and thus represents a melanocyte-derived melanoma, in contrast to the superficial spreading melanoma that is derived from rounded junctional nevus cells and can be regarded as a nevus cell–derived melanoma (451). Electron microscopy provides some support for this concept. The melanocytes of lentigo maligna are large, synthetically active cells with many dendrites. The melanosomes are essentially normal, except that they appear somewhat more elongated than those present in normal melanocytes (437,451). This is in contrast to superficial spreading melanomas, in which the melanosomes show considerable abnormalities. In a study of several immunohistochemical markers comparing lentigo maligna and superficial spreading melanomas, melanocytes of the latter showed greater proliferative activity, as reflected by PCNA staining, higher levels of basic fibroblast growth factor, and more blood vessels. In addition, staining for p53, considered to be a marker of chronic solar damage, is significantly greater in lentigo maligna than in superficial spreading melanomas (452). These results were considered to be in accordance with the biological behavior of superficial spreading and lentigo maligna melanomas, that is, the longer *in situ* phase of the latter (418). Although progression of lentigo maligna is often slow, some cases progress more rapidly, and complete excision of these lesions is recommended to prevent the development of a more dangerous melanoma (453).

Differential Diagnosis of Lentigo Maligna. Lentigo maligna may be associated with fields of atypical lentiginous melanocytic proliferation that in a small biopsy may not permit an outright diagnosis. Recognition of this fact is important in suggesting the potential utility of additional sampling, particularly for clinically suspicious lesions. Lentigo maligna with junctional nest formation may also be mistaken for a superficial dysplastic nevus, especially in a partial biopsy specimen. It is important in such lesions to note the occurrence of the proliferation in an atrophic epidermis devoid of elongation of rete ridges, the uniform (rather than random) atypia of the lesional cells, and, if present, the presence of follicular extension by the atypical melanocytes. As mentioned, invasion in lentigo maligna melanoma may be extremely subtle, particularly when the involved cells exhibit desmoplastic or small-cell (nevoid) features. Close attention to subtle yet uniform atypia, aided by immunohistochemical approaches to support melanocytic (e.g., versus fibroblastic) lineage, may be helpful in such problematic lesions.

Acral-lentiginous Melanoma

Acral melanoma occurs on the hairless skin of the palms and soles and in the ungual and periungual regions, the soles being the most common site (411,454). Acral melanoma is uncommon in all ethnic groups, but it is the predominant form of melanoma in individuals with darker skin. In groups such as Asians, Hispanics, Polynesians, and blacks, in whom the overall incidence of melanoma is low, most melanomas are of the acral type. However, the absolute incidence of acral melanoma in these groups is similar to that in whites, who have a much higher incidence of melanoma overall (455). These considerations suggest that different etiologic factors, likely not involving sunlight, are operative in acral than in other sites. Although the survival rate of patients with acral melanomas in most series is relatively poor (456,457), this is likely due to their typically advanced microstage and/or stage at diagnosis.

Clinically, *in situ* or microinvasive acral-lentiginous melanoma shows uneven pigmentation with an irregular, often indefinite border. The soles of the feet are most commonly involved. If the tumor is situated in the nail matrix, the nail and nail bed may show a longitudinal pigmented band, and the pigment may extend onto the nail fold (Hutchinson's sign). Tumorigenic vertical growth may be heralded by the

onset of a nodule, with development of ulceration (Fig. 28-19B). However, some acral melanomas may be deeply invasive while remaining quite flat because the thick stratum corneum seems to act as a barrier to exophytic growth.

Histopathology. The lesions are termed lentiginous because the majority of the lesional cells are single and located near the dermal–epidermal junction, especially at the periphery of the lesion (Fig. 28-25). However, usually some tumor cells can be found in the upper layers of the epidermis, especially near areas of invasion in the center of the lesions. The histologic picture differs from that of lentigo maligna because of irregular acanthosis, the lack of elastosis in the dermis, and the frequently dendritic character of the lesional cells (458). Early *in situ* or microinvasive lesions may show, especially at the periphery, a deceptively subtle histologic picture consisting of an increase in basal melanocytes and hyperpigmentation with only focal atypia of the melanocytes. However, in the center of the lesions, there is usually readily evident uniform, severe cytologic atypia. There may be a lichenoid lymphocytic infiltrate that may largely obscure the dermal–epidermal junction, and in some cases this may be so dense as to simulate an inflammatory process. In most of the lesions, both spindle shaped and rounded, pagetoid tumor cells are seen, and, in many cases, pigmented dendritic cells are prominent. Pigmentation is often pronounced, resulting in the presence of melanophages in the upper dermis and of large aggregates of melanin in the broad stratum corneum. As in lentigo maligna, when tumorigenic vertical growth phase is present, it is often of the spindle cell type and not uncommonly desmoplastic and/or neurotropic. In other instances, the invasive and tumorigenic cells in the dermis may be deceptively differentiated along nevoid lines.

Biology of Acral Melanoma

Curtin et al. studied melanomas and nevi for copy-number alterations by comparative genomic hybridization and found that melanomas of the palms, soles, and subungual sites were distinguished by the presence of multiple gene amplifications, about 50% of which were found at the cyclin D1 locus (459). Such amplifications are significantly less frequent in other cutaneous melanoma types and, if present, arise later in progression. Single basal melanocytes with similar gene amplifications were then identified in the histologically normal appearing skin immediately adjacent to a melanoma. These field cells

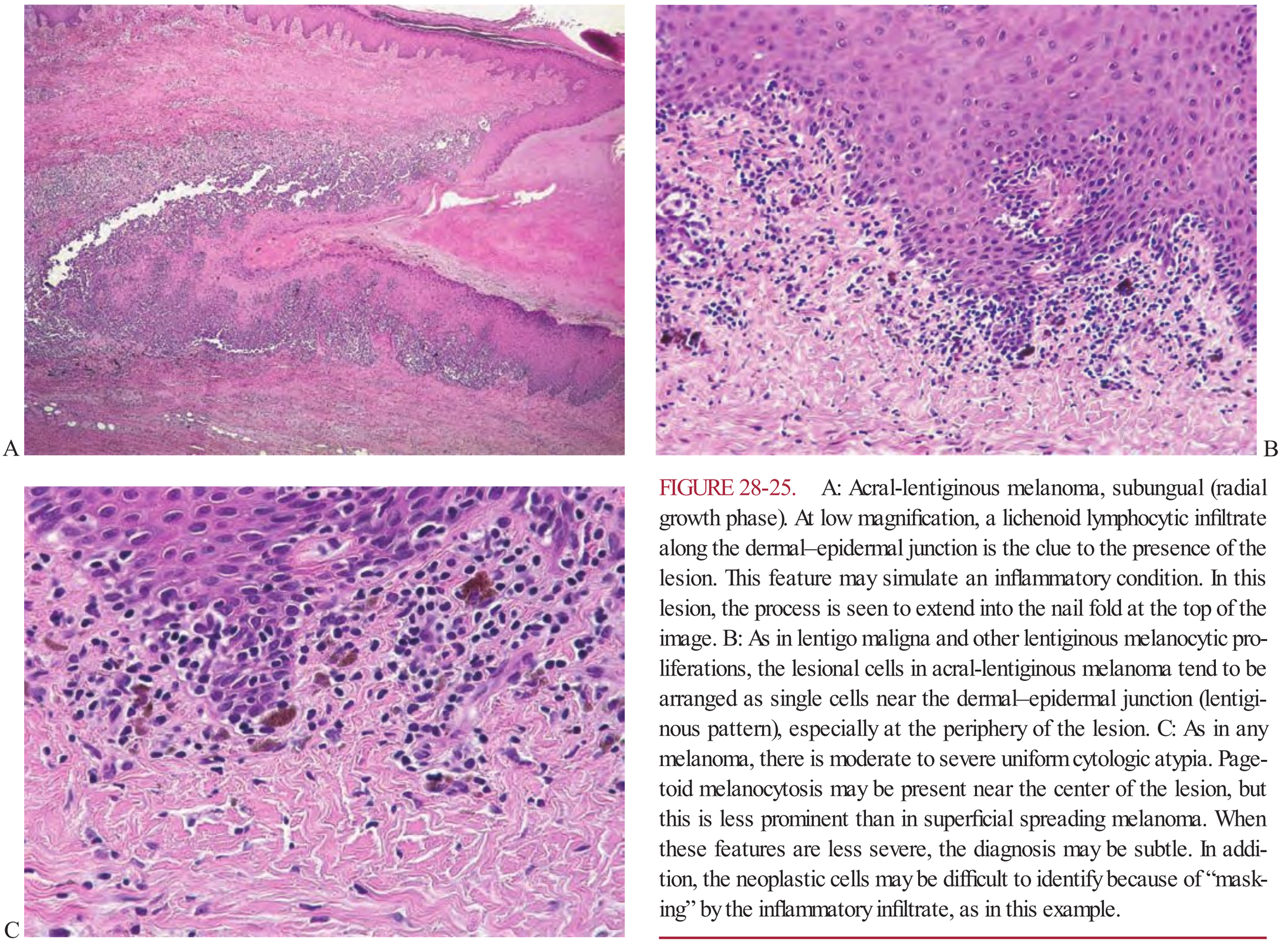


FIGURE 28-25. A: Acral-lentiginous melanoma, subungual (radial growth phase). At low magnification, a lichenoid lymphocytic infiltrate along the dermal–epidermal junction is the clue to the presence of the lesion. This feature may simulate an inflammatory condition. In this lesion, the process is seen to extend into the nail fold at the top of the image. B: As in lentigo maligna and other lentiginous melanocytic proliferations, the lesional cells in acral-lentiginous melanoma tend to be arranged as single cells near the dermal–epidermal junction (lentiginous pattern), especially at the periphery of the lesion. C: As in any melanoma, there is moderate to severe uniform cytologic atypia. Pagetoid melanocytosis may be present near the center of the lesion, but this is less prominent than in superficial spreading melanoma. When these features are less severe, the diagnosis may be subtle. In addition, the neoplastic cells may be difficult to identify because of "masking" by the inflammatory infiltrate, as in this example.

appear to represent subtle melanoma *in situ* and may represent minimal residual disease that could lead to local recurrences if not excised. If the biological significance of these cells in terms of local recurrence can be confirmed, their identification may lead to recommendations for management of these lesions in the future (459). Acral melanomas in general do not express the mutations of BRAF or NRAS that are frequent in the more common superficial spreading melanomas. In contrast, activating mutations of the KIT oncogene were found in 36% of acral melanomas in a recent study (449), a finding that could have therapeutic implications in metastatic tumors.

Differential Diagnosis of Acral Melanoma. The major consideration in the differential diagnosis of acral-lentiginous melanoma is the benign acral-lentiginous nevus, which was discussed earlier (150,151). Features that distinguish this lesion from melanoma include smaller size, greater symmetry, lack of pagetoid lateral spread, absence of high-grade uniform atypia (not always present, however, in some melanomas), absence of mitotic activity in the dermal component, and evidence of dermal nevocytic differentiation (150,151).

Mucosal Lentiginous Melanoma

After the skin and eyes, melanoma is most apt to arise in the juxtacutaneous mucous membranes, such as the oral mucosa (460), nose and nasal sinuses (461), vagina (462), and anorectal mucosa (463). Mucosal melanomas are analogous to acral melanomas in histologic appearance and aggressiveness, which has led to the use of the histologic term mucosal-lentiginous melanoma (464).

Superficial Atypical Melanocytic Proliferation of Uncertain Significance (SAMPUS)

Even though histology is the gold standard for melanoma diagnosis, it is not always possible to make absolute distinctions among melanomas with a predominantly junctional component and their benign simulants because of conflicting, uncertain, or unreliable criteria. A common problem is the distinction between a severely dysplastic nevus and an early melanoma *in situ* or an invasive but nontumorigenic melanoma, and this problem is especially difficult when one of the so-called "special sites" is involved (see section Nevi of Special Sites). When the process is entirely *in situ*, the descriptive term atypical intraepidermal melanocytic proliferation (AIMP) or some similar variant has commonly been used (465–467). When atypical cells are also present in the dermis, this term is obviously inappropriate or at least incomplete, and for some of these lesions we use the descriptive term superficial atypical melanocytic proliferation of uncertain significance (231). For *in situ* lesions, the more traditional term AIMP can be used, or the lesions can be referred to as intraepidermal atypical melanocytic proliferation of uncertain significance (IAMPUS). In any event these terms are descriptive diagnoses, not definitive diagnoses, and should always be accompanied by a differential diagnosis. For example, for a problematic lesion of the breast, we might use the term SAMPUS and in a note express a differential diagnosis that might include a nevus with severe dermal and epidermal dysplasia, a nontumorigenic melanoma, or an unusual presentation of a special-site nevus. The first lesion could have significance as a marker of risk for melanoma, the second could have locally recurring but not metastatic potential, and the last could have no significance at all for the patient. If melanoma is in the differential, we provide sufficient information for American Joint Committee on Cancer (AJCC) staging as a guide to therapy. If the lesion has a potential tumorigenic and/or mitogenic dermal component, and therefore potential competence for metastasis, the term "melanocytic tumor of uncertain malignant potential" is used, as discussed in a later section.

The Tumorigenic Compartment of Primary Malignant Melanoma (Vertical Growth Phase)

The morphology of the variant forms of nontumorigenic melanoma has been discussed. A tumorigenic vertical growth phase may develop in association with any of these to form a complex primary melanoma. In such cases, the histology shows a tumorigenic compartment adjacent to or within the confines of a nontumorigenic compartment. Nodular melanoma differs from these complex melanomas in that it is a tumorigenic melanoma with no clinically or histologically evident adjacent nontumorigenic compartment (410). The morphology of the usual or common forms of vertical growth phase are described later under "common forms of tumorigenic melanoma including nodular melanoma."

Occasional melanomas exhibit variant patterns that may lead to diagnostic confusion because they may be more characteristically seen in nonmelanocytic tumors. Several variants of melanoma deserve at least a brief description in the following sections: desmoplastic, neurotropic, polypoid, verrucous, balloon cell, signet cell, myxoid, so-called animal-type, nevoid, and minimal deviation melanoma. Other variants, which will not be described here, include small-cell, adenoid/papillary, and pleomorphic (fibrohistiocytic) melanomas (468), melanomas with rhabdoid cytoplasmic features (469,470), and the rare bone-forming or osteogenic melanoma (471).

Common Tumorigenic Melanoma Including Nodular Melanoma

Nodular melanoma by definition contains only tumorigenic vertical growth (sometimes associated with a precursor) and, because of this, has a poorer prognosis on the average than superficial spreading melanoma. However, when other risk factors such as thickness are controlled, the prognosis of nodular melanoma is not worse than that of other forms of melanoma (472). Nodular melanomas occur in slightly older patients than the common superficial spreading melanoma and are relatively more frequent in men (410). A nodular melanoma starts as an elevated, variably pigmented papule that increases in size quite rapidly to become a nodule and often undergoes ulceration. Certain rare primary dermal melanomas comprised of cytologically malignant melanocytes and lacking an *in situ*

component may be considered also in this category (473). The ABCD criteria reviewed earlier do not apply to nodular melanomas, which often present clinically as quite small, symmetric, and well-circumscribed papules or nodules (Fig. 28-19C). These may be conspicuously pigmented, oligomelanotic, or even amelanotic. The tumorigenic nodule that may develop in nodular melanoma does not differ clinically or histologically from that which may occur in relation to a preexisting nontumorigenic melanoma. Indeed, nodular melanomas may represent examples of telescoped tumor progression in which the antecedent radial phase has been so short lived as to be unapparent (474). The clinical importance of the nodular subtype has been emphasized recently; these lesions are more likely to present at a biologically advanced stage despite a comparatively short clinical history (475,476). The mutation profile of nodular melanoma is closer to that of superficial spreading melanoma than to the other subtypes, in that BRAF or NRAS are commonly mutated (477).

Histopathology of Nodular Melanoma and Common Vertical Growth Phase (Tumorigenic Melanoma)

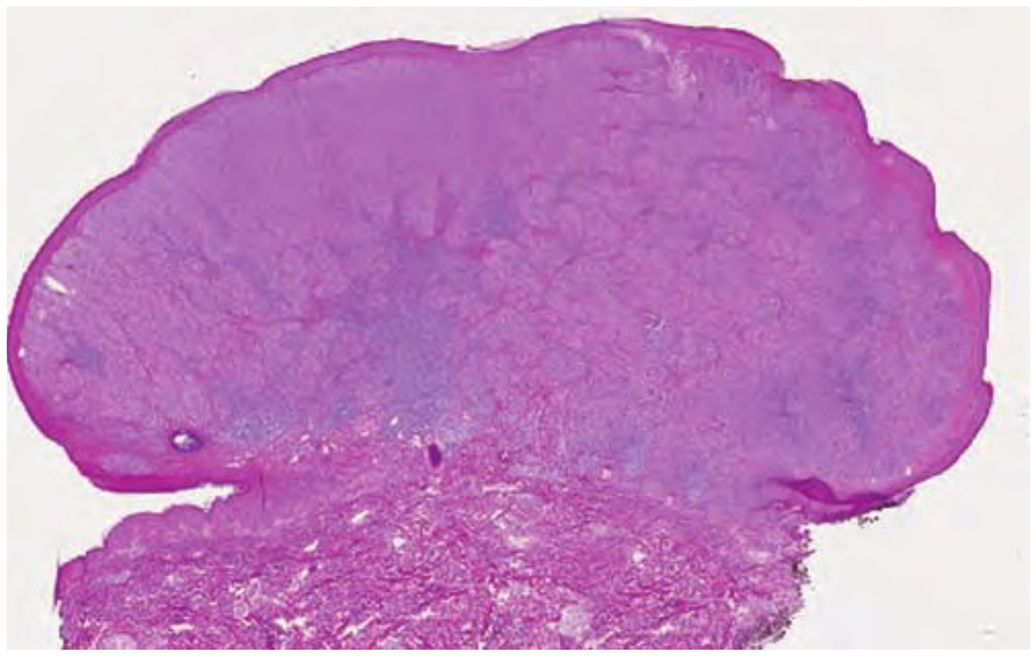
Architectural Features. In a typical tumorigenic melanoma, there is contiguous proliferation of neoplastic melanocytes in the dermis forming a tumor mass that is larger (usually much larger) than the largest nest in the overlying epidermis. Asymmetry is often apparent at the cytologic level as variation in cell size, shape, and pigmentation and in the distribution of the host response, such that one half of the lesion is not a mirror image of the other. However, the silhouette of the entire lesion may be quite symmetric, especially in a nodular melanoma that lacks an adjacent nontumorigenic component (Fig. 28-26A). Conversely, if a nontumorigenic radial-growth-phase compartment is present, asymmetry is likely to be more apparent at both the clinical and histologic levels. The tumor mass comprises uniformly atypical, cytologically fully malignant mitotically active cells usually growing in confluent nests or in sheets (Fig. 28-26B). Usually, the tumor mass fills and expands the papillary dermis (level III) or invades between coarse collagen fibers of the reticular dermis (level IV). Most level III melanomas and most melanomas greater than 0.75 mm in thickness are tumorigenic, whereas most level II or thin melanomas have no cluster in the dermis that is larger than the largest intraepidermal cluster and are therefore nontumorigenic. The epidermis is frequently ulcerated, or there is an adherent scale-crust. It is often stretched and attenuated in a phenomenon that usually does not occur in Spitz tumors and that has been termed consumption of the epidermis (188). Alternatively the epidermis may be irregularly hyperplastic and even show pseudoepitheliomatous hyperplasia, a pattern that has been termed verrucous melanoma (478).

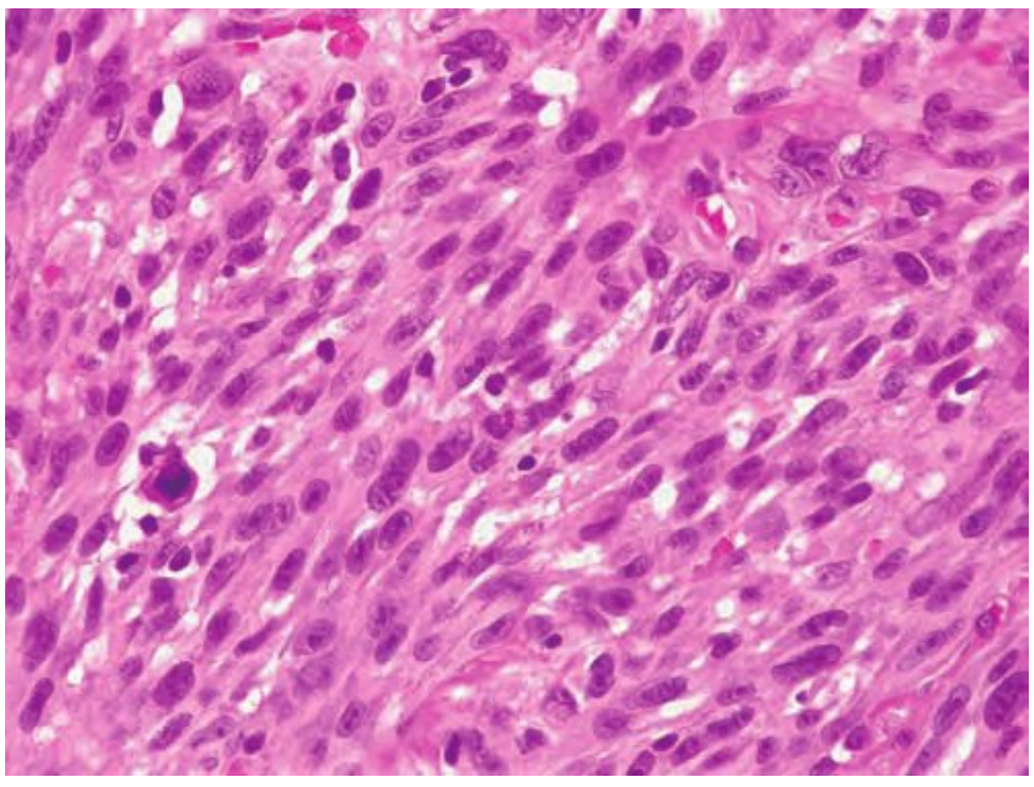
Perhaps the best-known single criterion for melanoma is the upward pagetoid extension of tumor cells into the epidermis overlying the melanoma. However, this pagetoid melanocytosis or pagetoid spread is not specific for melanoma (152). Although in nodular melanoma, permeation of the epidermis with tumor cells may be absent or may be limited to that portion overlying the dermal tumor, lateral extension of melanoma cells in the epidermis and papillary dermis beyond the confines of the dermal tumor is seen in the adjacent nontumorigenic compartment of complex primary melanomas [SSM, LMM, acral-lentiginous melanoma (ALM)]. This phenomenon greatly aids in histologic recognition of these tumors, and, conversely, the recognition of nodular melanomas, which lack this adjacent component, may be difficult. For this reason, nodular melanoma may be difficult or impossible to distinguish from a metastatic melanoma in the skin, and when such a tumor is amelanotic, the distinction from other cutaneous neoplasms may be impossible without immunohistochemistry.

The amount of inflammatory infiltrate in tumorigenic melanomas varies. As a rule, early invasive malignant and many *in situ* melanomas show a bandlike inflammatory infiltrate, often intermingled with melanophages, at the base of the tumor. In tumors that extend deep into the dermis, the inflammatory infiltrate is quite variable, but it is often only slight to moderate rather than pronounced. Lymphocytes extending among tumor cells are often associated with morphologic evidence of damage to individual tumor cells (apoptosis). These tumor-infiltrating lymphocytes (TILs) have been shown to have independent favorable prognostic significance (472). The infiltrate is a predominantly T-cell response (479). TILs extracted from melanomas (mostly metastatic cases) may be cytotoxic and may be directed against immunogenic melanoma-associated antigens (480).

Cytological Features. The tumor cells in the dermis show great variation in size and shape. Nevertheless, two major types of cells can be recognized; an epithelioid and a spindle-shaped cell type. Many tumors show both types of cells, but usually one type predominates. Generally, the lentiginous forms of melanoma (e.g., LMM and ALM) tend to show a predominance of spindle-shaped cells in their invasive dermal components, whereas superficial spreading and nodular melanomas tend to be composed largely of epithelioid cells (472). The epithelioid type of cell tends to lie in alveolar or nested formations and the spindle-shaped type of cells in irregularly branching formations. The alveolar formations of the epithelioid cells are surrounded by thin fibers of collagen containing a few fibroblasts. Tumors in which spindle cells predominate may resemble sarcomas or other spindle cell tumors but in most cases differ from them by the presence of junctional melanocytic activity.

The uniformly atypical nuclei of the cells that constitute the tumor nodule are larger than those of melanocytes or nevus cells, with irregular nuclear membranes, hyperchromatic chromatin, and, often, prominent nucleoli that tend to be irregular in size, shape, and number. The atypia is considered to be uniform if more than 50% of the cells have these

A 

B 


C

FIGURE 28-26. A: Tumorigenic melanoma, nodular type (vertical growth phase without radial growth phase). The nodules of tumorigenic melanomas tend to be symmetric at scanning magnification, although there may be an uneven distribution of pigment and of the lymphocytic response within many of the lesions. When there is no adjacent nontumorigenic radial-growth-phase component, as here, the lesion is termed nodular melanoma. If a radial-growth-phase component is present, the melanoma is classified according to the type of that compartment [e.g., superficial spreading (or acral-lentiginous, etc.) melanoma with tumorigenic vertical growth phase]. B: The lesional cells of nodular melanoma exhibit severe uniform cytologic atypia, usually with readily evident mitoses. In any given high-power field such as this, the appearances are indistinguishable from those of a vertical growth phase associated with a superficial spreading, lentigo maligna, or acral-lentiginous melanoma or from those of a metastasis (compare Fig. 28-23B, panel B in the present figure, and Figs. 28-31C, 28-36, and 28-39B). C: Nodular melanoma, S100 immunohistochemical stain. The brown reaction product in the lesional cells is striking, even at scanning magnification. Note the absence of S100-positive lesional cells in the adjacent skin.

characteristics, but more often than not, all or most of the cells are atypical. In addition to this uniform moderate or severe cytologic atypia, there is also a diagnostically important failure of the melanocytes in the deeper layers of the dermis to decrease in size (absence of maturation) (Fig. 28-21). This must not be confused, however, with the presence of an intradermal nevus beneath a melanoma, a fairly common feature. Not uncommonly, melanoma cells will recapitulate nevic cell maturation (so-called pseudomaturation), but in these instances the smaller cells at the base retain nuclear characteristics of malignant cells, and there will be cytologic continuity between these nevoid cells and the overlying more atypical lesional cells.

Mitotic figures are usually present in the lesional cells of the dermal and epidermal compartments of tumorigenic melanomas [they are present in the epidermal lesional cells in about one third of nontumorigenic melanomas and in the dermal compartment of 85% of tumorigenic melanomas (472,481)] (Fig. 28-23). Mitoses may also be seen in adjacent hyperplastic keratinocytes. The nuclei of these hyperplastic epidermal keratinocytes may be enlarged with prominent nucleoli, although they are not irregular or hyperchromatic. In contrast, mitotic figures are rarely seen in

benign nevi other than Spitz nevi, and even in the latter lesions the rate is usually low or zero (179).

Differential Diagnosis. Great difficulty may be encountered in the differentiation of a nodular melanoma from an atypical dermal or compound nevus. The actual incidence of a wrong diagnosis is not inconsiderable, judging from the frequency with which pathologists disagree in their opinions. When there is doubt, the uncertainty should be acknowledged and the differential diagnosis should be clearly indicated so that appropriate therapeutic intervention can be planned. Incisional biopsies are a common source of interpretive difficulty. The site of melanocytic lesions that have been partially removed by shave or punch biopsy should be excised to assure complete removal if there is any doubt at all about the diagnosis.

The most important attributes that differentiate the tumorigenic vertical growth phase of melanoma from nevi include *asymmetry*, *lack of maturation* of lesional cells with descent into the dermis, *mitotic activity*, and *uniform cytologic atypia*. Apoptotic tumor cells, which often accompany mitotically active lesions, may also be of assistance.

Considerations in the important distinction between thin melanomas and dysplastic nevi are discussed in the section Dysplastic Nevus and are presented in Table 28-5. The most important differential diagnostic consideration for nodular melanoma is the Spitz nevus. The criteria for this distinction are presented in Table 28-3 and discussed in the section Spitz Nevus.

In some instances, it may be difficult to recognize a highly undifferentiated melanoma as such. The specific identification of a tumor as melanoma depends on the identification of melanin or on appropriate immunohistochemical reactivity in an appropriate setting. The amount of melanin present varies greatly in melanomas. In some tumors, considerable melanin is found not only within the tumor cells, but also within melanophages located in the stroma. In others, there may be no evidence of melanin in hematoxylin-eosin stains. However, a Fontana-Masson silver stain usually reveals at least a few cells containing melanin (482). Some melanomas are completely devoid of pigment (amelanotic melanoma). Although amelanotic melanomas tend to be aggressive lesions, the prognosis is not different from that of pigmented melanomas when other staging and microstaging attributes are taken into consideration (483). If appropriate tissue is available, the DOPA reaction may be positive in at least part of the tumor (484), and electron microscopy shows some melanosomes and premelanosomes in nearly all cases (468,482,485). However, in practice, these methods have been largely supplanted by immunohistochemical techniques (468,482).

Immunohistochemistry. Most of the problems in distinguishing amelanotic or oligomelanotic tumorigenic melanomas from other tumors can be resolved by immunohistochemistry, using a panel of antibodies including S100, HMB-45, keratin (low and intermediate molecular weight such as AE1/3), and leucocyte common antigen (LCA) (43,486–489). On immunohistochemical testing, S100 protein is nearly always positive in melanoma (489). A keratin stain should be done in addition to staining for S100 protein to rule out not-uncommon S100-positive carcinomas (490). A few studies have reported positive keratin reactivity in melanomas, but this is unusual when standard methods are used in paraffin sections (490–492). Reactivity of melanomas, mostly metastatic, has been described with polyclonal but not monoclonal carcinoembryonic antigen, and occasional melanomas react with the epithelial marker epithelial membrane antigen (492). Melanomas, unlike most carcinomas, express vimentin, an intermediate filament that is usually associated with mesenchymal tissues (493). Lymphomas are usually positive with LCA, whereas S100 and HMB-45 are negative. The anaplastic large cell type of non-Hodgkin's lymphoma, which could present primarily in the skin, is quite likely to be confused with melanoma, and these tumors are usually positive for the CD30 (Ki-1) antigen, as well as LCA (CD45) (494). Occasional examples of histiocytic tumors such as epithelioid histiocytomas or juvenile xanthogranulomas may be confused with nodular melanomas, especially when foam cells or Touton giant cells are inconspicuous (219). It has been concluded that Melan-A and tyrosinase markers are sensitive and specific in making the diagnosis of a melanocytic lesion (222).

Several more specific but less sensitive antigens, of which the antigen recognized by HMB-45 (gp100) is prototypic, are used in addition to S100 in making the distinction between melanoma and nonmelanoma tumors. Like S100, HMB-45 is positive in many benign melanocytic tumors, and thus it is not specific for melanoma. Its sensitivity of about 70% overall is less than that of S100, for which the sensitivity is close to 100% but the specificity is low (490,491). HMB-45 expression is generally negative in desmoplastic and to a lesser extent other spindle cell melanomas (495). The specificity of the HMB-45 antigen depends on the context in which it is used. Benign melanocytic lesions that may react with HMB-45 include the junctional component of most nevi and the dermal components of dysplastic nevi, blue nevi, cellular blue nevi, deep penetrating nevi, and Spitz nevi. Thus, HMB-45 cannot be used to distinguish benign from malignant melanocytic neoplasms. If, on the other hand, the diagnostic differential is between melanoma and carcinoma, lymphoma, or sarcoma, the diagnostic specificity of a positive test is very high, albeit not 100%.

Use of HMB-45 has been augmented and in some institutions supplanted by other markers. Melan-A (MART-1) is an antigen initially recognized by T cells in melanoma patients, and, like HMB-45, is associated with the pigmentary apparatus. The sensitivity of this antigen is somewhat greater than that of HMB-45, and its specificity is about the same. The Melan-A antibody labels reactive cases strongly and clearly but is less sensitive in spindle cell melanomas and usually negative in the spindle cells of desmoplastic melanomas (488,496). It also must be noted that although Melan-A has more specificity than HMB-45 for detecting cells of melanocytic lineage, it also reacts with normal melanocytes and with nevus cells, limiting its utility as a potential marker for malignancy. Other markers

that have been studied recently include the melanoma-associated antigen (MAGE) series (497), microphthalmia-associated transcription factor (MITF) (498–500), and others. In a recent study, Xu et al. evaluated reactivity for alternative markers in 14 HMB-45–negative, nondesmoplastic melanomas (501). Melanocyte-specific transcription factor was positive in 9, Melan-A in 9, tyrosinase in 6, and MAGE-1 in 11. In 8 desmoplastic malignant melanomas, MAGE-1 was positive in 3, and all other markers were negative. The five markers tested were negative in all but two schwannomas, one with focal melanocyte-specific transcription factor and the other with tyrosinase and weak MAGE-1 reactivity. It was concluded that MAGE-1, melanocyte-specific transcription factor, tyrosinase, and Melan-A may be useful markers in the diagnosis of malignant melanocytic lesions when HMB-45 is negative (501).

In another study, a "panmelanoma cocktail" composed of HMB-45, MART-1, and tyrosinase labeled 98% of all melanomas but only 60% of desmoplastic melanomas, all of which were positive for S100. The panmelanoma cocktail is more specific than S100 and might be considered as a complementary marker to polyclonal S100 antibody, except for desmoplastic melanoma (502).

The markers discussed in the foregoing provide little information as to the benign or malignant nature of a lesion. However, the pattern of staining with HMB-45 can be of some assistance: melanomas tend to have more diffuse staining, whereas staining in benign lesions tends to be top-heavy, no doubt reflecting a form of maturation or senescence (503). In addition, the S100 subunit S100A6 has been of some use in distinguishing between Spitz tumor and melanomas, with a strong and diffuse staining pattern favoring the former (204). Finally, proliferation markers as well as other nuclear markers such as p53 (504), cyclin D (505), ploidy markers (506), and structures called nuclear organizer regions have been advocated (394). The most useful of these is Ki-67 (Mib-1). A high Ki-67 rate of, say, 10% or more of reactive cells would favor a malignant diagnosis, whereas a low rate of 2% or especially zero activity would favor a benign diagnosis (507). In our experience, although we often order a Ki-67 study to assess proliferative activity, most diagnostically equivocal tumors fall into the gray zone of Ki-67 reactivity between these cut-points. Other markers have not been studied in sufficient detail for us to recommend their use.

Desmoplastic and Neurotropic Melanoma

Desmoplastic melanomas present attributes of melanocytic, fibroblastic, and schwannian differentiation, often mixed within a single lesion (508). The lesions occur on chronically sun-damaged skin, usually in elderly patients. The lower lip is a relatively common site, sometimes in younger patients (509). Other cases occur, often in relation to lentiginous melanomas, in acral and mucosal sites (510–514). In a large series of 280 cases, the male-to-female ratio was 1.75:1, and the median patient age was 61 years. The median tumor thickness was 2.5 mm, and 44% of cases were amelanotic. Five-year survival was 75%. Significant predictors of overall survival were a high mitotic rate and tumor thickness. All of the desmoplastic melanomas exceeded 1.5 mm in thickness and were Clark level IV or V. There was a significant increase in local recurrence when neurotropism was present. The rate of local recurrence was not higher for desmoplastic melanoma than for other cutaneous melanomas (515).

Desmoplasia is most often seen in a spindle cell vertical growth phase of lentigo maligna melanoma (516) or acral-lentiginous melanoma (454,517). However, desmoplastic changes can be seen occasionally in tumors with rounded or undifferentiated melanoma cells. The collagen in desmoplastic melanomas is arranged as delicate fibrils that extend between the tumor cells and separate them from one another. The relationship between tumor cells and stroma is thus similar to that seen in sarcomas, in contrast to most melanomas, in which an epithelial pattern of collagen fibers surrounding groups or clusters of tumor cells may be demonstrated, for example, with a reticulin stain. Of interest, neurotized nevi may also show the pattern of individual cells surrounded by collagen that characterizes desmoplastic melanomas, and the arrangement of the cells of desmoplastic melanomas in wavy fiber bundles comprised of S-shaped or serpentine cells may also recall the schwannian patterns of neurofibromas, neurotized nevi, and malignant schwannomas.

Histopathology. In desmoplastic melanoma, scanning magnification usually demonstrates an alteration of the architecture of the dermis, which may be subtle or more prominent. Frequently, this alteration extends throughout the full thickness of the reticular dermis into the fat. Typically, nodular clusters of lymphocytes and occasional plasma cells are present in the tumor or at its periphery, serving as a valuable scanning magnification clue (Fig. 28-27A). At higher magnification, the melanoma cells are usually elongated and amelanotic and are embedded in a markedly fibrotic stroma, so that it is often difficult to decide which are fibroblasts and which are melanoma cells. This problem is enhanced by the relative absence of nuclear atypia in many of the neoplastic spindle cells, although close scrutiny will usually reveal cells with nuclear hyperchromasia and contour irregularities not typical of resting or activated benign mesenchymal cells (Fig. 28-27B). Because of the frequent absence of melanin, differentiation from a fibrohistiocytic or a neural lesion may be difficult. Staining with S100 protein antibody usually marks many of the spindle-shaped cells, indicating that they are not fibroblastic (Fig. 28-27C) (518), but nevi, neurofibromas, and neurogenic sarcomas are also typically S100 positive. The HMB-45 or Melan-A antigens are usually not demonstrable in the spindle cell compartment of desmoplastic melanomas, but they may be focally demonstrable in superficial dermal or *in situ* epithelioid melanocytes (Fig. 28-27D). Indeed, Melan-A reactivity in a spindle cell lesion (in the spindle cells themselves) may be taken as evidence against the diagnosis of a desmoplastic melanoma (24). Similarly, HMB-45 reactivity would also support a diagnosis of a deep spindle cell proliferation other than desmoplastic melanoma (e.g., a relatively amelanotic blue

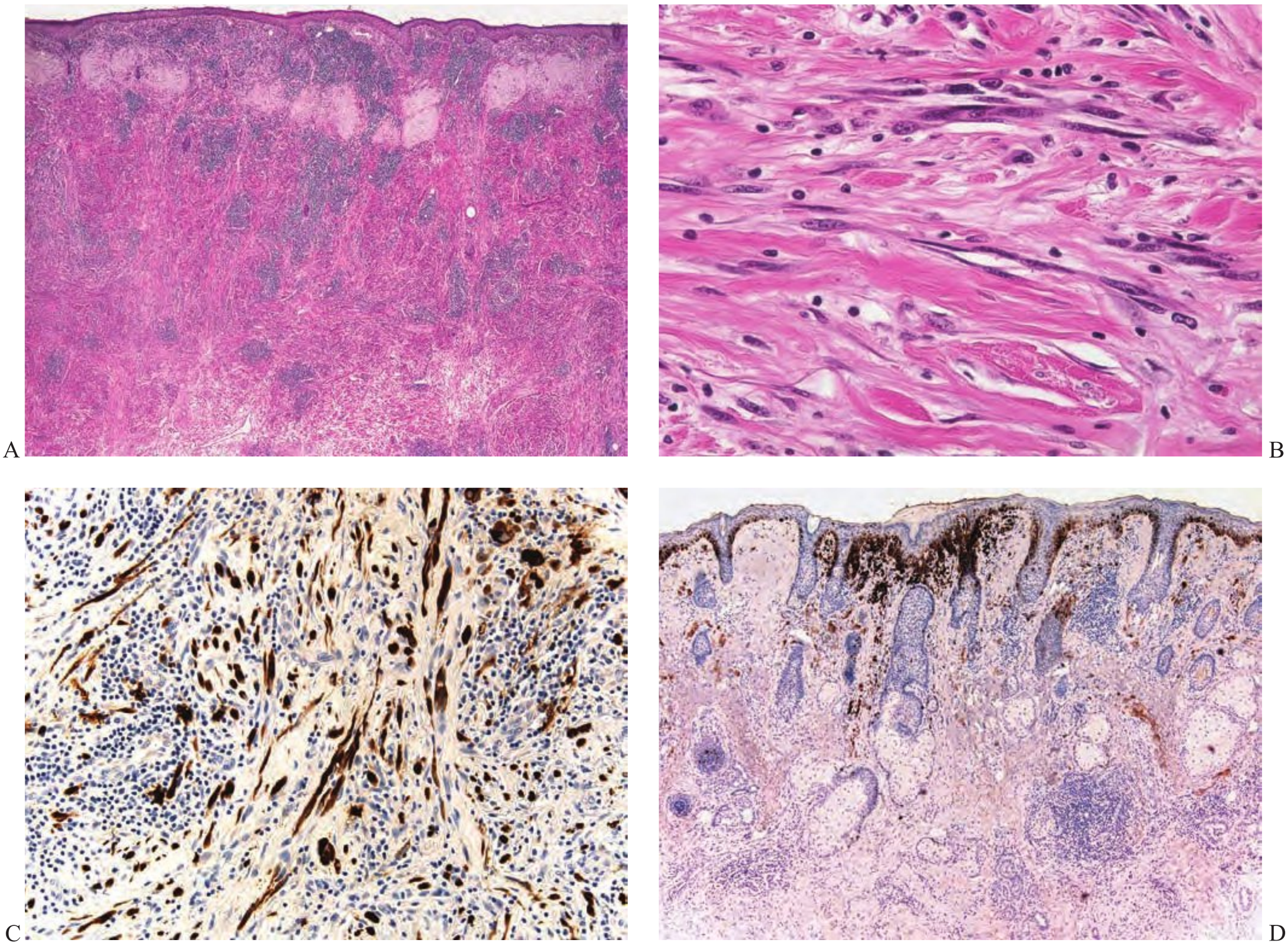


FIGURE 28-27. A: Desmoplastic melanoma. At scanning magnification, the architecture of the reticular dermis is altered by a cellular infiltrate including nodule clusters of lymphocytes, appearances that can simulate an inflammatory infiltrate. B: Desmoplastic melanoma. Atypical spindle cells arranged in loose fascicles extend into the deeper dermis and subcutis, beneath the epithelioid cell component. This subtle proliferation is easily overlooked, resulting in potential "undercalling" of the diagnosis and microstage. C: Desmoplastic melanoma. The spindle cells are S100 positive. S100 stain is of great value in delineating the boundaries of desmoplastic melanomas but should be interpreted cautiously because it is not specific for melanoma cells. D: Desmoplastic melanoma. An immunohistochemical study for Melan-A focally stains the in situ and superficial dermal epithelioid cell component of the melanoma. The deeper spindle cells are uniformly negative.

nevus). The distinction from a *neurogenic sarcoma* may be very difficult or impossible in such cases when there is no pigment and there is no characteristic superficial radial growth phase component (519) . Some of these lesions might alternatively be regarded as *superficial malignant epithelioid schwannomas*. The prognostic implications are similar, whichever diagnostic term is used. When such a lesion is marked by strong and diffuse S100 positivity, we usually make a diagnosis of desmoplastic melanoma, even in the absence of an *in situ* component or pigment. Desmoplastic melanomas have been shown to produce fibrogenic cytokines, neurotrophins, and neurotrophin receptors, which together can account for their desmoplastic and neurotropic propensities (520–522). Occasionally lesions termed *osteogenic desmoplastic melanoma* have been described and may be difficult to differentiate from an osteosarcoma (523). Aside from the diagnostic challenges posed by these differentiation patterns, such lesions may provide evidence of the inherent plasticity of a subpopulation of melanoma stem cells that drives the tumorigenic potential of advanced lesions.

Although the reported survival rate for desmoplastic melanoma in the early literature was poor, this is likely because many of these cases had already recurred at the time the diagnosis was made. A report of a series of desmoplastic melanomas that had been prospectively diagnosed and definitively treated

at their initial presentation showed that the survival rate was no different than for usual forms of melanoma when thickness, mitotic rate, host response, and other risk factors were controlled. Indeed, the probability of survival is relatively good for prospectively diagnosed and definitively treated desmoplastic melanoma because, despite the considerable thickness of many of these lesions, the prognostically important mitotic rate and lymphocytic responses are often favorable (414). In a recent report, expression of N-cadherin was correlated with a worse prognosis (524). By routine histology, desmoplastic melanomas have been classified into two types: Pure desmoplastic melanomas are characterized by predominant fibrosis and have a better 5-year survival of 90% compared to 70% in mixed tumors, in which fibrosis was well developed only in parts of an otherwise nondesmoplastic (i.e., epithelioid) melanoma (525). In a comparative study, whereas desmoplastic melanomas were more locally aggressive than thickness-matched controls, positive sentinel nodes were limited to patients with thick primary tumors, and survival rates were similar to those for patients with other melanomas of similar thickness (526).

Neurotropic melanoma is often a variant of desmoplastic melanoma (515,519,527–530). There are fascicles of spindle cell melanoma that have invaded cutaneous nerves, often extending within the fiber itself (endoneurial invasion) as opposed to the perineural invasion that is more characteristic of neurotropic carcinomas. The involvement of nerves may therefore be quite subtle, with the first clue being the impression of slight hypercellularity within a given nerve branch. The neurotropism usually occurs in association with a spindle cell vertical component with fibrosis (Fig. 28-28). However, some neurotropic melanomas lack these latter features of desmoplastic melanoma. Many of these are spindle cell tumorigenic melanomas of acral-lentiginous or lentigo maligna type, but some are composed of epithelioid cells. Desmoplastic and spindle cell melanomas tend to express a high level of p75 neurotrophin receptor antigen, as well as other neurotrophins and their receptors, which may contribute to the high predisposition for perineural extension in the desmoplastic subset of spindled melanomas (521,522) and could be useful in diagnosis. Neurotropism in a primary melanoma is associated with increased risk for local recurrence, even after standard definitive therapy, and may also be associated with increased mortality (414).

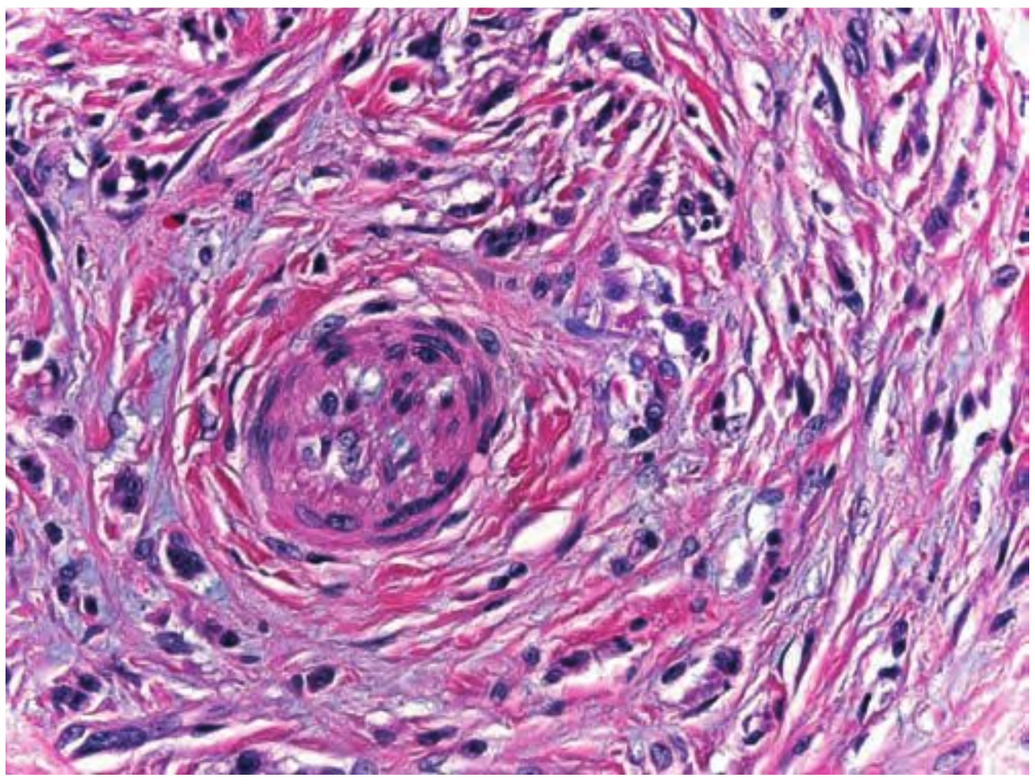


FIGURE 28-28. Neurotropism in a desmoplastic melanoma. A nerve in the center of the image contains atypical neoplastic spindle cells both in the nerve itself (endoneurial invasion) and in the perineurium (perineural invasion). The adjacent stroma contains neoplastic spindle cells separated by desmoplastic stroma.

Reexcision Specimens. Evaluation of reexcision specimens for desmoplastic and neurotropic melanomas can present considerable difficulties. S100 staining can be useful, but it has been demonstrated that S100-positive cells may be present in benign scars (531–533). It is important that these procedures encompass a margin of normal tissue around the scar, both for completeness of excision and because of the difficulty of excluding subtle melanoma involvement of the scar. In this regard, it is helpful to remember that residual melanoma is likely to present at the periphery of the scar and to infiltrate normal tissue adjacent to it. The specimens should be carefully coated with India ink or colored dyes, and the inked margin should be carefully scrutinized for residual invasive melanoma and for subtle neurotropic involvement of small nerves. A clue to the presence of melanoma, both in nerves and in the stroma, is the presence of clusters of lymphocytes, which sometimes may almost completely obscure the tumor cells themselves. Moreover, persistent S100-positive spindle cell melanoma cells tend to occur in small clusters and fascicles rather than as single, often dendritic cells, as is the case with S100-positive dendritic cells of hematopoietic lineage that may be detected in scar tissue.

Immunohistochemistry. As previously discussed, desmoplastic and to a somewhat lesser extent other spindle cell melanomas tend to differ from the more common epithelioid cell melanomas in their immunohistochemical reactivity. Although S100 is almost always positive, the more specific markers such as HMB-45 and Melan-A/MART-1 are usually negative, except for occasional reactivity of a minor epithelioid cell component that is sometimes present in the epidermis or superficial dermal component of the neoplasm (Fig. 28-27D). In a study of 20 desmoplastic melanomas, all 20 were positive for S100 protein, 7 were positive for MITF, 6 for HMB-45, and 11 for tyrosinase (500). In another study, only 4 of 13 spindle cell and desmoplastic melanomas (all positive with anti-S100 and negative with HMB-45) were immunoreactive with Melan-A/MART-1 (2 focally, 2 diffusely) (488). Thus, S100 reactivity is of key importance in distinguishing these tumors from fibroblastic lesions. However, it is of no use in the distinction from neural tumors or from desmoplastic nevi. In contrast, Melan-A/MART-1 reactivity is usually present in desmoplastic nevi, including sclerotic blue nevi, and such reactivity may be very helpful in ruling out a desmoplastic melanoma in some such lesions (26), although not pathognomonic.

Differential Diagnosis. It is very important to differentiate desmoplastic melanoma from benign conditions, including benign melanocytic and neural tumors, fibrous and fibrohistiocytic tumors, and other spindle cell malignancies. Neurotized nevi and neurofibromas share serpentine spindle cell and wavy fiber bundle patterns of schwannian differentiation with desmoplastic melanomas but lack an *in situ* melanoma component and lack atypia and mitotic activity, as well as lymphocytic infiltrates, in the dermal component. According to a study by Harris et al., similarities between desmoplastic nevi and desmoplastic melanomas included the presence of atypical cells and HMB-45 expression in the superficial portion of the lesions (196). The infrequent location on the head or neck, the absence of mitotic figures, a significantly lower number of Ki-67–reactive cells, and the presence of HMB-45 expression in the deep area of the lesions helped to distinguish desmoplastic nevi from desmoplastic melanoma (196). The diagnosis of desmoplastic melanoma should be made with great caution if the dermal spindle cell component is positive for Melan-A (24). Fibrous tumors such as connective tissue nevi (534) or cellular dermatofibromas can be distinguished by immunohistochemical studies, including negative S100 staining. Other considerations include low-grade malignancies such as fibromatoses and dermatofibrosarcoma protruberans and fully malignant lesions such as leiomyosarcoma and malignant schwannoma. The latter group of lesions may overlap biologically as well as morphologically, and their management is the same, namely complete excision and follow-up. Because spindle cell melanomas may be confused with other malignant spindle cell neoplasms (e.g., malignant tumors of neural cells, smooth muscle, fibrohistiocytic cells, and spindle cell variants of squamous cell carcinoma), particularly when careful search fails to reveal evidence of *in situ* growth, immunohistochemical screening by the panel approach is recommended in such instances. Rarely, spindle cell melanomas may form vessel-like structures and, when such lesions occur on the scalp of elderly individuals, produce confusion with angiosarcoma. Immunohistochemical identification of S100 protein and exclusion of CD31 endothelial reactivity may be helpful in such instances (535). Misdiagnosis of desmoplastic melanomas as one or another of the benign lesions listed is not uncommon because attributes of malignancy such as anaplasia or frequent mitoses are often not prominent features of desmoplastic melanomas. The large size and asymmetric silhouette of many of these lesions differ from what is seen in most benign lesions. An important, sometimes subtle clue to the diagnosis at low power is the frequent presence of a lymphocytic infiltrate, distributed as nodular aggregates of infiltrating lymphocytes throughout the tumor, which are not seen in neurofibromas, nevi, or most fibrohistiocytic lesions. Lymphocytes may also be clustered about nerves involved by tumor cells in neurotropic melanomas. Other helpful diagnostic attributes, which may not be readily evident unless sought because of a high index of suspicion, include the presence of an atypical intraepidermal melanocytic component, which may be subtle and not always diagnostic of frank melanoma, and usually the presence on diligent search of at least a few mitoses in the dermal component of the lesion.

Polypoid Melanoma

Also termed pedunculated melanoma, this term designates a melanoma that presents as a protruding nodule connected to the underlying skin by a pedicle or stalk (536). The surface of the nodule often shows erosion or ulceration (537). Because these tumors are bulky, the prognosis is often poor but probably not worse than predicted by other risk factors (538). By convention, polypoid melanomas, even when the greatly expanded papillary dermis is not filled, are considered to represent level III invasion unless tumor cells extend into the reticular dermis (level IV).

On histologic examination, the nodule is filled with melanoma cells, whereas the underlying stalk or pedicle may be free of tumor cells and in other cases the tumor may infiltrate the pedicle and the dermis adjacent to the pedicle.

Verrucous Melanoma

These melanomas present as a markedly hyperkeratotic, tumorigenic nodule that may simulate a verruca, verrucoid benign keratosis, or a verrucous carcinoma clinically (408,434,478,539,540). Histologically as well, the lesions are associated with marked keratosis and verrucous hyperplasia of keratinocytes that may assume pseudoepitheliomatous proportions and raise a question of squamous cell carcinoma unless the underlying neoplastic melanocytes are appreciated (541). Some other lesions are misdiagnosed histologically as benign nevi or seborrheic keratoses (478), highlighting the potential importance of histologic sampling of changing or symptomatic nevic or keratosis-like lesions. Verrucous changes of adjacent keratinocytes are sometimes observed adjacent to acral and especially subungual melanomas, which are often mistaken clinically for warts on initial presentation if pigment is not prominent. In such instances, an inadequate biopsy that does not include the underlying neoplasm could appear to be consistent with a wart.

Balloon Cell Melanoma

Usually in addition to more characteristic melanoma cells of the epithelioid type, some melanomas contain aggregates of "balloon cells" (542). These balloon cells, characterized by their abundant, clear cytoplasm, may show relatively little nuclear atypia and thus may resemble those seen in a balloon cell nevus. The clear cytoplasm is the result of vacuolar degenerative alterations affecting melanosomes and may expand the cytoplasm in a manner that compresses the nucleus, partially obscuring its size and cytologic features helpful in identifying a malignant phenotype. However, the overall architecture of the lesion and the presence of at least foci of detectable cytologic atypia, usually with mitotic activity, identify the tumor as a melanoma. Immunohistochemistry (Melan-A, HMB-45, and/or tyrosinase reactivity) may sometimes be required to distinguish the lesions from other clear cell or foamy tumors, such as renal cell carcinoma or xanthoma, respectively (543).

Transitions from the melanoma cells to balloon cells are usually seen. The metastases of a balloon cell melanoma may or may not be composed largely of balloon cells, and balloon cell metastases have been described from a melanoma that did not contain them in the primary tumor (544). In addition, a metastatic balloon cell melanoma has been described in the absence of a known primary (545). Thus, this possibility should be considered in the differential diagnosis of metastatic clear cell tumors. The cells exhibit immunopathologic reactivity characteristic of melanoma.

Signet Cell Melanoma

Melanomas that contain prominent signet-ring cells may be confusing and must be distinguished from adenocarcinomas, tumors of vascular endothelium or adipose tissue, lymphomas, and epithelioid smooth muscle tumors (546–548). The signet cell morphology may be recognized in the primary tumors or only in metastatic sites. Similar cells may be seen in benign nevi, and a somewhat similar change may also occur as a result of freezing artifact (547). Immunohistochemistry may be used to confirm the diagnosis of a melanocytic lesion and rule out competing possibilities. In evaluating these results, it should be recognized that expression of both carcinoembryonic antigen (only seen using polyclonal antibodies) (549,550) and keratin (492) has been described in melanomas.

Myxoid Melanoma

A histologic pattern of prominent myxoid stroma has been described in some primary and metastatic melanomas (551,552). In addition, a myxoid clear cell sarcoma has been described (553). The differential diagnosis may be very broad, including lipoblastic, myoblastic, fibroblastic, neurogenic, or chondroblastic tumors with myxoid stroma (551). If the diagnosis is suspected, immunohistochemistry can be done to support the diagnosis. Fontana stain may reveal melanin pigment, and electron microscopy in a few cases has shown melanosomes.

Animal-Type Melanoma (Macrophagic Melanoma)

Rare tumors comprised of asymmetric, predominantly dermal nodules of heavily pigmented cells mimic melanocytic neoplasms seen in horses and laboratory animals and thus have been termed animal-type melanomas (554). The tumor cells are heavily stuffed with melanin granules, often obscuring the nucleus, and for this reason the tumors have been referred to as "melanophage-like" (555). Behavior of these lesions is unpredictable. In two published series totaling 20 cases (554,556), the lesions were described as blue-black nodules with irregular borders from 1.0 to 4.0 cm in size located on the scalp, lower extremities, back, and sacrum. Sections showed confluent dermal sheets of round or short, spindle-shaped, heavily melanized cells whose nuclei, where discernible, were large with irregularly thickened membranes, coarse, somewhat hyperchromatic chromatin, and prominent, often spiculated nucleoli. Mitoses were infrequent. Four lesions had an epidermal component. One patient suffered metastases to regional lymph nodes, liver, and lungs with lethal effect, whereas all of the others were alive with variable follow-up, despite 5 of them having regional lymph node metastases, 1 having hepatic metastases, and 3 having local satellite metastases. In a more recent study of 14 cases, the term pigment-synthesizing melanoma was suggested for these lesions, which were considered to be a distinctive, possibly low-grade form of melanoma (556).

Pigmented Epithelioid Melanocytoma

This is a recently described melanocytic tumor that may resemble and thus encompass animal-type melanoma, as well as epithelioid blue nevi as seen in the Carney complex and some cellular blue nevi (557). This lesion is considered to represent a distinctive tumor that affects males and females equally, with a median age of occurrence of 27 years (range 0.6 to 78 years). Multiple body sites may be affected, with extremities being the most common. Histologically there is a deep dermal nodule of heavily pigmented epithelioid and/or spindled melanocytes (Fig. 28-29), and some lesions occur in association with combined nevi. Ulceration may be present in occasional lesions, a finding generally not present in epithelioid blue nevi. These lesions may be identical to animal-type melanoma, and, in this study, also may be difficult to distinguish from some epithelioid blue nevi. Although tumor cells may be deceptively bland and mitoses and necrosis inconspicuous or absent, regional lymph node involvement has been seen in 46% of cases studied. However, there were no deaths. Metastases were not observed in the cases of epithelioid blue nevi seen in association with the Carney complex, which is a multiple neoplasia syndrome featuring cardiac, endocrine, cutaneous, and neural tumors, as well as a variety of pigmented lesions of the skin and mucosae including lentigines, epithelioid blue nevi, and psammomatous melanocytic schwannoma (558). Extranodal spread is rare in pigmented epithelioid melanocytoma, and even with involvement of draining lymph nodes, the clinical course may be remarkably indolent. Similar lesions have been recently designated as pigment-synthesizing melanomas and regarded as a low-grade form of melanoma that may lack some of the signs of more aggressive melanomas of similar bulk, such as frequent mitoses, ulceration, and high-grade atypia (556). Further study with extended outcome analyses of animal-type melanoma, epithelioid blue nevi, and their relationship to the category of pigmented epithelioid melanocytoma is indicated to clarify the biological potential of this difficult category of melanocytic neoplasms.

Minimal Deviation Melanoma

Recognized by only some authors, this lesion is referred to as borderline type when it is limited to the papillary dermis and as minimal deviation type when it extends into the reticular dermis (232,559). These tumors are considered to exhibit less cytologic atypia than the common forms of melanoma, although the architectural characteristics of melanoma are usually present. Accordingly, they may be considered to show morphologic overlap between an atypical nevus and a melanoma with fully evolved anaplasia. The lesions in their vertical phase consist of uniformly expansile nodules, and the

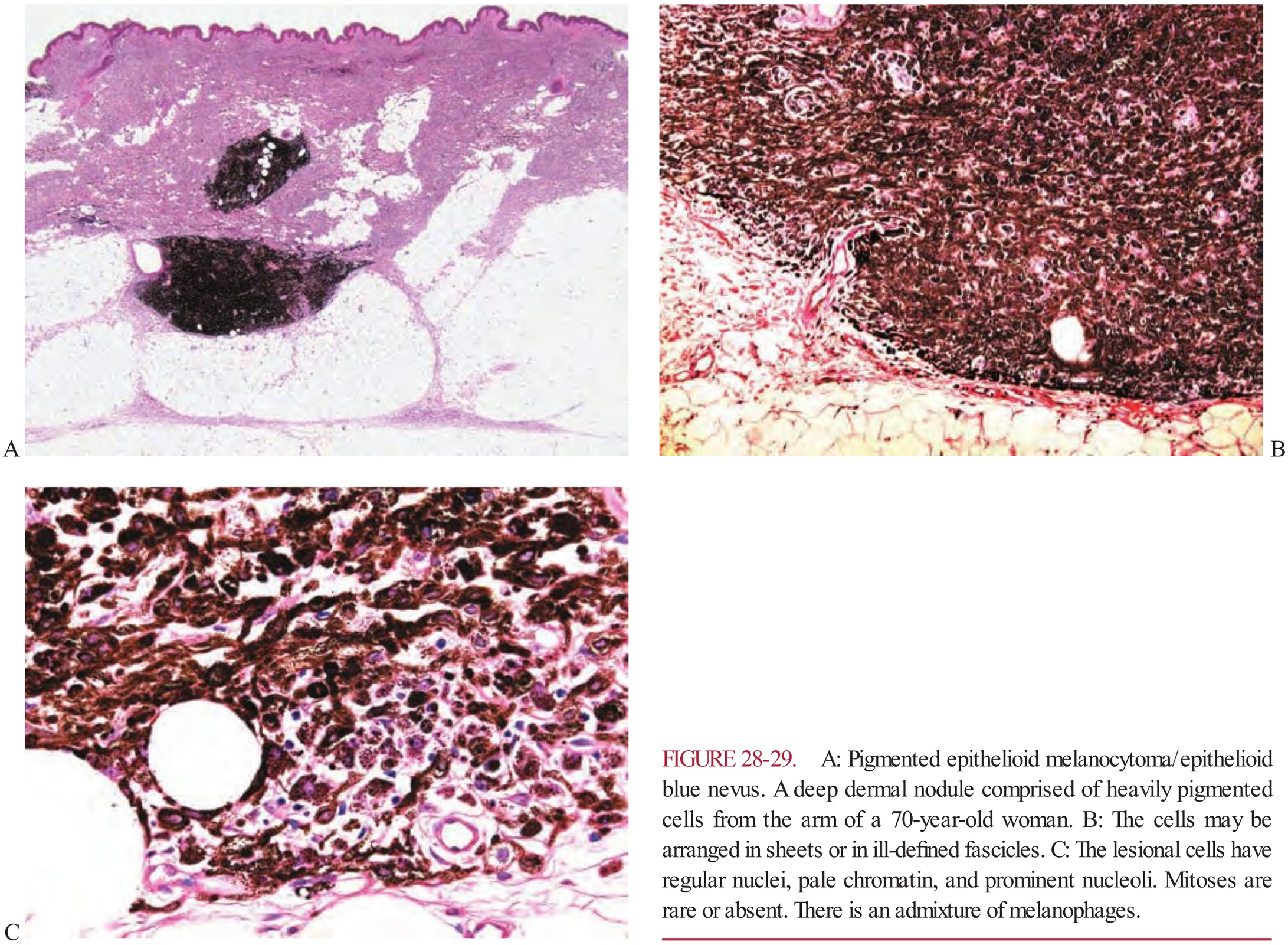


FIGURE 28-29. A: Pigmented epithelioid melanocytoma/epithelioid blue nevus. A deep dermal nodule comprised of heavily pigmented cells from the arm of a 70-year-old woman. B: The cells may be arranged in sheets or in ill-defined fascicles. C: The lesional cells have regular nuclei, pale chromatin, and prominent nucleoli. Mitoses are rare or absent. There is an admixture of melanophages.

cells in the nodules tend to be arranged in uniform patterns. If the tumor cells are epithelioid in type, they may resemble cells of ordinary acquired nevus. In the spindle cell variants, the tumor cells may resemble the cells of a Spitz nevus or, if pigmented or arranged in compact fascicles, a pigmented spindle cell nevus. Because of the resemblance to nevus cells, the term nevoid melanoma has also been used. However, nevoid melanoma (discussed in the next subsection) technically differs from most so-called borderline/minimal deviation melanomas by virtue of a more nevoid architecture, albeit formed by mitotically active cells. In one study, expression rates of the proliferation marker Ki-67 in borderline/minimal deviation melanomas were intermediate between those seen in nevi and in superficial spreading melanomas (560). Even though recurrences, metastases, and death may occur, most minimal deviation melanomas are believed to be biologically not as aggressive as common melanomas. However, prognosis is probably more accurately predicted by multivariable prognostic models.

Nevoid Melanoma

Although related to minimal deviation melanoma, this term has been used somewhat differently. Nevoid melanomas have been defined as lesions that, to a greater or lesser extent, mimic a benign nevus histologically, often with an emphasis on a nevoid architecture (in contrast to minimal deviation melanoma, in which melanoma architecture tends to be preserved) (561,562). Usually, the resemblance is most apparent at scanning magnification, on which lesions may appear symmetric, nested, and devoid of radial growth, features that can lead to a missed diagnosis if sufficient attention is not paid to cytologic and subtle architectural features (563). Discriminating attributes include high cellularity with "sheetlike" growth, cellular atypia, mitoses, infiltration of adnexa, infiltrative growth in the deeper dermis, and the absence of maturation (Fig. 28-30). Tumor thickness was the most important prognostic criterion (562). Nevoid melanomas are generally considered to have the same biological potential as other melanomas with similar microstaging attributes (121,562). Key to the recognition of a nevoid melanoma is a high index of suspicion and the identification of mitotic activity and cytologic atypia in the dermal component of the lesion (121,562,563). According to McNutt, reactivity of the intradermal component for HMB-45 antigen, without antigen retrieval, or for Ki-67 antigen can show that the dermal cells have an activated and hyperproliferative phenotype and, in combination with histologic criteria, can help to support a diagnosis of nevoid malignant melanoma (564).

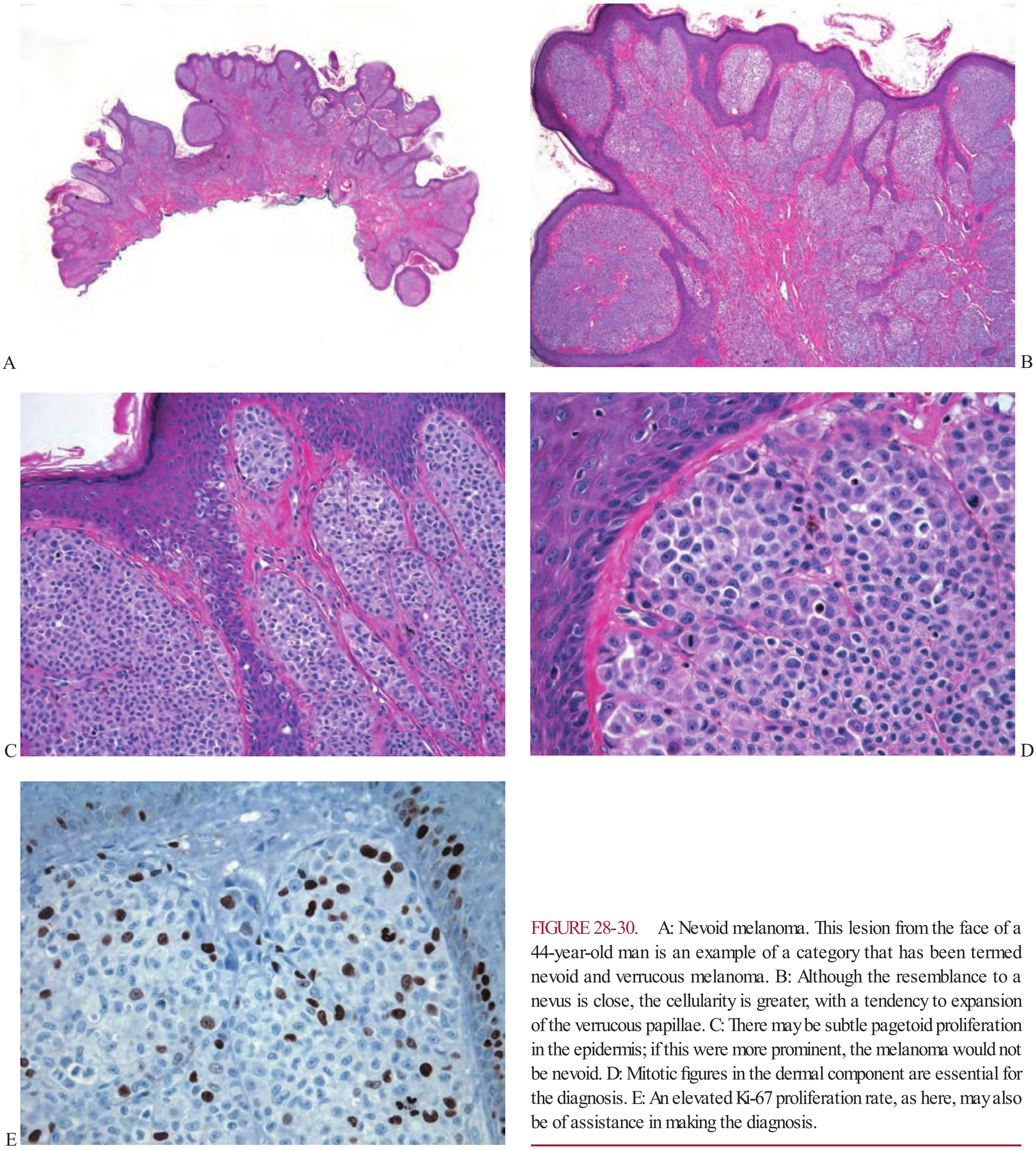


FIGURE 28-30. A: Nevoid melanoma. This lesion from the face of a 44-year-old man is an example of a category that has been termed nevoid and verrucous melanoma. B: Although the resemblance to a nevus is close, the cellularity is greater, with a tendency to expansion of the verrucous papillae. C: There may be subtle pagetoid proliferation in the epidermis; if this were more prominent, the melanoma would not be nevoid. D: Mitotic figures in the dermal component are essential for the diagnosis. E: An elevated Ki-67 proliferation rate, as here, may also be of assistance in making the diagnosis.

Epidemiology, Prognosis, and Management of Melanoma

Risk Factors for the Development of Melanomas

Phenotypic risk factors for the development of melanoma can offer clues to the etiology and pathogenesis of the disease. These have been identified through case–control studies and through follow-up of cohorts of patients, often from high-risk melanoma clinics. The major risk factors include age, family or personal history of prior melanoma, the presence of potential precursors such as nevi and dysplastic nevi, a history of exposure to the sun, a skin susceptibility to solar damage, and the

presence of indicators of chronic solar damage. Type I skin that burns easily and tans poorly is a risk factor, as are behavioral factors, such as living in a sunny climate, a history of weekend and vacation sun exposure, and a history of sunburn episodes. The presence of indicators of exposure to the sun and of susceptibility to solar damage such as freckles and actinic skin changes are also strongly associated with melanoma risk (46,565). Even more closely correlated with risk is the presence on the skin of potential precursors, including attributes of nevi such as the total number of banal nevi, the presence of large nevi, and, especially, the presence and number of dysplastic nevi (337). Among these risk factors, melanocytic nevi and indicators of acute, intermittent sun exposure are more strongly related to superficial spreading and nodular melanoma (566,567), whereas skin type, ethnic background, and measures of total accumulated exposure to the sun (chronic, continuous sun exposure) are more strongly related to lentigo maligna melanoma (568). Age is also a strong risk factor, operating in a continuously progressive fashion in lentigo maligna melanoma and perhaps also in acral and mucosal melanomas, in contrast to a more complex pattern for superficial and nodular melanoma (455). Many of these factors are under genetic control, and a family history of melanoma constitutes another major risk factor, especially as the number of melanomas in a family increases. Only a relatively small proportion of these familial melanomas is attributable to the presence of a major high-penetrance melanoma risk gene, such as CDKN2A (p16) or CDK4, both of which are tumor suppressors that act through the retinoblastoma (Rb) pathway (569–571). Other genes contributing to risk may have lower penetrance but may be present in more individuals in the population, thus accounting for a more substantial proportion of cases (i.e., a higher attributable risk). Examples of such genes include the melanocortin receptor MC1R, which controls skin pigmentation (572), and DNA repair genes (573).

Preexisting Melanocytic Nevus

It is well known that melanomas can develop in congenital nevi and in dysplastic nevi. Histologically, remnants of a banal nevus are found in a substantial number of melanomas, on the order of about 10% to 35%, and evidence of associated melanocytic dysplasia may be seen in up to about 40% (105,281,385–388,574–576). Analysis has demonstrated that this relationship is likely to be nonrandom (577). Remnants of a dysplastic nevus adjacent to a radial growth phase (usually of the superficial spreading type) can be distinguished from the latter using the criteria presented in Table 28-3. Remnants of a dermal component of a nevus deep to a melanoma can be distinguished from the melanoma cells by the following criteria (Fig. 28-31): (a) The dermal nevus cells are smaller; (b) they are arranged in nests that tend to be small and uniform in size and shape; (c) there may be evidence of maturation from superficial to deep within the nevus but not the melanoma cell population; (d) there is no evidence of continuous differentiation from a more obviously malignant superficial component to the nevoid cells at the base of the tumor; (e) there is no high-grade atypia, and there are no mitoses in the dermal nevus cells; and (f) nevus cells tend to disperse as single cells if they enter the reticular dermis, whereas melanoma cells tend to infiltrate as sheets or clusters (Fig. 28-32). This paradoxically less invasive pattern is related to the greater proliferative capacity of melanoma cells: Invasion probably initially involves single cells that then proliferate to form the final pattern of sheets or fascicles in the reticular dermis. For the same reason, cutaneous metastases tend to be sharply demarcated, expansive lesions (113). Occasional examples of differentiated dermal melanoma cells may meet some of these criteria and thus present difficulties of interpretation (see section Nevoid Melanoma).

It has recently been demonstrated that in some cases, loss of heterozygosity at the 9p21 locus (the locus of the cell cycle control gene CDKN2A) is detected simultaneously in a melanoma and its associated nevus (578). Recent studies have also demonstrated the same mutations in the oncogene NRAS in melanomas and in their associated nevi studied by microdissection (579). These results are consistent with a causal relationship for the development of melanoma within a preexistent associated nevus and also support the hypothesis that these genetic alterations play an important necessary but not sufficient role in development of some early melanomas because they are found in histologically benign melanoma-associated nevi (578).

In addition to dysplastic nevi and banal dermal nevi, superficial and deep congenital pattern nevi are also commonly associated with melanomas (281). An exception to the general rule that melanoma arises at the epidermal–dermal border is observed occasionally in congenital nevi, in which a melanoma may arise deep in the dermis. However, these proliferations should be distinguished from benign cellular/proliferative nodules that may occur in congenital nevi (293). In very rare instances, a melanoma may develop within or beneath an intradermal nevus, resulting in a dermal nodule of atypical cells (580).

Multiple Primary Melanomas

People who have had a cutaneous melanoma are at risk of developing additional melanomas, with an incidence of approximately 5% in the first 10 years after diagnosis (581). The occurrence of multiple and familial melanomas has already been pointed out in relation to dysplastic nevi (582–586). A prior melanoma is a strong risk factor for subsequent melanoma, especially in young patients and in familial melanoma kindreds (358,360). It is important to differentiate an additional melanoma from a metastatic melanoma, especially from an epidermotropic metastasis (563,587) because the prognosis of an independent primary is likely to be much better than that of a metastasis. This may be difficult, however, because some epidermotropic metastases closely mimic primary melanomas, and, accordingly, correlation with clinical parameters (e.g., more than one lesion) may be critical in differentiating a second primary from a metastasis in such

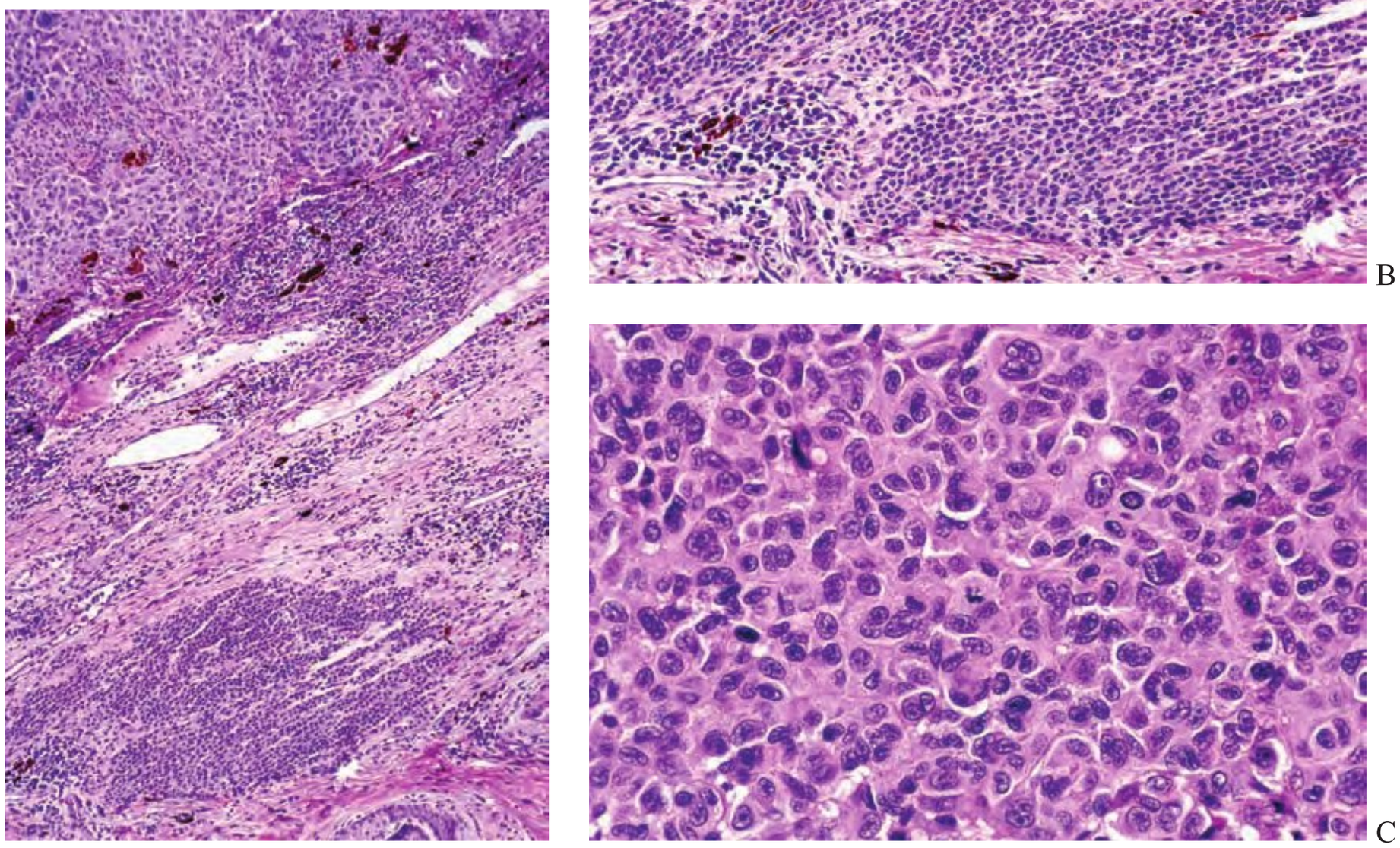


FIGURE 28-31. A: Nevus cells deep to a tumorigenic melanoma. A collection of smaller cells is present at the interface of the papillary and reticular dermis deep to a tumor of vertical-growth-phase melanoma. B: The nevus cells are smaller than the cells of the tumorigenic melanoma. C: The tumorigenic melanoma cells have large, hyperchromatic nuclei with irregularly clumped nuclear chromatin and with mitotic figures.

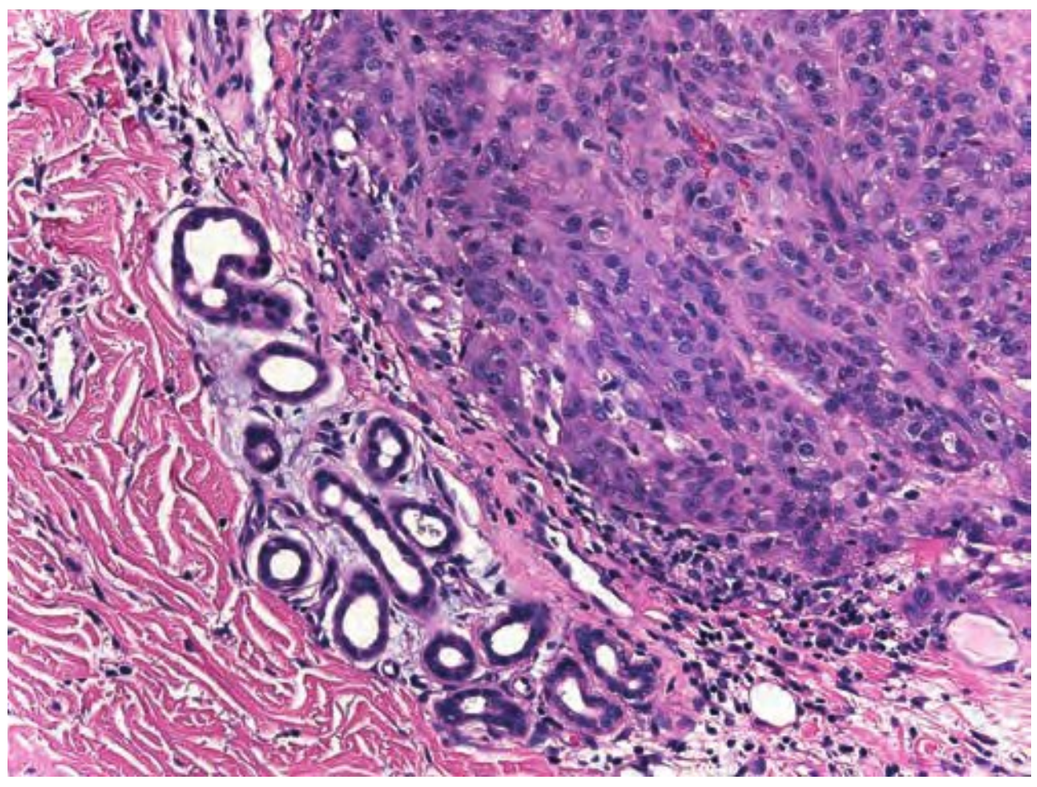


FIGURE 28-32. Infiltration of tumorigenic melanoma at the base of the lesion. The cells tend to be arranged in clusters or sheets. In benign nevi, the cells in the papillary dermis may be clustered, but when they enter the reticular dermis they tend to disperse as single cells (compare with Fig. 28-10F).

instances. Individuals with multiple primary melanomas have also been found to have a modestly increased incidence of a family history of melanoma, dysplastic nevi, and basal cell carcinoma, an earlier age of onset, and a relatively small incidence of CDKN2A mutations (588–591). Therefore, in addition to the multiple primary melanoma index case, other family members can benefit from screening and regular surveillance of their skin.

Malignant Melanoma in Infancy and Childhood

Malignant melanoma is a disease primarily of adults. The incidence of *prepubertal melanoma* is very low. In a few instances, it has occurred as multiple metastases resulting from transplacental transmission (592). Occasionally, a melanoma arises in infancy or childhood in a giant congenital nevus (Fig. 28-12B) (253,257,258,262). Outside of these situations, three patterns of primary melanoma have been described in children (593). In most instances, the melanoma shows a histologic picture similar to that in adults, and the prognosis depends on thickness and other microstaging attributes. In other cases, the tumors are composed of small blastic malignant cells, and the

course is usually aggressive, although sometimes unpredictably so, especially in tumors that arise in congenital nevi. In a few instances, the histologic picture is reminiscent of that seen in Spitz nevi (593–595). In some of these cases, metastases occur that are limited to the regional lymph nodes and the child survives after adequate treatment (223,593). However, spitzoid melanoma with a fatal outcome in a child has been reported (593). These lesions may be considered to represent a special category of spitzoid melanomas of childhood, in which there may be a relatively high incidence of regional metastasis but a relatively low (but not zero) risk of more distant progression (596). Some of these lesions may be best termed melanocytic tumors of uncertain malignant potential because criteria for reliable distinction between benign and malignant examples of these lesions are not well defined (231). This designation may also be relevant to even overt melanomas in children because such lesions appear to overall show a better prognosis than would be anticipated in adulthood.

Biopsy of Melanoma

The question of whether an incisional biopsy is permissible in a lesion that is highly suspected of being a melanoma has been widely discussed. Some authors have opposed the performance of an incisional biopsy because of a belief that it might cause metastatic spread (597). In other studies, no deleterious effect of a preceding biopsy was noted (598–601). It is difficult in studies of this sort to control for other risk factors, which might be expected to be more prevalent in the larger tumors for which an incisional biopsy might be contemplated.

Because a correct diagnosis and accurate prognostic staging are more likely to be accomplished when the entire tumor can be studied, an excisional biopsy is advisable whenever feasible, and only in occasional instances such as very large lesions is an incisional biopsy indicated (602). If a tumorigenic vertical growth phase is present, it should be entirely contained within the biopsy, if possible. A shave biopsy or curetting is not optimal because it may result in inadequate material for diagnosis; it may also make impossible a determination of the depth of penetration of the tumor, which is very important for prognosis and for planning of the extent of surgical procedures (see Prognosis). Shave or punch biopsies that completely encompass the lesion are, of course, acceptable. However, a positive deep margin is commonly found in a shave biopsy, and this may compromise the ability accurately to diagnose and stage the lesion (603).

Multivariable Prognostic Models

The gold standard for considering any putative prognostic marker to be clinically important is its inclusion as an independent variable in a multivariable analysis. Many such studies have been published for the traditional histopathologic and clinical variables reviewed here. Based on these multivariable analyses, prognostic models have been published, either requiring the use of a calculator to determine a regression function or, more simply, using published tables to provide a quantitative probability estimate (472,604–621). Although these models are useful in planning therapy and especially in the development and execution of clinical trials, thickness and ulceration are the factors in predominant use for planning of therapy for stage I melanoma. Prognostic modeling may be considered as a form of staging of the primary tumor (so-called microstaging).

Staging of Melanoma

The purpose of staging is to define subsets of cases with a similar prognosis for management and investigational purposes. The five-stage (0 to IV) clinicopathologic staging system of the AJCC primarily considers aspects of the tumor (T), the presence and size of nodal metastases (N), and the presence and sites of distant metastases (M) to determine a stage based on all three attributes (TNM). The 5-year survival for newly diagnosed localized primary melanoma cases (stages 0 to II) is about 80%, compared to 35% survival when lymph nodes are involved (stage III). Using the prognostic models to be discussed, subsets of cases with more or less favorable prognosis can be identified. When distant metastases are present, the survival at 5 years is on the order of 10% (613,622).

TNM Staging System for Melanoma

The TNM system of tumor staging considers factors related to the primary tumor, to regional lymph nodes (and other regional soft tissues), and to distant metastases to result in a classification that is associated with the probability of survival. The factors considered in the primary tumor (T) category include some of the microstaging attributes discussed earlier. Thus, the TNM classification combines staging and microstaging information in a single format. In the current system (which became official with the publishing of the sixth edition of the *AJCC Cancer Staging Manual* in 2002) (613,622,623), the T attributes are classified pathologically after excision of the melanoma (pT), as described later (622). The TNM model therefore considers pathologic attributes of the primaries, but staging for metastases is defined in part clinically. For example, lymph node metastases are defined in terms of the number of lymph nodes involved, as well as volume, and are coded as micrometastasis if lymph node metastasis has been diagnosed at sentinel node biopsy or at elective lymphadenectomy and as macrometastasis if clinically positive and pathologically confirmed by therapeutic lymphadenectomy (622). Among macrometastases, the size of nodes is no longer used in staging, based on evidence that the number of nodes but not their size is significant prognostically (624–629). In other prognostic models, it has been demonstrated that microstaging of the primary tumor retains prognostic significance in melanoma patients who are clinically negative but pathologically positive for metastases to regional nodes (630–632), and this is also reflected in the new AJCC staging system, in which ulceration retains significance in some patients with nodal metastases. The new system has been reviewed by Schuchter (633).

The latest revision (2002) of the TNM categories is presented in Table 28-7, and the final stage groupings are given in

TABLE 28-7 Melanoma TNM Classification (622,623)

T classification

	Thickness (mm)	Ulceration/Clark level status
T1	≤1.0	a: without ulceration and level II/III b: with ulceration or level IV/V
T2	1.01–2.0	a: without ulceration b: with ulceration
T3	2.01–4.0	a: without ulceration b: with ulceration
T4	>4.0	a: without ulceration b: with ulceration

N classification

	Number of metastatic nodes	Nodal metastatic mass
N1	1	a: micrometastasis* b: macrometastasis†
N2	2–3	a: micrometastasis* b: macrometastasis† c: in-transit met(s)/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in-transit met(s)/satellite(s) with metastatic node(s)	

M classification

	Site	Serum lactate dehydrogenase
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

*Micrometastases are diagnosed after sentinel or elective lymphadenectomy.
†Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

TABLE 28-8 Stage Groupings for Cutaneous Melanoma (622,623)

	Clinical staging			Pathologic staging		
	T	N	M	T	N	M
0	Tis	N0	M0	Tis	N0	M0
IA	T1a	N0	M0	T1a	N0	M0
IB	T1b	N0	M0	T1b	N0	M0
	T2a	N0	M0	T2a	N0	M0
IIA	T2b	N0	M0	T2b	N0	M0
	T3a	N0	M0	T3a	N0	M0
IIB	T3b	N0	M0	T3b	N0	M0
	T4a	N0	M0	T4a	N0	M0
IIC	T4b	N0	M0	T4b	N0	M0
III	Any T	N1	M0			
		N2				
		N3				
IIIA				T1–4a	N1a	M0
				T1–4a	N2a	M0
IIIB				T1–4b	N1a	M0
				T1–4b	N2a	M0
				T1–4a	N1b	M0
				T1–4a	N2b	M0
				T1–4a/b	N2c	M0
IIIC				T1–4b	N1b	M0
				T1–4b	N2b	M0
				Any T	N3	M0
IV	Any T	Any N	Any M1	Any T	Any N	Any M1

Table 28-8 (613,622,623). Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, clinical staging should be used after complete excision of the primary melanoma, with clinical assessment for regional and distant metastases. Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage 1A patients do not require pathologic evaluation of their lymph nodes. There are no stage III subgroups for clinical staging. The definitions have been recommended by the AJCC Melanoma Staging Committee and approved by both the AJCC Executive Committee and the TNM Committee of the International Union Against Cancer (Union Internationale Contra Cancer, UICC). The revised melanoma staging system has been approved by the World Health Organization Melanoma Program as well as the European Organization for Research and Treatment of Cancer Melanoma Group (634). These new definitions incorporate substantial revisions from previous (1983 and 1997) versions of the melanoma staging categories and classifications (623,635,636).

The TNM staging system incorporates clinical and pathologic attributes of the primary neoplasm (microstaging attributes) in the definition of the stage groups. Tumors in stage groups I and II are nonmetastatic, and stage III may or may not be associated with distant metastasis (Table 28-8). Stage IV is always metastatic. Because these stages are different from those defined in other staging systems, it is clear that the system in use (e.g., AJCC stage X) should be clearly specified when staging is used as a basis for therapy or prognosis.

The staging system is primarily based on survival studies done in several collaborating institutions. Survival rates for 17,600 patients categorized according to the AJCC staging system are shown in Table 28-9. Survival times were calculated from onset of primary melanoma diagnosis and are considered

TABLE 28-9 Survival Rates for Melanoma by TNM and Staging Categories (622,623)

Pathologic stage	TNM	Number of patients	1-Yr Survival	2-Yr Survival	5-Yr Survival	10-Yr Survival
IA	T1aN0M0	4,510	99.7 ± 0.1	99.0 ± 0.2	95.3 ± 0.4	87.9 ± 1.0
IB	T1b	1,380	99.8 ± 0.1	98.7± 0.3	90.9 ± 1.0	83.1 ± 1.5
	T2a	3,285	99.5 ± 0.1	97.3 ± 0.3	89.0 ± 0.7	79.2 ± 1.1
IIA	T2b	958	98.2 ± 0.5	92.9 ± 0.9	77.4 ± 1.7	64.4 ± 2.2
	T3a	1,717	98.7 ± 0.3	94.3 ± 0.6	78.7 ± 1.2	63.8 ± 1.7
IIB	T3b	1,523	95.1 ± 0.6	84.8 ± 1.0	63.0 ± 1.5	50.8 ± 1.7
	T4a	563	94.8 ± 1.0	88.6 ± 1.5	67.4 ± 2.4	53.9 ± 3.3
IIC	T4b	978	89.9 ± 1.0	70.7 ± 1.6	45.1 ± 1.9	32.3 ± 2.1
IIIA	N1a	252	95.9 ± 1.3	88.0 ± 2.3	69.5 ± 3.7	63.0 ± 4.4
	N2a	130	93.0 ± 2.4	82.7 ± 3.8	63.3 ± 5.6	56.9 ± 6.8
IIIB	N1a	217	93.3 ± 1.8	75.0 ± 3.2	52.8 ± 4.1	37.8 ± 4.8
	N2a	111	92.0 ± 2.7	81.0 ± 4.1	49.6 ± 5.7	35.9 ± 7.2
	N1b	122	88.5 ± 2.9	78.5 ± 3.7	59.0 ± 4.8	47.7 ± 5.8
	N2b	93	76.8 ± 4.4	65.6 ± 5.0	46.3 ± 5.5	39.2 ± 5.8
IIIC	N1b	98	77.9 ± 4.3	54.2 ± 5.2	29.0 ± 5.1	24.4 ± 5.3
	N2b	109	74.3 ± 4.3	44.1 ± 4.9	24.0 ± 4.4	15.0 ± 3.9
	N3	396	71.0 ± 2.4	49.8 ± 2.7	26.7 ± 2.5	18.4 ± 2.5
IV	M1a	179	59.3 ± 3.7	36.7 ± 3.6	18.8 ± 3.0	15.7 ± 2.9
	M1b	186	57.0 ± 3.7	23.1 ± 3.2	6.7 ± 2.0	2.5 ± 1.5
	M1c	793	40.6 ± 1.8	23.6 ± 1.5	9.5 ± 1.1	6.0 ± 0.9

censored for patients who were alive at the last follow-up or who died without evidence of melanoma (613,622).

Pathology of Microstaging Attributes in Common Use

As discussed, the 2002 AJCC staging system, which is used worldwide, incorporates several attributes of primary and metastatic melanomas, such as Breslow's thickness, Clark's levels of invasion, and the presence or absence of ulceration in the primary tumor. These and other attributes that may contribute to the assessment of prognosis are discussed in the following sections.

Vertical Growth Phase

The morphology of vertical growth phase has already been presented. Here we discuss its significance as a prognostic attribute in relatively thin melanomas with vertical growth and in level II melanomas ostensibly without vertical growth. In one series, metastases occurred in 2% of melanomas less than 0.76 mm thick. The cases that metastasized all had tumorigenic vertical growth phase. The rate of metastasis for tumorigenic melanomas less than 0.76 mm in thickness was 15%, whereas in nontumorigenic (radial growth phase) melanoma of any thickness (most are less than 1 mm), the metastatic rate was zero (345,422). In rare instances of metastasizing thin melanomas, vertical growth phase is absent; most if not all of these cases in our experience and in the literature have had extensive partial or complete regression (see later section) (472,637–640). As already mentioned, two reproducibility studies were done for vertical growth phase in thin melanomas, and they concluded that this determination can be reliably made by practicing pathologists (426,641). A recent study investigated prognostic factors in metastasizing thin, level II melanomas and concluded that vertical growth phase (i.e., the focal presence of tumorigenic or mitogenic growth) was the only statistically significant factor. It was proposed that growth phase evaluation should be added to the recommendations for melanoma histologic reporting, at least for level II superficial spreading melanomas (425). Even though vertical growth phase is the most common explanation for metastasizing thin melanoma (345,425), not all such lesions contain this feature (642).

Clark's Levels of Invasion

Although tumor thickness is now considered to be the most important prognostic attribute, the levels of invasion as defined by Clark (408,643) have prognostic value, at least in certain subsets of cases (644,645) or more broadly, depending on the databases studied (621,646). They also have descriptive value. The different levels appear to reflect the sequential acquisition of new properties by evolving tumors and should be included in pathology reports (646,647). They are defined as follows, with survival rates for prospectively diagnosed and definitively treated clinical stage I cases in parentheses (648):

- Level I (100% 10-year disease-free survival): There is confinement of the melanoma cells to the epidermis and its

appendages. These *in situ* melanomas (AJCC stage 0) presumably lack the capacity to invade through a basement membrane.

- Level II (96% survival): There is extension into the papillary dermis, with at most only a few melanoma cells extending to the interface between papillary and reticular dermis. These melanomas are microinvasive but lack the capacity to form tumors in all but a few cases. Almost all of the level II tumors that metastasize have a small tumorigenic papule (VGP), as previously defined.
- Level III (86% survival): There is extension of the tumor cells throughout the papillary dermis, filling it and impinging on the reticular dermis, without, however, invading it. These melanomas are competent to form tumors in the papillary dermis, a loose mesenchyme that is specialized to support epithelium.
- Level IV (66% survival): Tumors are not only invasive and tumorigenic but also have the capacity to invade the dense, sparsely vascular mesenchyme of the reticular dermis.
- Level V (53% survival): Tumors invade the subcutaneous fat. Observer agreement for Clark level has been found to be fair to good (649).

To avoid confusion, it must be emphasized that the original descriptions of Clark and coworkers were often interpreted to equate level II invasion with radial growth and levels III, IV, and V invasion with vertical growth. Based on the current recognition that the occasional level II lesion may show focal tumorigenic or mitogenic growth (equated with an early form of vertical growth and some potential for metastasis), the Clark schema embodies the acknowledgment that not all level II melanomas are pure radial growth. Moreover, such a system also provides for the extremely unusual situation in which a deeper level (e.g., a thin, level IV lesion) could be devoid of tumorigenic or mitogenic growth and thus have prognostic attributes more in keeping with a nonmetastasizing lesion.

Breslow's Thickness of the Tumor

Tumor thickness is the most important factor in predicting survival for stage I patients. Breslow, in 1970, first measured tumor thickness objectively with a micrometer (650,651). The depth of invasion is measured from the top of the granular layer to the deepest extension of the tumor; in ulcerated lesions, measurement is from the ulcer base overlying the deepest point of invasion. In the initial report, metastasis did not occur in lesions less than 0.76 mm in greatest thickness. Since then, there have been reports of metastases from "thin" melanomas, although this continues to be rare (652,653). Metastasis from "thin" melanomas or from level II melanomas appears usually to be explained by the presence of tumorigenic and/or mitogenic vertical growth phase (425,621). In a computer simulation studying the biology of progressive tumor growth, tumor thickness was related not only to time (the most important factor), but also to tumor cell motility, a decreased rate of tumor cell loss, and pronounced proliferation in the tumor cells, attributes that are also believed to correlate with aggressiveness of tumors (654). In this regard, it may be important to realize that individual melanomas may grow over time at highly variable rates, and it is potentially inaccurate to extrapolate and generalize about *in vivo* melanoma growth based on the behavior and doubling times exhibited by cultured melanoma cells *in vitro* or by clinical metastases at the end stage of the melanoma's evolution.

In determining the depth of penetration, whether by level or by measurement, the following rules were suggested by Lever and Schaumberg-Lever (655): (a) Melanocytes in junctional nests are not considered invasive, even though they may push into the papillary dermis. (b) If deep nests of melanoma cells arise from the epithelium of cutaneous appendages, they are not used in measurement from the surface. (c) A column of melanocytes extending from the lower border of the lesion into the deep dermis at nearly a right angle is not measured because it is likely that the column arises from an appendage; this supposition can usually be verified by serial sections or keratin stains (Fig. 28-33) (656). Observer agreement for Clark level has been found to be excellent (649).

One potential problem with level designation occurs in determining whether the existence of rare malignant cells surrounded by thickened collagen bundles at the interface of the papillary and reticular dermis constitutes true level IV involvement. This is more than a theoretical concern, in that level IV involvement in lesions that are less than 1 mm thick may trigger sentinel node sampling at some centers. There is no definitive answer to this dilemma, and in practice we generally recommend that such lesions be diagnosed with the descriptive statement that early level IV invasion cannot be excluded.

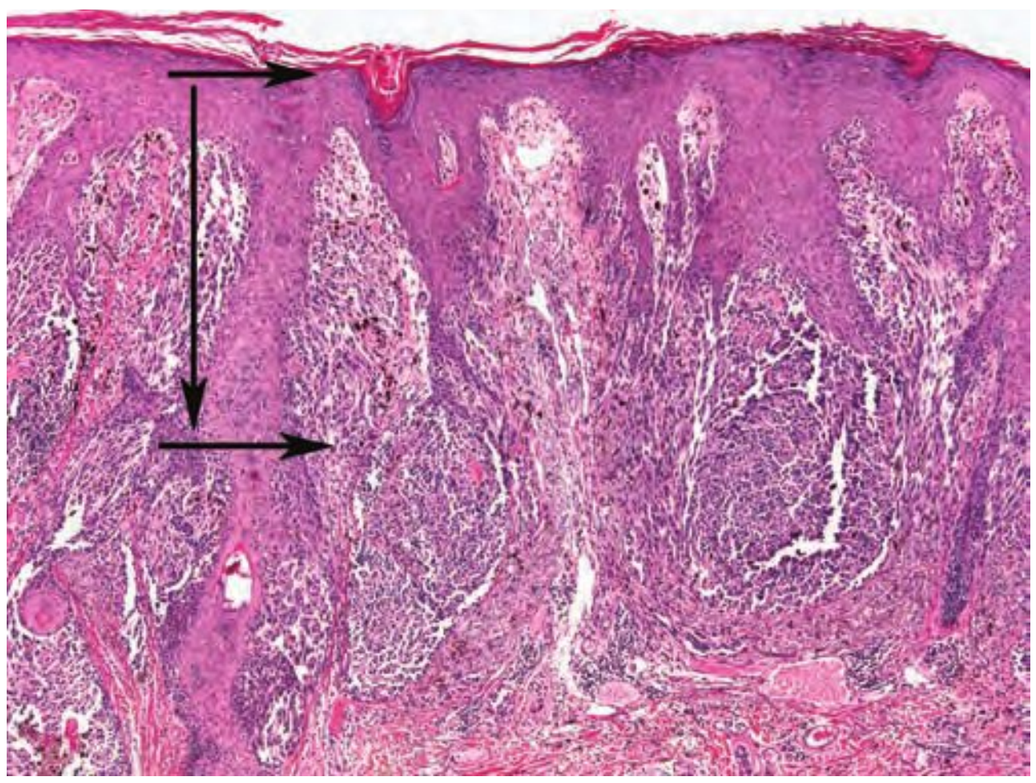


FIGURE 28-33. Extension of melanoma down a hair follicle. In a lentigo maligna melanoma, at right center, a hair follicle is largely replaced by melanoma cells that are confined to the epidermis and adventitial dermis of the follicle. This melanoma is nontumorigenic. Invasive cells at the base of the follicle should not be used for thickness measurement. Arrows indicate where measurement should be taken perpendicular from the top of the granular layer to the deepest invasive tumor cell.

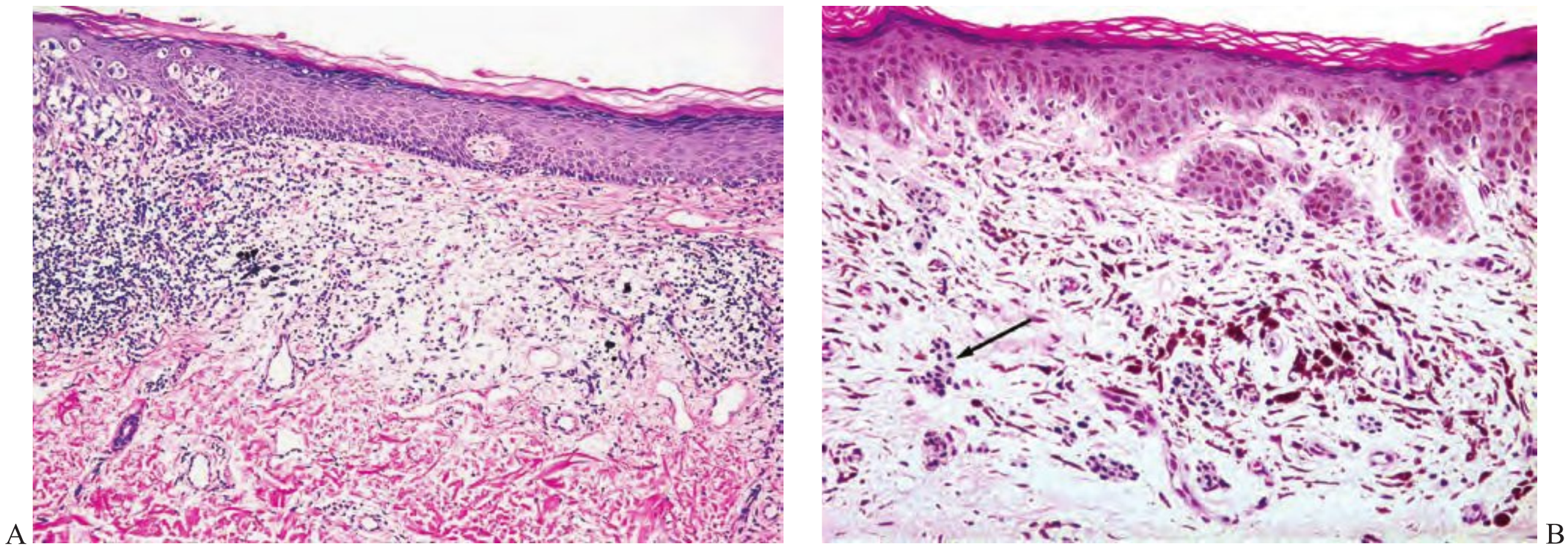


FIGURE 28-34. A: Partial regression of the radial growth phase. At left, there are melanoma cells in the epidermis and papillary dermis. To the right, there is fibrosis with lymphocytes and melanophages in the papillary dermis. B: In another area of partial radial-growth-phase regression, the papillary dermis is widened by fibroblasts with lymphocytes and melanophages. Remnants of a nevus are seen in the regressive fibroplasia (arrow), apparently unaffected by the regression process.

Partial and Complete Regression of Melanoma

Partial regression is common in melanomas. Usually, it is observed in the nontumorigenic compartment ("RGP regression"). Regression is defined as a focal area in which there is delicate, often edematous fibroplasia of the papillary dermis, often accompanied by proliferation of dilated blood vessels, and usually with a sprinkling of melanophages and lymphocytes, with melanoma present in the epidermis and/or papillary dermis to one or both sides but not within the area of regression (Fig. 28-34). Fibrogenic cytokines have been demonstrated in these areas of regression (313). Paradoxically, partial regression of the radial growth phase has been associated in some series with poorer prognosis (472,638–640,657), perhaps because a more significant dermal component had been present and had metastasized before it regressed. Interobserver agreement for regression as a prognostic attribute has been found to be poor in several studies (658,659), perhaps because of failure to agree on criteria.

In contrast to the apparent negative correlation of radial-growth-phase regression with prognosis, tumor-infiltrating lymphocytes within the vertical growth phase, which may be considered as a potentially different form of immunologic regression ("VGP regression") are associated with improved survival rates (Fig. 28-35A) (472,660–662). Regression of the vertical growth phase has not been well described. Occasion-

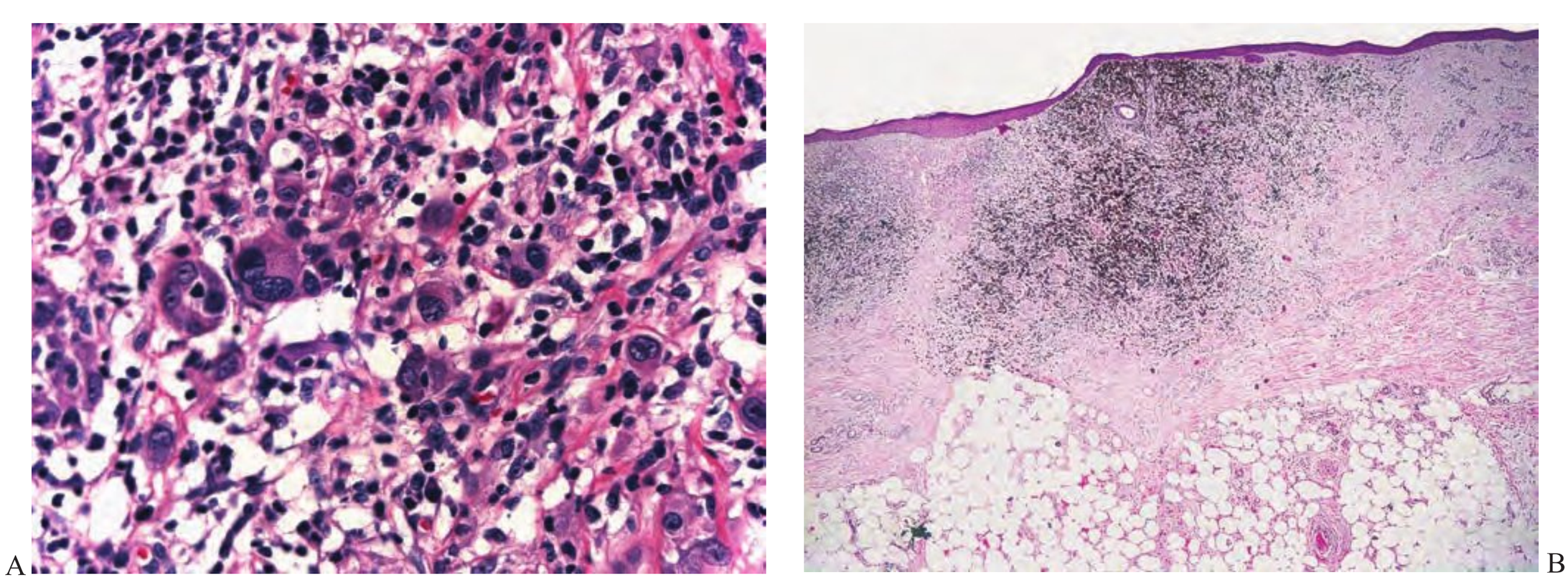


FIGURE 28-35. A: Tumor-infiltrating lymphocytes at the base of the vertical growth phase of a primary melanoma. Lymphocytes that are among the tumor cells, often associated with evidence of apoptosis of the cells, are a favorable prognostic attribute. B: Tumoral melanosis. A localized collection of pigmented melanophages is present in the dermis, consistent with regression of a tumorigenic melanoma or of another pigmented tumor.

ally, one sees an area of fibrosis and melanophages apparently partially replacing a portion of a tumor nodule, and, very infrequently, this process may proceed to completion, resulting in a collection of melanophages in the dermis that could represent the residual evidence of a preexisting tumor nodule. This phenomenon has been aptly referred to as tumoral melanosis (Fig. 28-35B) (663). Not all of these cases are due to regression of a melanoma; pigmented basal cell carcinomas or other pigmented skin tumors may regress and produce similar findings (664).

In occasional cases of metastatic melanoma with no obvious primary tumor, clinical examination may reveal a hypopigmented or irregularly hyperpigmented atrophic patch in the skin of the nodal drainage region (665). Some other cases of apparently regressed primary melanoma may present as clinically pigmented, variegated lesions, clinically suspicious for melanoma. Some of these have presented with concomitant metastases, but some, in our experience, have not been associated with metastasis. Although the diagnosis of melanoma cannot be made with certainty in these latter cases, we have seen at least one case in which metastatic melanoma developed after a period of follow-up. In the case of depigmented lesions histologic examination shows telangiectasia and some pigmented macrophages in the papillary dermis, and in the case of still pigmented lesions an irregular band of melanophages and inflammatory cells in the upper part of the dermis. In some cases, serial sections may reveal a few melanoma cells in the dermis or in the subcutaneous tissue. It is presumed that in patients who present with metastatic melanoma without a clinically overt primary lesion, such completely regressed primary sites may be responsible, although they may evade detection. In such instances, it is important not to implicate other detectable melanocytic lesions (e.g.. dysplastic nevi, melanoma *in situ*) as primary sources of metastasis by default.

Tumor-Infiltrating Lymphocytes

The presence of TILs that are actually among and in contact with the tumor cells of the vertical growth phase has been shown to have powerful independent prognostic significance (Fig. 28-35A) (472,660,666–668). The presence of TILs in lymph node metastases is also associated with better survival (669). The prognosis is best for tumors with a "brisk" TILs response, defined as lymphocytes forming a continuous band beneath the tumor or diffusely throughout its substance. Tumors with "absent" TILs have the worst prognosis, and a "nonbrisk" response (discontinuous band) is associated with an intermediate prognosis. It has been demonstrated that the TIL response is a strong independent predictor of sentinel lymph node involvement in a model that also included thickness, ulceration, and male sex (670). The presence of a noninfiltrative lymphocytic infiltrate around the tumor, usually at its base, is not associated with prognosis (472). The lymphocytic infiltrate tends to diminish with increasing thickness of the primary melanoma and is usually scant in deeply invasive tumors. The histologic determination of the TIL response has been shown to be reproducible (671).

Mitotic Rate

Mitotic rate has been associated with prognosis in multiple studies (599,608,619,672–674,693,695,695a,695b). However, other well-conducted, large studies have not identified this relationship in multivariable models (612,673–678). The differences among these studies may have to do with differences in the determination of mitotic rate or with interactions between mitotic rate and other variables such as ulceration. In some large studies, mitotic was not systematically considered (613,622,679). When it is determined in the tumorigenic compartment of primary melanomas, the mitotic rate has been shown to have powerful independent significance (472). Areas where mitoses are counted should include those where they appear to be the highest (the "hot spot"). The prognosis is best when the mitotic rate is zero and worst when the rate is greater than 6 mitoses per square millimeter (472). The presence of mitoses may also be useful in identifying thin melanomas with a propensity to metastasize (Fig. 28-21B) (673,674,680). Interobserver agreement for tumor mitotic rate has been found to be excellent (649). In a recent series of studies, the property of mitogenicity, or the presence of any dermal mitoses, has been found to be a significant independent prognostic factor in patients with thin AJCC stage I melanomas (617,621,681). Mitogenicity is of course one of the attributes that define the presence of vertical growth phase (682). Especially in these thin tumors, where the volume of the dermal component is small and accurate quantitation is difficult, this attribute is likely to be more reliably recorded by pathologists.

Ulceration

Ulceration is defined by the loss of continuity of the epithelium over the surface of the tumor (Fig. 28-36). Evidence of a host reaction to the ulceration is also required to exclude epithelial loss due

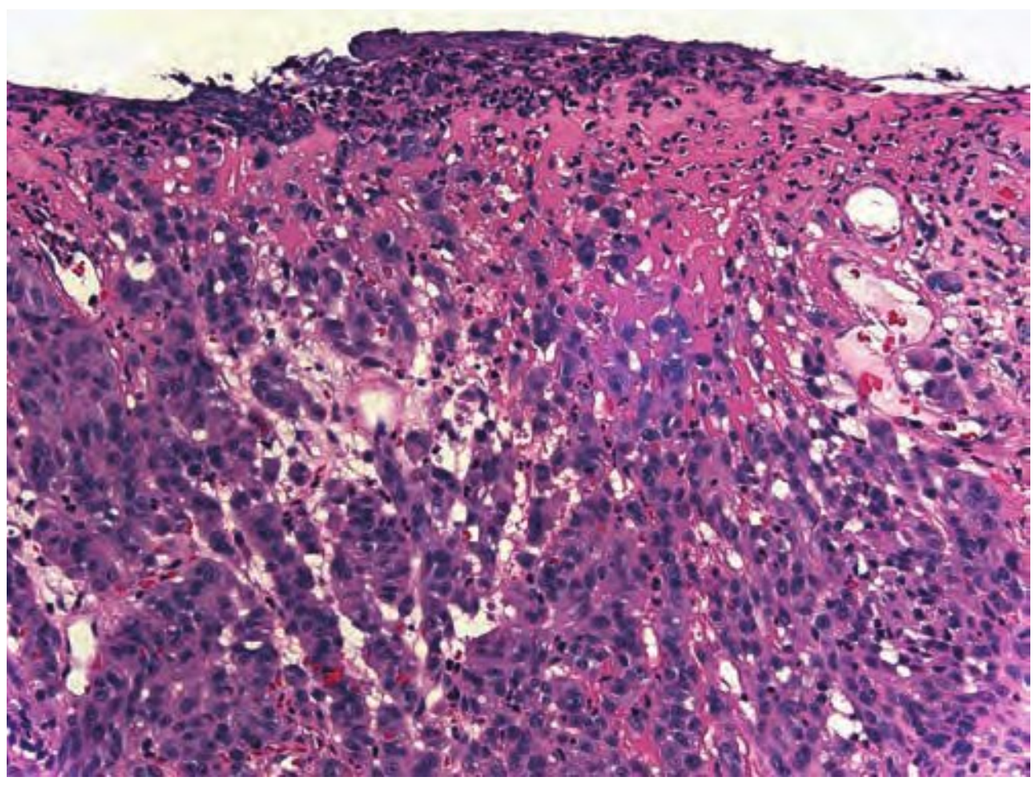


FIGURE 28-36. Ulcerated melanoma. An ulcer is defined as an area of loss of continuity of epithelium over the surface of the lesion, with evidence of a host reaction. The example here shows a neutrophilic and fibrinous exudate on the surface of the ulcer.

to biopsy trauma (683). Even with a host response, it may be difficult or impossible to determine whether ulceration is secondary to the tumor or a result of excoriation or environmental trauma. Nonetheless, this attribute has prognostic significance in most multivariable analyses (607,612,613,667,678,684–692). Other studies, particularly those in which mitotic rate is an independent variable, have not identified ulceration as an independently significant prognostic attribute (472,608,693–695). In the AJCC staging data, ulceration in stage I reduces the 5-year survival rate from 88% to 83% (613). A potentially useful prognostic algorithm has been published in which ulceration is the primary stratifying variable (472,609). Ulceration is a key substratifying variable in the latest AJCC staging system for melanoma (see tables presented earlier) (613). Interobserver agreement for ulceration has been found to be excellent (649,683).

Vascular or Lymphatic Invasion

Although often correlated with survival as a single variable (472), the presence of vascular or lymphatic invasion has infrequently been found to correlate with survival in large series of cases studied by multivariable analysis (696,697). In a recent publication, two types of vascular invasion were studied: vascular invasion with tumor cells within blood or lymphatic vessels (Fig. 28-37) and uncertain vascular invasion, with melanoma cells present within the wall of the vessel, immediately adjacent to the endothelium. The presence of either type of vascular involvement significantly reduced the survival associated with melanoma. Angiotropism, defined as cuffing of the external surface of vessels with tumor cells, also known as extravascular migratory metastasis, has also been associated with aggressive behavior (698). In a multivariate analysis, vascular involvement was the second-most-important factor (after tumor thickness) in the primary tumor in predicting survival (699). Vascular invasion also appears to be a strong predictor of the likelihood of a positive sentinel lymph node (700) and of development of in-transit metastases in follow-up (701). Lymphovascular invasion may also be seen in metastases, and its presence should lead to a consideration of a metastasis simulating a primary, such as an epidermotropic metastatic melanoma (702).

New markers are available that distinguish between vascular and lymphatic channels in paraffin sections and increase the sensitivity of detection of lymphovascular invasion. Use of the marker of lymphatic vessels D2-40 demonstrates an increased number of lymphatic vessels in melanomas compared to nevi and may be used to increase the frequency and specificity of detection of lymphatic invasion in melanomas (703). Tumor vascularity has also been correlated with survival in some studies (704,705). However, in another matched-pair analysis, tumor vascularity was found not to correlate with survival rates (706).

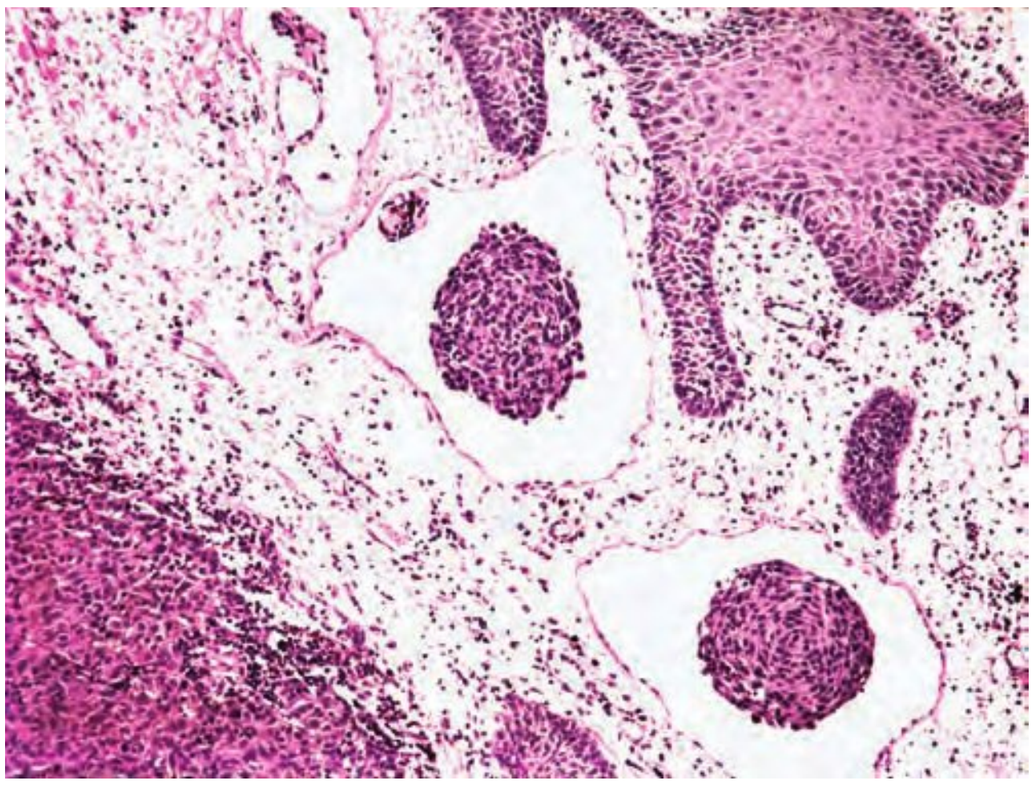


FIGURE 28-37. Lymphatic invasion. Although not often recognized except in very thick tumors, lymphatic invasion is probably an adverse prognostic attribute.

Satellites

Satellites are defined as discontinuous foci of tumor (metastases) located within 5 cm of a primary melanoma, whereas in-transit metastases are beyond 5 cm but still regional. The presence of satellites is a significant staging attribute in the current AJCC staging system, defining a lesion as stage IV, with a poor prognosis (613,622,679,697). Microscopic satellites are independently associated with worse prognosis (707,708). These are defined as tumor nests, greater than 0.05 mm in diameter, in the reticular dermis, panniculus, or vessels beneath the principal invasive tumor mass but separated from it by normal tissue on the section in which the Breslow measurement was taken (Fig. 28-38). In a recent study, the presence of microscopic satellites was associated with a greater likelihood of sentinel node positivity (709).

Other Clinicopathologic Prognostic Factors

Various factors in addition to thickness of the tumor have been cited as influencing the prognosis of clinical stage I melanoma, but many of them are directly related to thickness. In different clinicopathologic databases, multivariate analyses have led to prognostic models that differ somewhat in the predictive variables that are shown to have independent significance. Several features, however, have appeared in two or more of the studies.

Histogenetic Type. Among the histologic factors, the type of tumor, whether nodular or superficial spreading, does not, in most studies, independently affect the prognosis (447,472,710), despite a suggestion in some studies that the prognosis for lentigo maligna melanoma may be slightly better (711). Nodular melanomas, on average, are thicker than superficial spreading melanomas and thus have a worse prognosis overall (712,713). However, the prognosis is the same for nodular and other types of melanoma of similar thickness, and in multivariable analyses, nodular type is not an independent predictor (472,608,667, 711). The scarcity or absence of melanin in the tumor cells (amelanotic melanoma), indicative of poor differentiation, affects the prognosis adversely in some series but does so most likely because of correlations with tumor thickness and other variables (Fig. 33-28) (472). As already discussed, differences among these histogenetic types appear to reside more in the areas of etiology and pathogenesis than in prognosis or behavior. However, emerging data are demonstrating that the underlying oncogenic genotype of the different clinicopathologic entities may vary in a more or

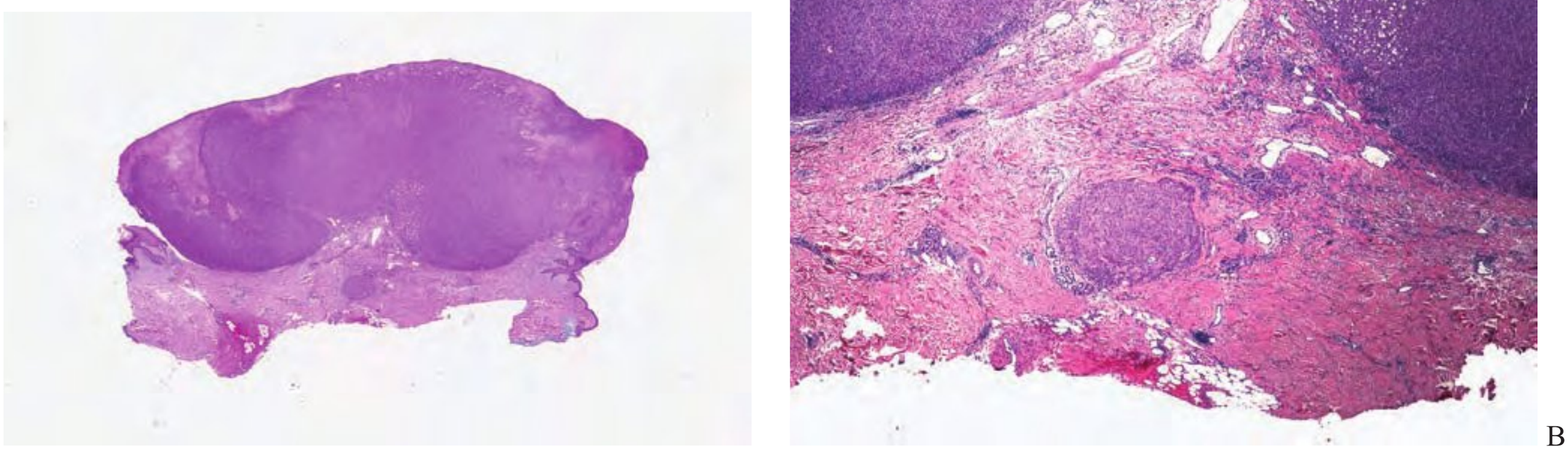


FIGURE 28-38. A: Microscopic satellite present at the base of a bulky tumorigenic vertical-growth-phase melanoma. B: The satellite is located in the superficial reticular dermis.

less predictable manner, so that assessment of characteristics of tumors that predict genotype profiles may be relevant to pathology in the future as therapies directed against these oncogenes are developed (419,449,459).

Lesional Location. Among the favorable clinical factors is location of the tumor on the hair-bearing portions of the limbs, in contrast to location on the trunk, neck, and head or palms and soles (612,667,687,714–717). In one of these studies, lower trunk, thigh, lower leg, foot, lower arms, hands, and face were identified as intermediate sites, with the remaining sites representing higher risk (714). In other studies, however, the palms and soles and the distal lower extremity were included in the higher-risk sites (472,717).

Gender. There is general agreement that women have a better prognosis than men, owing partly, but not entirely, to the higher incidence in women of lesions on the extremities, where the prognosis is favorable compared to the trunk (472,612, 667,716,718–720). The age of the patient has an adverse prognostic effect in some series (612,614,667,716,718,721).

Biological Markers

Biological markers derived from the study of the primary tumors or of host attributes may be expected to add to the precision of present prognostic models. The most consistently useful marker studied appears to be the proliferation marker Mib-1 (Ki-67), which has been found to be significantly related to mortality risk in a number of studies (680, 722–728). Other markers, in general, have not been studied in sufficiently large series of cases or have not been reproduced in other data sets, and no marker is in general use for this purpose.

Local Excision

Formerly, the margin of resection of the primary tumor was regarded by most authors as optimal at about 5 cm beyond the perimeter of the lesion (729). However, a much narrower margin is now acceptable. Margin width recommendations were reviewed by an NIH consensus conference in 1992 (730). A margin of 0.5 to 1.0 cm was recommended for excision of a melanoma *in situ*, with a margin of 1 cm for melanomas less than 1.0 mm thick and a 2- to 3-cm skin margin for thicker lesions (731–733). A worldwide cooperative study showed that in patients with primary melanomas no thicker than 2 mm, excisions with margins of 1 cm gave results as good as excisions with margins of 3 cm (734). A critical review of the literature revealed no evidence of an adverse effect on outcome in terms of survival from melanoma with narrowing of margins to 1 cm. A slightly increased rate of local recurrence was observed in some studies, especially with thicker primary tumors. This analysis therefore did not support the use of resection margins greater than 1 cm for invasive melanoma of any thickness (735). Others have considered similar or lesser margins (736,737). This hypothesis may be worthy of testing in a future randomized trial (738). Detailed therapeutic guidelines for melanoma are available online from the National Comprehensive Cancer Network (http://www.nccn.org).

In examining a resected specimen for melanoma, we generally serially embed the area of the biopsy scar and sample the specimen margin with perpendicular sections. The specimen is first inked to identify the true margin surface. After taking the initial margin section, the specimen is bread-loafed macroscopically, and any remaining lesions suspicious for possible satellites are also submitted for histologic examination. The margin widths discussed earlier are clinical margins, measured from the clinically visible periphery of the melanoma. Therefore, careful histologic examination of the excised tumor and its margins is mandatory because margins may be involved in spite of a clinically normal appearance. It is not necessary, however, to measure the margin width histologically in the resection specimen, as long as the width is adequate. In our practice, we generally alert the clinician when the margin width is less than 0.1 cm (less than 1 mm) in a resection specimen. The dermis and

subcutis should also be evaluated carefully (grossly and microscopically for the presence of satellites, which may have prognostic significance, and which may occasionally be present at the margin). Satellites are rare in relation to thin tumors, but in one study, they were detected in 22% of the reexcision specimens from melanomas greater than 2.25 mm in thickness (739). The presence of neurotropism should also be carefully sought and reported in melanoma resection specimens, especially of course if this neural invasion extends to the specimen margin.

Therapeutic and Elective Lymph Node Dissection

A clinically positive lymph node in a patient with primary cutaneous melanoma should be biopsied, and if the node is histologically positive, a full regional node dissection should be done as a therapeutic procedure (therapeutic regional lymph node dissection) with curative intent and to gain local control (740). For clinically negative lymph nodes, the role of elective regional lymph node dissection is controversial. Theoretically, regional nodes could be regarded as necessary filters that must be bypassed by all melanomas that metastasize systematically. However, it is clear that many melanomas metastasize by the hematogenous route to distant organs without ever involving regional nodes. Thus, lymph node involvement in many cases may be simply a marker of a melanoma that has already metastasized.

The incidence of regional lymph node involvement increases with the thickness of the tumor. Involvement of the regional lymph nodes is extremely rare in melanomas with a thickness of less than 0.76 mm. It is therefore generally agreed that elective regional lymph node dissection is not indicated for these melanomas (most of which are nontumorigenic) (741–743). For tumors 0.76 mm thick or thicker, the data are conflicting (742–747), and recent therapeutic trials have not completely resolved the issues (690,748,749). The next generation of trials of selective lymphadenectomy will likely be more conclusive (see next section).

Melanoma patients with palpable lymph nodes are at a high risk of having distant metastases. The number of involved lymph nodes and the depth of the tumor are important prognostic factors. Patients who have metastases in less than 20% of their resected regional lymph nodes and a tumor thickness of less than 3.5 mm have a 5-year disease-free survival rate of 80%, compared with 18% for patients who have a tumor thickness greater than 3.5 mm or metastases in 20% or more of their resected lymph nodes (630). Of interest, the size of involved nodes is not related to survival (750). The presence of brisk TILs in a lymph node metastasis is a favorable prognostic attribute and was associated in one study with a survival rate of 83%, compared to 29% in patients whose metastases lacked TILs. Multivariate analysis confirmed the prognostic value of TILs in predicting disease-free survival in patients with regional node metastases (669).

Selective Lymphadenectomy (Sentinel Lymph Node Dissection)

Selective lymphadenectomy was developed by Morton as a means of sampling regional lymph nodes while avoiding most of the complications of an elective dissection (751). The sentinel lymph node is identified by injections into the region of the melanoma of radioactive colloid and a vegetable dye ("blue dye"). The sentinel node is defined as the first in the regional lymph node basis to contain these markers ("hot and blue"). Studies have demonstrated that if the sentinel node is negative, the probability of metastases being found in the remainder of the lymph node basin is very low. In early studies, the sentinel node was evaluated by frozen sections with rapid S100 staining (752). Currently, the standard procedure is to examine the node with paraffin hematoxylin-eosin sections, with S100 as a sensitive marker, and with HMB-45 or, more recently, Melan-A, as a more specific though less sensitive marker (753). Use of a cocktail of antibodies to MART-1, Melan-A, and tyrosinase has also been proposed (754). In evaluating the S100 stain, reactive dendritic cells, which are present in most sentinel nodes, must be distinguished from metastatic melanoma deposits. Capsular nevic rests must also be distinguished; these are located in capsular or sinusoidal collagen rather than in sinuses, lack significant cytologic atypia, and stain with S100 and sometimes with HMB-45 or Melan-A, although usually less intensely than is seen in authentic melanoma deposits.

True melanoma micrometastases are often present as immunoreactive cells in the subcapsular sinuses and/or the lymph node parenchyma, generally with correlative detection of cytologically malignant cells in corresponding hematoxylin-eosin–stained sections. Such deposits may be measured to provide some indication of tumor bulk, and if extension through the nodal capsule has occurred, this feature should be noted. In situations in which immunohistochemically suspicious cells are present but diligent attempts to confirm them as malignant cells in hematoxylin-eosin sections fails, the findings should be reported descriptively, indicating that the features are suspicious but not conclusive. Often, isolated MART-1– or HMB-45–positive cells may be identified, usually as only one or two cells in the lymphoid parenchyma, and it may be unclear whether these represent true micrometastases. In one recent report, although such cells were regarded as potential authentic single-cell micrometastases, patients with such changes did not exhibit differences in survival from those with negative sentinel nodes over a mean follow-up of 38.1 months (755). Moreover, not all MART-1/Melan A–positive cells in lymph node parenchyma necessarily represent metastatic melanoma, as emphasized in a recent study in which such cells were detected in lymph nodes of some nonmelanoma patients undergoing lymphadenectomy for breast cancer (756).

The clinical rationale for selective lymphadenectomy was recently reviewed by the National Comprehensive Cancer Network (757), citing data from the third interim analysis of the results from a large multicenter trial (758). In patients with primary melanoma 1.2 to 3.5 mm in thickness, there was no significant difference in melanoma-specific survival rates between the two groups (the 5-year disease-free survival was 78% for the biopsy group and 73% for the observation group). However, considering only patients with nodal metastases, those who had

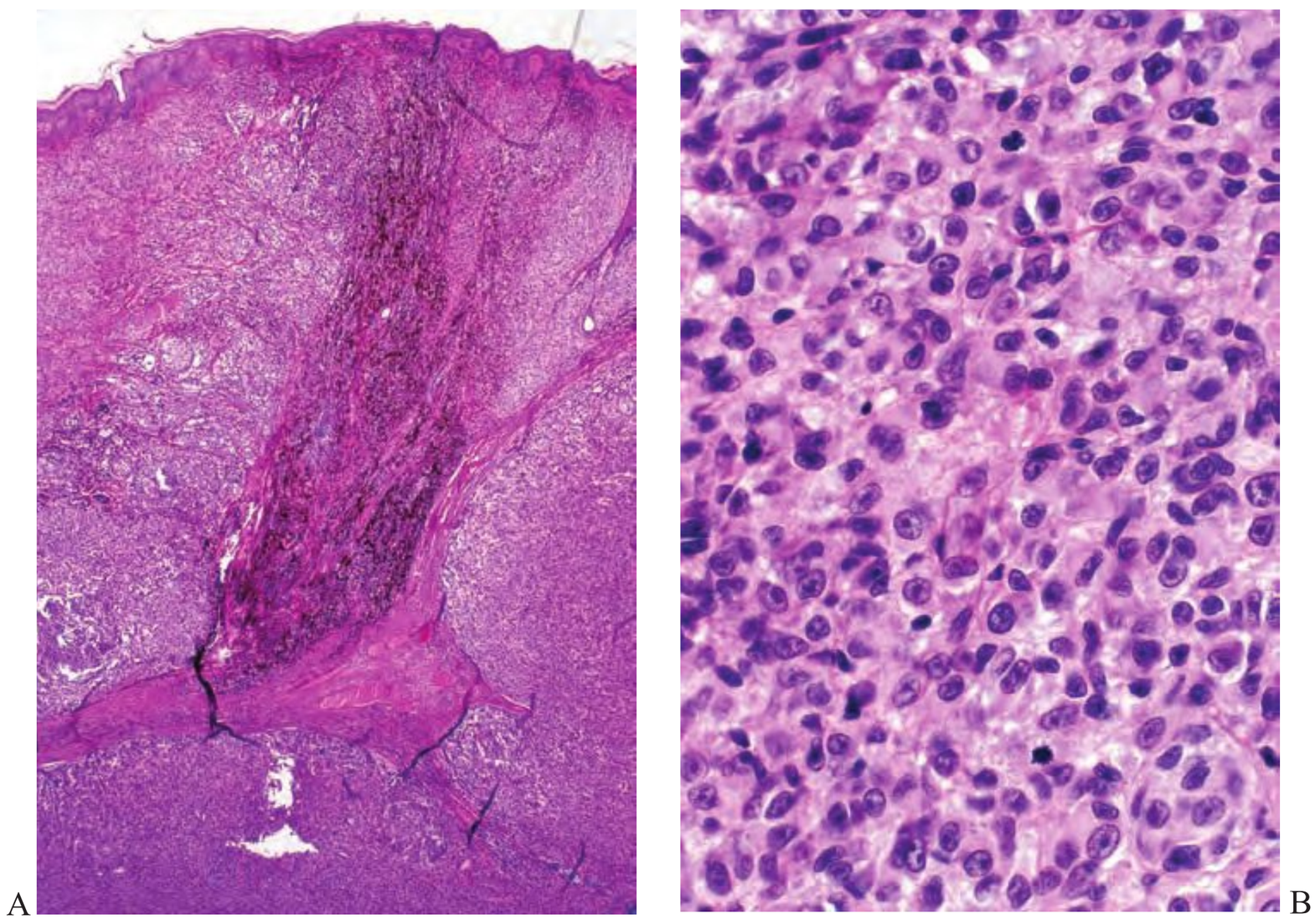
immediate lymph node dissection after a positive sentinel lymph node biopsy (SLNB) had a higher survival rate than patients who had delayed lymphadenectomy for clinical disease (72% vs. 52%). This difference has been attributed to a lower nodal tumor burden in the sentinel node–positive patients than the clinically node-positive patients. It is concluded that "these results confirm that SLNB is of prognostic value and that the procedure can identify patients with low volume nodal metastases whose survival is superior to that of patients whose nodal metastases are detected on clinical examination" (757).

The Association of Directors of Anatomic and Surgical Pathology (ADASP) has published guidelines for the processing of lymph nodes, including sentinel nodes submitted for evaluation of metastatic disease. It is recommended that small nodes be submitted in their entirety or that larger nodes be sectioned at 3- to 4-mm intervals and entirely submitted. Intraoperative examination should be limited to those cases in which the procedure is likely to influence management (e.g., to confirm clinically and grossly positive nodes so that a complete node clearance can proceed). ADASP recommends that more than one section be performed on each sentinel node block. It is considered not clear how many sections and levels are optimal (759). Although the ADASP committee does not provide recommendations for immunostains, or even endorse this procedure unequivocally, in most centers it is the practice to perform S100 (more sensitive, less specific) and either HMB-45 or Melan-A (more specific, less sensitive) staining on one profile from each submitted sentinel node (760).

Malignant Blue Nevus

There exist potentially malignant melanocytic neoplasms that are unusual and do not necessarily qualify for application of the prognostic attributes of conventional vertical-growth-stage melanoma. These include the malignant blue nevus and a conceptual family of neoplasms of uncertain biological/malignant potential discussed in the next section. Malignant blue nevus is a rare tumor. It may arise in a blue or cellular blue nevus (761–764), a giant congenital nevus (289), or in a nevus of Ota (13), or it may be malignant from the start (765) . Malignant blue nevi may involve the dermis and may be ulcerated or may present as a deep-seated expansile mass (765). In some lesions classified as malignant blue nevus, metastases occur that are limited to the regional lymph nodes, and the patient survives after removal of the tumor and the involved lymph nodes (762). There may be overlap in these cases with the phenomenon of cellular blue nevi with regional metastases. In other cases, however, death occurs as the result of widespread metastases (44,761,765,766). Unfortunately, reliable distinction between these two groups of cases is not possible.

Histopathology. Recognition of the lesion as a malignant blue nevus rather than a common melanoma is based on the absence of junctional activity and the presence of at least some bipolar tumor cells with branching dendritic processes typically containing melanin granules, representing a background component of blue nevus or cellular blue nevus (Fig. 28-39A–D) (44,761,765). In some cases, pigment may be scant.



A B

FIGURE 28-39. A: Malignant blue nevus. A bulky melanocytic tumor with variegated patterns of architecture and pigmentation is present in the dermis without an associated in situ component in the epidermis. B: An area of solid growth showing severe uniform atypia and frequent mitoses. (continued)

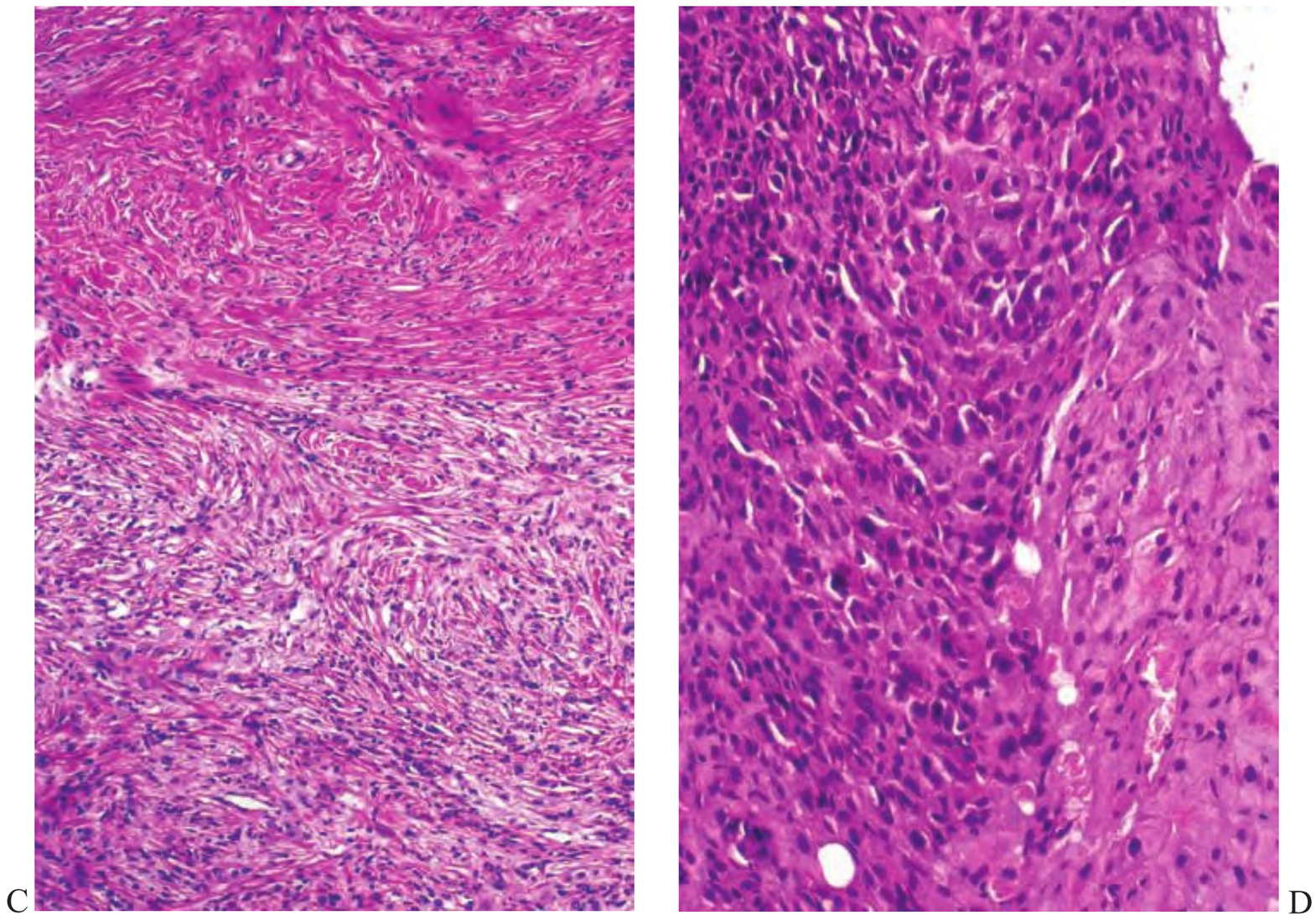


FIGURE 28-39. Continued. C: An area of blue nevus-like pattern at the top, with a more cellular blue nevus–like pattern at the bottom. D: Liver metastasis from a malignant blue nevus. Neoplastic melanocytes (left) in liver tissue (right) from a needle biopsy.

In addition to showing the standard features of malignancy, such as invasiveness of the tumor, atypia with hyperchromatism, pleomorphism and irregularity of the nuclei, and presence of atypical mitoses, malignant blue nevi often show areas of necrosis as evidence of their malignant nature (762,765). The combination of uniform cytologic atypia, high-grade atypia, spontaneous tumor necrosis, and more than a few mitoses may be considered diagnostic of malignant blue nevus in a lesion with a characteristic associated blue nevus pattern. Such cases are easily recognized as fully malignant neoplasms. Some lesions that do not meet all of these criteria; for example, some lesions that have lacked necrosis have metastasized (763). Atypical tumors with the overall appearance of cellular blue nevus that show only some of these features, especially if these are present in minor degree, may be signed out descriptively as melanocytic tumor of uncertain potential (see later section).

Histogenesis. Although some authors have regarded the tumor cells as related to Schwann cells (762), electron microscopic studies have shown the presence of melanosomes in the cells and a lack of cytoplasmic enclosures of unmyelinated axons, which would be seen if the tumor cells were Schwann cells. Although the melanosomes in many cells are devoid of melanin (765), incubation with DOPA has shown that they are strongly DOPA positive (44). Thus, it is evident that the tumor cells are melanocytes. Genetic data regarding the pathogenesis of malignant blue nevi are not available.

Differential Diagnosis. Malignant blue nevus differs from conventional primary melanoma by the absence of junctional activity and the presence of associated common and/or cellular blue nevus. However, distinction of a malignant blue nevus from a metastatic melanoma can be difficult because metastatic melanoma is occasionally found without a demonstrable primary melanoma. The primary melanoma may have involuted or may be located at an obscure internal site. The presence of dendritic cells indicative of an associated blue nevus or cellular blue nevus component is then the most reliable criterion favoring a diagnosis of malignant blue nevus instead of a metastatic melanoma. In doubtful cases, the differential diagnosis of metastatic melanoma should be expressed, and a workup for another primary should be considered clinically.

Melanocytic Tumors of Uncertain Malignant Potential (MELTUMP)

This is a descriptive term for a heterogeneous group of melanocytic tumors that exhibit some features indicative of possible malignancy, such as nuclear atypia, macronucleoli, mitotic activity, necrosis, or ulceration, but in number or

degree insufficient to justify a malignant diagnosis (231,767). Accordingly, they reflect the biological reality that occasional melanocytic lesions that do not meet criteria for fully evolved melanoma cannot be predicted to be benign with 100% accuracy.

Histopathology. Tumors appropriately placed in this descriptive category may be quite bulky neoplasms, of the order of several millimeters in diameter and thickness, composed of pigmented, often spindle-shaped cells. The overall cellularity may be relatively low compared to that of fully malignant melanomas. There may be occasional mitoses, but not more than one or a few per section plane. Abnormal mitoses, if present, are usually indicative of frank malignancy. Focal areas of individual-cell necrosis may be present, but if there are areas of confluent geographic necrosis or if an ulcer is present, a frankly malignant diagnosis is appropriate. There may be a few enlarged melanocytes in the epidermis but, if there is an intraepidermal component that can be identified as a radial growth phase of melanoma of any of the common types, a diagnosis of melanoma should be made.

Other examples include melanocytic tumors that superficially resemble ordinary nevus variants but that also include some (but not all) features associated with a malignant diagnosis. For example, a compound or dermal nevus with significant atypia within the dermal component, a Spitz nevus–like proliferation with some degree of asymmetry and deep mitotic activity, or a deep penetrating nevus with unusual features could all be placed in this category. In general, uncertain malignant potential implies an intradermal architecture with some features of tumorigenic growth (and, hence, some overlap with vertical-growth-phase melanoma), as opposed to a SAMPUS that is devoid of a dermal tumorigenic component, thus having no metastatic potential (albeit with some potential to progress or recur on incomplete excision).

Differential Diagnosis. This descriptive diagnosis is one of exclusion, and the differential diagnosis includes specific neoplasms described elsewhere in this chapter, including atypical and Spitz nevi/tumors, so-called minimal deviation melanomas, some deep penetrating nevi, cellular neurothekeoma (discussed in the chapter on neural tumors), atypical cellular blue nevi, and certain nevoid melanoma variants.

Some lesions that may be placed in this descriptive category (that also have been discussed previously) are composed of tumoral intradermal proliferations of dendritic to epithelioid cells stuffed with abundant and coarsely divided pigment that may obscure the nucleus (554). Sometimes these cells are difficult to distinguish from melanophages. They are also reminiscent of dermal melanophores seen in some vertebrates, which in animals may occasionally give rise to malignant tumor resembling malignant blue nevi. Some of these lesions may have prominent epidermal involvement, with pagetoid spread of the heavily pigmented lesional cells into the epidermis and a dermal component that is broader in the papillary than in the reticular dermis. These lesions, despite their unusual cytology, have architectural features that are relatively characteristic of melanoma. There is overlap between these lesions and the lesions termed pigmented epithelioid melanocytomas, which in turn overlap with epithelioid blue nevi (557) on one hand and with pigment-synthesizing melanomas on the other hand (556). Some related lesions for which criteria for malignancy are not deemed to have been fully met may also be placed in the descriptive category of uncertain malignant potential (231). Still other very rare lesions present as nodular clusters of authentic melanophages (tumoral melanosis) (663). These lesions may be examples of complete regression of a pigmented vertical-growth-phase nodule, a very rare phenomenon that is quite differential from the partial regression frequently observed in the radial-growth-phase compartment of common melanomas.

Management. The existence of these difficult or uncertain cases, in which diagnostic agreement is not likely to be achieved even among experienced observers, suggests a need for a practical means of dealing with these cases in the best interests of the patients. In this regard, two principles apply. First, lesions should be managed by means sufficient to provide adequate therapy for the most clinically significant entity in the differential diagnosis of an uncertain neoplasm, and second, patients and their physicians are entitled to know that their lesion cannot be diagnosed specifically with presently available means. A pathology report in such a case should not provide a false assurance of confidence in any given diagnosis. In these cases, we typically recommend management with the differential diagnosis of melanoma taken into consideration and provide microstaging attributes sufficient at least for AJCC staging of the lesion as melanoma (768). The dimensions of a reexcision procedure could follow guidelines for the AJCC stage of the "melanoma," or at a minimum should be discussed with the patient and include a margin of normal tissue around the scar and any residual lesion.

In addition, a sentinel lymph node sampling procedure may be discussed with the patient. Sentinel lymph node sampling has been offered to patients with atypical or uncertain melanocytic tumors in a number of centers (224,227,769,770). Some of these cases have been found to be associated with lymph node metastases. In such circumstances, there may be a temptation to revise the diagnosis to "malignant melanoma." However, as previously discussed, there have been reports of lesions with characteristics of Spitz nevi that have metastasized to regional lymph nodes, sometimes followed by prolonged, perhaps indefinite survival (223,771,772). Similar situations have been reported in relation to cellular blue nevi (31,773). Therefore, in a situation in which a melanocytic tumor of uncertain malignant potential is found to be associated with regional lymph node metastases, we report the metastasis as "metastatic melanocytic tumor of uncertain malignant potential," where the word "malignant" refers to clinical course as a consequence of persistence and inexorable progression of disease rather than simply the ability of a neoplasm to travel to a draining lymph node. We indicate that the biological potential

of this metastatic tumor remains uncertain. However, the prognosis is clearly more guarded in the presence of such metastases, and, in such circumstances, the possibility of adjuvant therapy including interferon may be taken into consideration (227).

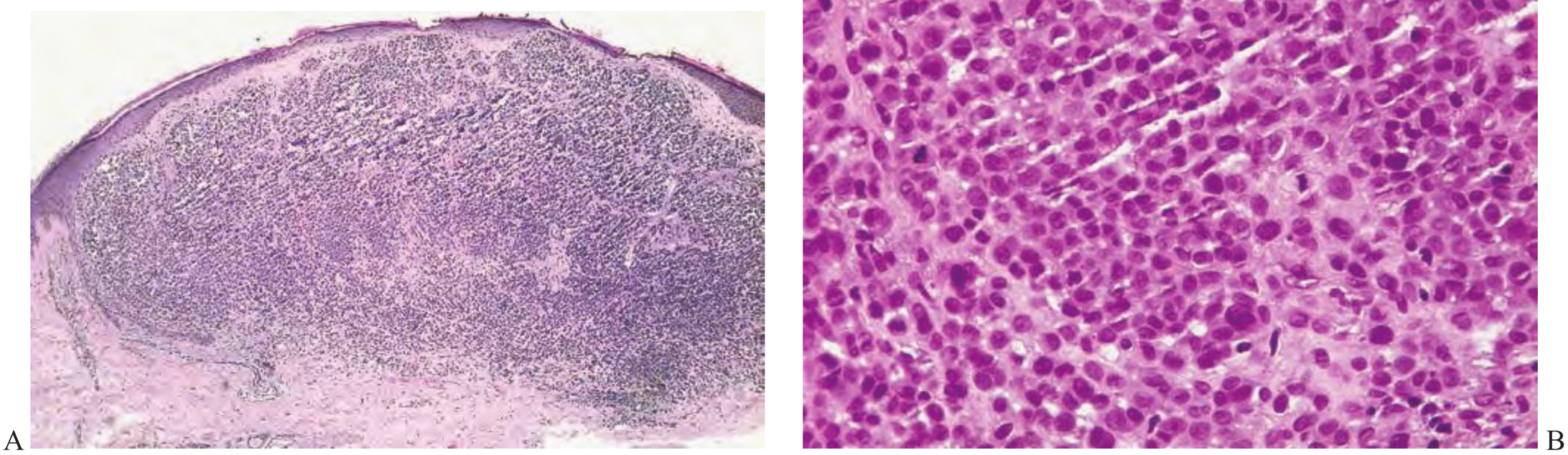
Metastatic Melanoma

Metastatic spread, uncommon in relation to thin melanomas, is quite common in tumors thicker than 2 mm. Regional skin and lymph node metastases usually present earlier than hematogenous metastases. Although metastases tend to occur within 5 years after onset of the disease, their appearance may be delayed, especially in thin melanomas (774). Late metastases, beyond 10 years, do occur, but they are relatively rare (775,776).

Clinically evident cutaneous metastases are arbitrarily called satellites if they are within 5 cm of the primary tumor and in-transit metastases if they are beyond this limit but still regional. The presence of these metastases is compatible with long-term survival but is usually associated with eventual relapse in distant sites (777). The prognosis for patients with distant metastatic disease is very poor. In one study, the median survival overall was 7.5 months; patients with cutaneous, nodal, or gastrointestinal metastases had a median survival of 12.5 months and an estimated 5-year survival rate of 14% (778). In a recent study of patients who had undergone metastasectomy for pulmonary metastatic melanoma, there was an estimated survival advantage of 10 to 12 months (764,779). Resection of a solitary metastasis (e.g., to lung, brain, liver, or gastrointestinal tract) may occasionally be associated with a remarkably good outcome, but such instances are exceedingly rare (780,781).

In about 4% to 10% of the patients who present initially with metastases of melanoma, no primary tumor can be found. The sex ratio, age incidence, family history, survival rates, and patterns of recurrence and further metastases in these patients with unknown primary melanomas are consistent with an unnoticed cutaneous lesion as the site of origin for the metastatic disease (782). Although a primary tumor may in some instances be in an internal organ or perhaps secondary to malignant transformation of extracutaneous nevus cell rests (as in lymph node capsules), it seems likely that in most instances it was located in the skin and regressed spontaneously. In a study of 40 patients with unknown primary melanoma, patients with lymph node metastasis survived significantly longer than patients diagnosed with lymph node metastasis concurrent with a known cutaneous primary melanoma. The prevalence of dysplastic nevi was intermediate between that reported among primary melanoma patients and that reported among population controls, suggesting the likelihood of a primary cutaneous origin for the metastatic melanoma (783). In some instances, there is a history of a spontaneously resolving pigmented lesion, and one may see at that site either a hypopigmented area or an irregular, flat, pigmented lesion, consistent with complete regression of a putative primary melanoma at that site (784).

Histopathology. The histologic appearance of melanoma metastases in the skin resembles the tumorigenic vertical growth phase of a primary melanoma but usually differs from that of a primary melanoma by the absence of an inflammatory infiltrate and of junctional activity (Fig. 28-40). However, primary melanomas may occasionally fail to involve the epidermis and may also not show an inflammatory infiltrate,



A B

FIGURE 28-40. A: Dermal metastatic melanoma. Metastatic melanoma often presents as a fairly symmetric cellular nodule in the reticular dermis or subcutis. The lesions are often quite small at the time they are excised and presented for an initial diagnosis of metastatic spread. B: Cytologically, the cells are uniformly atypical, as in tumorigenic primary melanomas (compare Figs. 28-23B, 28-26B, 28-31A, 28-36, and 28-39B with each other). Sometimes, especially in superficial or epidermotropic cutaneous metastases, atypia is deceptively minimal. The identification of mitotic activity and of lymphatic invasion may be very helpful in making the diagnosis.

particularly when they are deeply invasive. Furthermore, in occasional instances, even metastases exhibit a prominent lymphocytic infiltrate (669) and can contact the overlying epidermis in a way that is suggestive of junctional activity, with nests of atypical melanocytes in the epidermis. Some metastatic melanomas may have a nevoid phenotype, and clinicopathologic correlation (e.g., follow-up) may be required to differentiate them from a primary nevoid melanoma or even from a nevus (785). In the latter situation, careful examination of specimen levels will generally reveal mitotic activity and apoptotic cells in true nevoid metastases.

Microscopic satellites have been defined as deposits of tumor more than 0.05 mm in diameter and separated from the primary mass by normal tissue, such as reticular dermis collagen (707). These should be identified and reported because they are elements of the AJCC staging system (622). In a study of the use of immunohistochemistry to increase sensitivity of detection, small satellite micrometastases were detected in 12.4% of 265 melanoma cases. The presence of these micrometastases has been correlated with sentinel node positivity (709,786).

Epidermotropic metastatic melanoma refers to a metastatic deposit that is initially localized to the papillary dermis and involves the overlying epidermis. Most of these lesions occur in an extremity regional to a distal primary melanoma. Epidermotropic metastasis is characterized by (a) thinning of the epidermis by aggregates of atypical melanocytes within the dermis, (b) inward turning of the rete ridges at the periphery of the lesion, and (c) usually no lateral extension of atypical melanocytes within the epidermis beyond the concentration of the metastasis in the dermis (787). However, this distinction can be very difficult at times, and cases have been reported in which there was lateral extension beyond the dermal component (587,788). In some other cases, the metastatic cells are small and nevoid, with few if any mitoses, and in these instances of differentiated or nevoid epidermotropic metastatic melanoma or epidermotropic metastatic melanomas with maturation the lesions can be mistaken for compound nevi (563).

Generalized Melanosis in Metastatic Melanoma

This is a rare phenomenon that may be associated with widespread melanoma metastases. It is characterized by diffuse, slate-blue discoloration of the entire skin, the conjunctivae, and the oral and pharyngeal mucous membranes, often with melanuria. Melanin granules have been observed also in blood smears within neutrophils and monocytes. Autopsy reveals a similar discoloration in the intima of the large arteries and of many visceral organs (789).

Histologically, numerous melanin granules are seen located within macrophages throughout the dermis, especially around capillaries. They stain with the Fontana-Masson stain and are DOPA positive. In addition, some dermal vessels are focally plugged with dark, amorphous DOPA-positive material. In most instances, only melanophages have been found. It is assumed that the melanin is produced by distant melanoma cells and then carried by the blood to the skin, to be deposited within dermal melanophages (789,790). In a few cases, two types of pigmented cells have been identified in the dermis, particularly in semithin sections: melanophages and individually scattered melanoma cells appearing larger and less pigmented than the melanophages. At autopsy, melanin phagocytosis is seen in many organs, especially in the Kupffer cells of the liver and the cells lining the sinusoids of the lymph nodes, spleen, and adrenal glands (790).

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CHAPTER 29

Nigel Kirkham

Tumors and Cysts of the Epidermis

CLASSIFICATION OF TUMORS OF THE EPIDERMIS

Epidermal tumors can be divided into tumors of the surface epidermis and tumors of the epidermal appendages. In each of the two classes, benign and malignant tumors occur.

Benign tumors in general are characterized by (a) a symmetric architecture and a circumscribed profile; (b) a tendency to differentiate along organized tissue lines; (c) uniformity in the appearance of the tumor cell nuclei; (d) architectural order in the arrangement of the tumor cell nuclei; (e) restraint in the rate of growth; and (f) absence of metastases.

Malignant tumors, in contrast, are characterized by (a) a less symmetric architecture and a poorly circumscribed profile; (b) a variable but often poorly differentiated phenotype; (c) atypicality in the appearance of the tumor cell nuclei, which show pleomorphism, that is, great variability in size and shape, and anaplasia, that is, hyperplasia and hyperchromasia; (d) architectural disorder in the arrangement of the tumor cell nuclei with loss of polarity; (e) rapid growth with the presence of mitoses, including atypical mitoses; and (f) potentiality to give rise to metastases.

Of the criteria of malignancy just cited, only the potentiality to give rise to metastases is decisive evidence for the malignancy of a tumor. For metastases to form, the tumor cells must possess a degree of autonomy that nonmalignant cells do not have. This autonomy enables malignant tumor cells to induce foreign tissue to furnish the necessary stroma in which they can multiply.

In addition to malignant tumors, one finds in the surface epidermis so-called premalignant tumors, better regarded as tumors located largely *in situ*. Although cytologically malignant, they are biologically still benign. The World Health Organization has classified tumors of the surface epidermis (1).

LINEAR EPIDERMAL NEVUS

Linear epidermal nevi, or verrucous nevi, may be either localized or systematized.

In the *localized type*, which is present usually but not invariably at birth, only one linear lesion is present. It consists of closely set, papillomatous, hyperkeratotic papules. It may be located anywhere—on the head, trunk, or extremities. Being located on only one side of the patient, it is often referred to as *nevus unius lateris* (Figs. 29-1 and 29-2). In its configuration, the localized type of linear epidermal nevus resembles the inflammatory linear verrucous epidermal nevus (ILVEN), but the latter differs clinically by the presence of erythema and pruritus and histologically by the presence of inflammation and parakeratosis (2,3) (see Chapter 7).

In the *systematized type*, papillomatous hyperkeratotic papules in a linear configuration are present not just as one linear lesion, as in the localized type, but as many linear lesions. These linear lesions often show a parallel arrangement, particularly on the trunk. They may be limited to one side of the patient or may have a bilateral, symmetric distribution. The term *ichthyosis hystrix* is occasionally used, perhaps unnecessarily, for instances of extensive bilateral lesions (4).

Localized and, more commonly, systematized linear epidermal nevi may be associated with skeletal deformities and central nervous system deficiencies, such as mental retardation, epilepsy, and neural deafness (5).

The presence of a basal cell epithelioma within a linear epidermal nevus has been observed occasionally, particularly on the head in cases in which the linear epidermal nevus has been associated with either a nevus sebaceous or a syringocystadenoma papilliferum (see Chapter 30) (6). In areas other than the head, it is very rare (7). Similarly, development of a squamous cell carcinoma has been described only rarely (8,9), but in one instance the squamous cell carcinoma had metastasized to a regional lymph node (10).

Histopathology. Nearly all cases of the localized type of linear epidermal nevus and some cases of the systematized type show the histologic picture of a benign papilloma (4,11). One observes considerable hyperkeratosis, papillomatosis, and acanthosis with elongation of the rete ridges resembling seborrheic keratosis (Fig. 29-3).

Occasionally in cases of the localized type, but quite frequently in cases of the systematized type, particularly those with a widespread distribution, one observes the rather striking histologic picture referred to either as *epidermolytic hyperkeratosis* (12) or as *granular degeneration of the epidermis* (13). It is the same process that was first recognized in all cases of bullous congenital ichthyosiform erythroderma, a disorder that is often referred to as *epidermolytic hyperkeratosis* (see Chapter 6). It has since been



FIGURE 29-1. Epidermal nevus. The nevus lies in a fold of the external ear and has a papillary appearance.

found to occur in several other conditions as well (see Isolated and Disseminated Epidermolytic Acanthoma).

The salient histologic features of epidermolytic hyperkeratosis are (a) perinuclear vacuolization of the cells in the stratum spinosum and in the stratum granulosum; (b) irregular cellular boundaries peripheral to the vacuolization; (c) an increased



FIGURE 29-2. Linear epidermal nevus. This example is pigmented and lies in the midline, on the back of the neck.

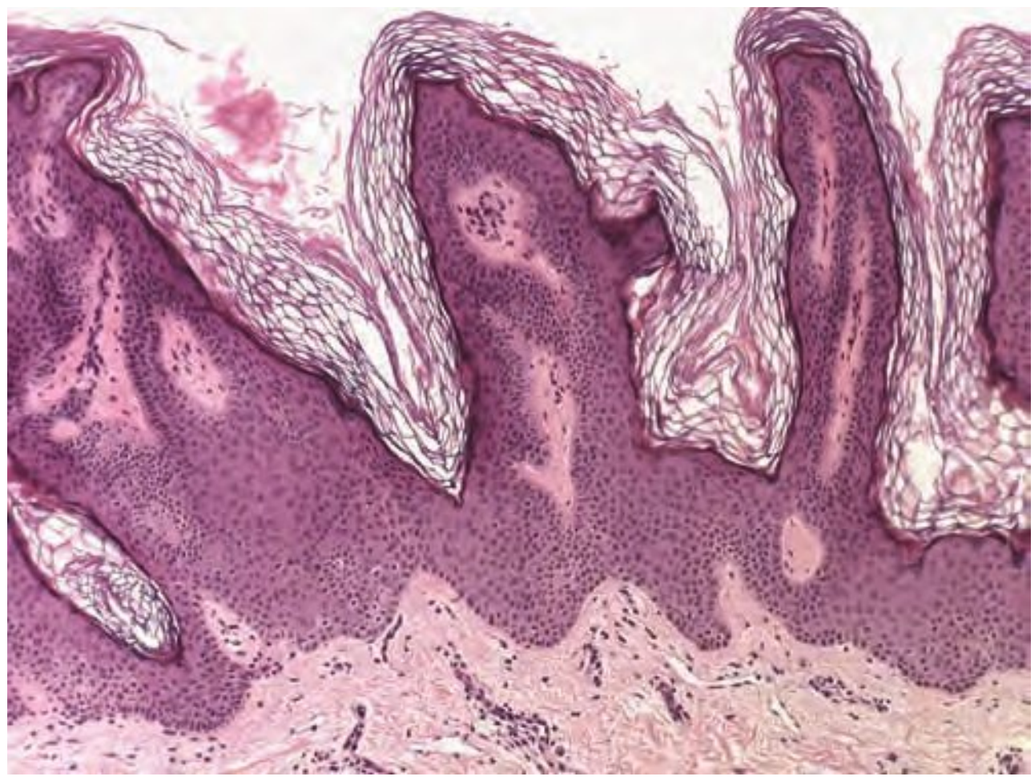


FIGURE 29-3. Epidermal nevus. The nevus shows orthokeratotic hyperkeratosis and flat-topped papillary projections.

number of irregularly shaped, large keratohyaline granules; and (d) compact hyperkeratosis in the stratum corneum (13,14).

In some instances, histologic examination of unilateral linear lesions reveals features of acantholytic dyskeratosis as seen in Darier's disease (see Chapter 6). In some patients, these linear lesions have been present since birth or infancy (15), but in most instances they have arisen in adult life (16). Because acantholytic dyskeratosis is not specific for Darier's disease, the proposal has been made to designate such cases not as Darier's disease, but as acantholytic dyskeratotic epidermal nevus (16).

Differential Diagnosis. The histologic picture of a benign papilloma, as found in most cases of linear epidermal nevus, can also be seen in seborrheic keratosis, verruca vulgaris, and acanthosis nigricans. Even though these four conditions have in common hyperkeratosis and papillomatosis, they can be differentiated easily in typical cases; however, one is occasionally unable to make a diagnosis any more specific than benign papilloma. Thus, in the following three situations, clinical data are required for differentiation from linear epidermal nevus: (a) the hyperkeratotic type of seborrheic keratosis, which is characterized by the absence of basaloid cells and horn cysts and instead shows upward extension of epidermis-lined papillae; (b) old verrucae vulgares, which no longer show vacuolization of epidermal cells or columns of parakeratosis (see Chapter 25); and (c) acanthosis nigricans showing more pronounced acanthosis and greater elongation of the rete ridges than usual (see Chapter 17).

NEVOID HYPERKERATOSIS OF NIPPLE AND AREOLA

Nevoid hyperkeratosis and papillomatosis of nipples and areola presents as sharply demarcated papules and plaques, often appearing at puberty or during pregnancy and persisting unchanged. There are no associated systemic or dermatologic

conditions. The main differential diagnosis is seborrheic keratosis (17).

Histopathology. There are papillomatous elongations of the epidermis with hyperkeratosis and areas of keratotic plugging (18). This condition represents a nevoid form of hyperkeratosis (19).

NEVUS COMEDONICUS

A nevus comedonicus consists of closely set, slightly elevated papules that have in their center a dark, firm, hyperkeratotic plug resembling a comedo. Nevus comedonicus, like linear epidermal nevus, usually has a linear configuration and occurs as a single lesion. In some instances, however, there are multiple bilateral linear lesions (20) or lesions that are randomly distributed rather than linear (21). Lesions may be present on the palms or soles in addition to other areas (22,23). Such cases may represent a combination of nevus comedonicus with a porokeratotic eccrine duct nevus (see text following).

Histopathology. Each comedo is represented by a wide, deep invagination of the epidermis filled with keratin. These invaginations resemble dilated hair follicles; in fact, as evidence that they actually represent rudimentary hair follicles, one occasionally finds in the lower portion of an invagination one or even several hair shafts (20). One or two small sebaceous gland lobules may also be seen opening into the lower pole of invaginations (21).

In several instances, the keratinocytes composing the follicular epithelial wall have shown the typical changes of epidermolytic hyperkeratosis (see text following) (24), indicative of a relationship of nevus comedonicus to systematized nevus verrucosus (see Chapter 30).

POROKERATOTIC ECCRINE OSTIAL AND DERMAL DUCT NEVUS

Porokeratotic eccrine ostial and dermal duct nevus may be limited to a palm (25) or to a sole (26) but may be present on both hands and feet and elsewhere (27,28). It also may involve not only eccrine ducts, but also involve hair follicles on the hairy parts of the body (29).

Histopathology. In the porokeratotic eccrine duct nevus, each invagination consists of a dilated eccrine duct containing a parakeratotic plug. The absence of the granular layer at the base of the plug together with the presence of keratinocytes showing vacuolization of their cytoplasm results in a histologic picture resembling that of porokeratosis (see Chapter 6) (25–27).

ISOLATED AND DISSEMINATED EPIDERMOLYTIC ACANTHOMA

Isolated epidermolytic acanthoma, histologically characterized by the presence of "epidermolytic hyperkeratosis," does not have a characteristic clinical appearance or location. Usually it occurs as a solitary papillomatous lesion less than 1 cm in diameter (30–32). Occasionally, several lesions are seen in a localized area (33,34). One case has been described that was probably secondary to trauma (35).

Disseminated epidermolytic acanthoma occurs as numerous discrete, flat, brownish papules 2 to 6 mm in diameter resembling seborrheic keratoses. The upper trunk, especially the back, is the site of predilection (36,37).

Histopathology. In addition to hyperkeratosis and papillomatosis, one observes pronounced epidermolytic hyperkeratosis, also referred to as *granular degeneration*, throughout the stratum malpighii, sparing only the basal layer, just as seen in linear epidermal nevi with epidermolytic changes. One observes both intracellular and intercellular edema of the epidermal cells and keratohyaline granules that are coarser than normal and extend to a greater depth in the stratum malpighii (30).

Differential Diagnosis. Myrmecia warts, caused by human papilloma virus type 1 (HPV-1), also show perinuclear vacuolization and an abundance of keratohyaline granules, representing a type of "granular degeneration" similar to that seen in epidermolytic hyperkeratosis. However, in myrmecia warts, the keratohyaline granules are eosinophilic and coalesce in the upper layers of the epidermis to form large, homogeneous, eosinophilic "inclusion bodies." In verrucae vulgares, usually caused by HPV-2, foci of vacuolated cells and clumped basophilic keratohyaline granules may be present, but these changes are limited to the upper layers of the epidermis. In addition, both myrmecia warts and verrucae vulgares show focal parakeratosis rather than orthokeratosis as seen in epidermolytic hyperkeratosis (see Chapter 25).

INCIDENTAL EPIDERMOLYTIC HYPERKERATOSIS

Epidermolytic hyperkeratosis is seen not only in isolated and disseminated epidermolytic hyperkeratosis (see text preceding) but also as a *regular* finding in epidermolytic hyperkeratosis, or bullous congenital ichthyosiform erythroderma (see Chapter 6), and in epidermolytic keratosis palmaris et plantaris and as an *occasional* finding in linear epidermal nevus and nevus comedonicus. In addition, epidermolytic hyperkeratosis may represent an *incidental* histologic finding in many different types of lesions, largely but not exclusively tumors. It has also been observed in normal oral mucosa adjacent to lesions of squamous cell carcinoma and basal cell epithelioma (38).

Histopathology. Epidermolytic hyperkeratosis may be seen throughout an entire lesion of solar keratosis (39) and in the entire lining of trichilemmal cyst (40). More commonly, however, the histologic features of epidermolytic hyperkeratosis are seen as a small focus, often limited to a single epidermal rete ridge, in such diverse lesions as sebaceous hyperplasia (41), intradermal nevus, hypertrophic scar (42), superficial basal cell epithelioma (43), seborrheic keratosis, the margin of a squamous cell carcinoma, lichenoid amyloidosis, and granuloma annulare

(12). In some instances, the process is limited to one or two intraepidermal sweat duct units (42). It is more frequently seen in dysplastic nevi than in ordinary melanocytic nevi (43).

ISOLATED AND DISSEMINATED ACANTHOLYTIC ACANTHOMA

This condition usually occurs as a solitary papule or small nodule (45), although there may be multiple lesions (46,47). No characteristic clinical appearance or location exists, although multiple lesions have been seen largely in the genital region (26,50).

Histopathology. Acantholysis is the most prominent feature. The pattern may resemble that of pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, or benign familial pemphigus (45). Acantholysis may be combined with dyskeratosis, in which case the histologic picture resembles that of Darier's disease as the result of the presence of corps ronds and grains (12,46,47). Because of this the alternative name of *dyskeratotic acanthoma* has been suggested (48).

INCIDENTAL FOCAL ACANTHOLYTIC DYSKERATOSIS

Analogous to epidermolytic hyperkeratosis, acantholytic dyskeratosis is seen as a *regular* histologic feature in Darier's disease (see Chapter 6), transient acantholytic dermatosis, and warty dyskeratoma. It also is an *occasional* finding in acantholytic dyskeratotic epidermal nevus, a variant of linear epidermal nevus. In addition, again like epidermolytic hyperkeratosis, focal acantholytic dyskeratosis is observed occasionally as an *incidental* histologic finding in a variety of lesions, including vascular nevi (49).

Histopathology. Focal suprabasal clefts with overlying acantholytic and dyskeratotic cells, some of which have the appearance of corps ronds (Fig. 29-4), have been seen as a single focus in the epidermis overlying such diverse lesions as dermatofibroma, basal cell epithelioma, melanocytic nevus, and chondrodermatitis nodularis helicis (40), as well as in pityriasis rosea (51) and acral lentiginous malignant melanoma (Fig. 29-2) (52).

ORAL WHITE SPONGE NEVUS

First described in 1935 (53), oral white sponge nevus is a benign autosomal dominant disorder that affects noncornifying stratified squamous epithelia. It may be present at birth or have its onset in infancy, childhood, or adolescence (54). Extensive areas of the oral mucosa and sometimes the entire oral mucosa have a thickened, folded, creamy white appearance. In some instances, the rectal mucosa (53), vagina (55), nasal mucosa (56), or esophagus (57) is also involved. This distribution of lesions suggests that mutations in the epithelial keratins K4 and/or K13 may be responsible: A three base-pair deletion in the helix initiation peptide of K4 has been reported in affected members of two families (58). Further studies of one large family suggested that a K13 gene was responsible (59).

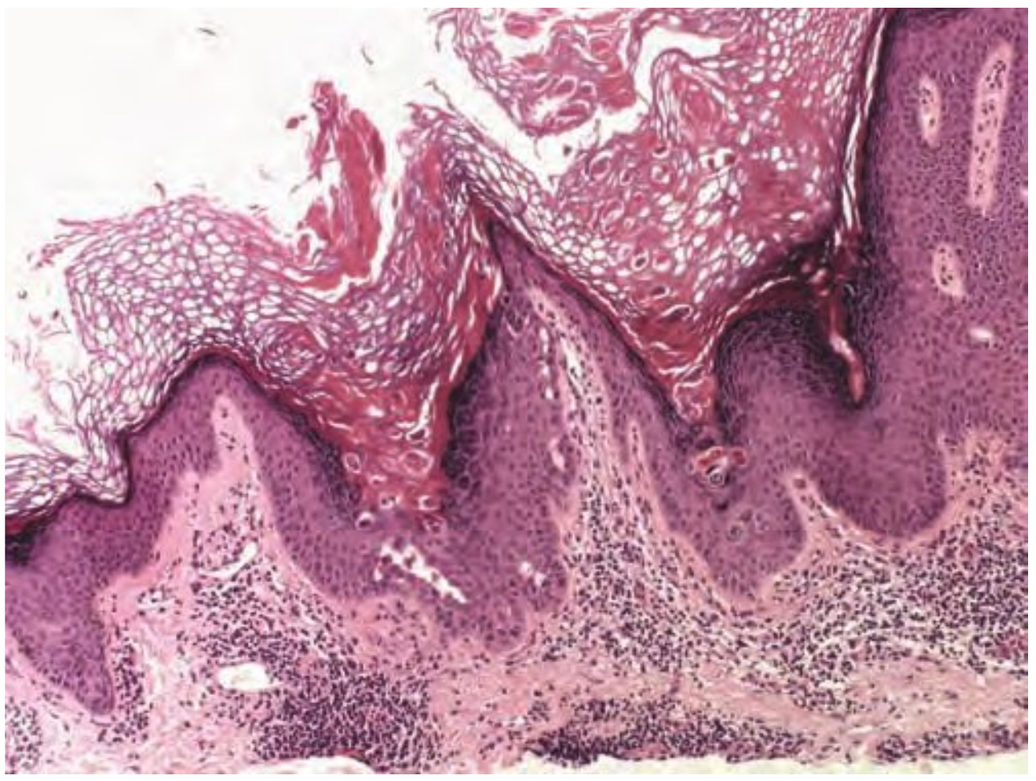


FIGURE 29-4. Incidental focal acantholytic dyskeratosis. Focally, within the biopsy, there is suprabasal cleft formation with overlying dyskeratotic cells.

The oral lesions seen in pachyonychia congenita are both clinically and histologically indistinguishable from a white sponge nevus (see Chapter 6) (56).

Histopathology. The oral epithelium shows hyperplasia with much more pronounced hydropic swelling of the epithelial cells than is normal for the oral mucosa. The swelling, though extensive, is focal (60). It extends into the rete ridges but spares the basal layer (61). The nuclei appear smaller than normal (54). The surface shows parakeratosis, as does the normal oral mucosa, and only rarely are there small accumulations of keratohyaline granules (55).

Pathogenesis. On electron microscopic examination, large cytoplasmic areas of the epithelial cells appear optically empty or contain only faint granular material. Tonofilaments are limited to the perinuclear and peripheral areas. The intercellular areas show irregular dilation, and large, irregularly shaped vacuoles are present within the cytoplasm (62). A possibly fundamental disturbance is the presence of numerous intracellular Odland bodies or membrane-coating granules (see Chapter 3), which are not extruded into the intercellular spaces (63).

Differential Diagnosis. The histologic picture of oral white sponge nevus is identical to that seen in pachyonychia congenita (see text preceding) and to that of oral focal epithelial hyperplasia (62) and of leukoedema of the oral mucosa (see text following).

LEUKOEDEMA OF THE ORAL MUCOSA

Leukoedema of the oral mucosa is a common condition that, when pronounced, shows a clinical and histologic resemblance

to oral white sponge nevus. However, leukoedema differs from white sponge nevus by being patchy rather than diffuse, by having exacerbations and remissions and adult onset, and by not being inherited (64).

Histopathology. In leukoedema of the oral mucosa, as in oral white sponge nevus, the suprabasal epithelial cells show marked intracellular edema. The nuclei appear smaller than normal.

LINGUA GEOGRAPHICA

In geographic tongue, also referred to as superficial migratory glossitis, the dorsum of the tongue shows irregularly shaped red patches surrounded by a whitish, raised border a few millimeters wide (65). It is usually asymptomatic, with local loss of filiform papillae leading to the development of ulcer-like lesions that rapidly change color and size (66).

Histopathology. Whereas the dorsum of the tongue normally shows a granular and a horny layer, these layers are absent in the red patches of lingua geographica. Along the whitish border, the epithelium shows irregular thickening and infiltration of neutrophils. In its upper portion, the epithelium shows collections of neutrophils within the interstices of a spongelike network formed by degenerated and thinned epithelial cells (67,68). The histologic picture thus shows Kogoj's spongiform pustules, which are indistinguishable from those seen in pustular psoriasis.

Pathogenesis. The presence of spongiform pustules generally is regarded as diagnostic of pustular psoriasis and as almost specific for it (see Chapter 7), even though it rarely occurs in other pustules, such as those caused by *Candida albicans* (69). It has therefore been suggested that geographic tongue represents a localized form of pustular psoriasis (70). However, even though pustular psoriasis and lingua geographica may both show annular lesions on the tongue, pustular psoriasis of the mouth generally shows clinical evidence of pustules and is usually seen also in other areas of the mouth. It is therefore best to regard lingua geographica as a separate entity.

SEBORRHEIC KERATOSIS

Seborrheic keratoses are very common: sometimes single but often multiple. They occur mainly on the trunk and face but also on the extremities, excluding palms and soles. They usually do not appear before middle age, but are present in about 20% of the elderly (70). They are sharply demarcated, brownish in color, and slightly raised, often appearing as though stuck on the surface of the skin. Most have a verrucous surface, and a soft, friable consistency. Some have a smooth surface but characteristically show keratotic plugs. Although most lesions measure only a few millimeters in diameter, some occasionally reach a size of several centimeters. Crusting and an inflammatory base are found if the lesion has been subjected to trauma.

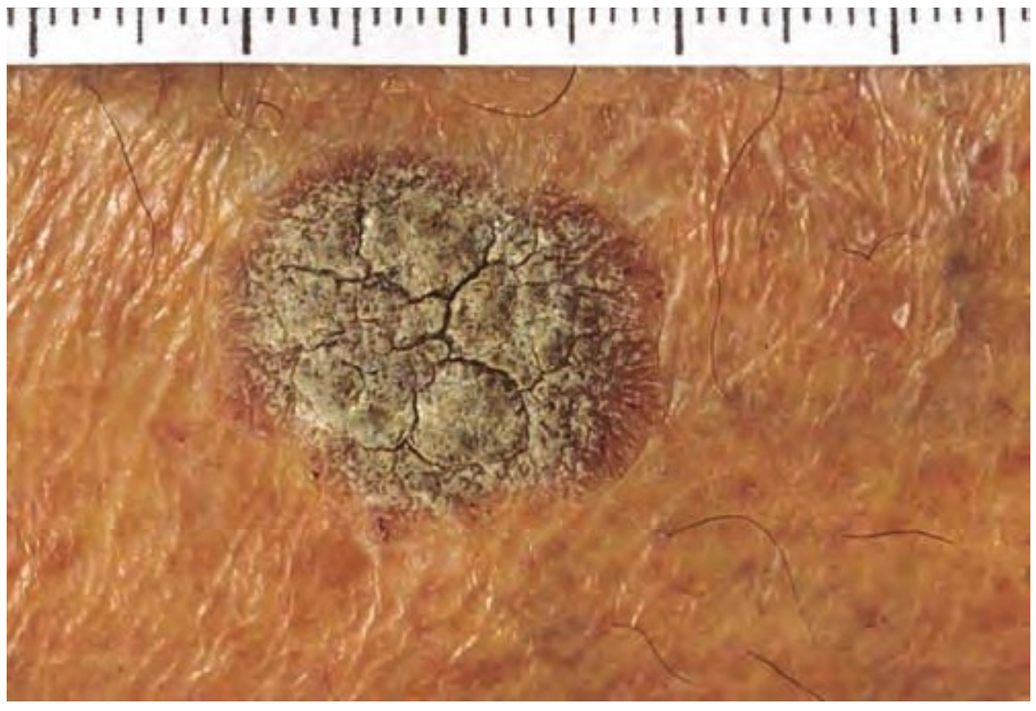


FIGURE 29-5. Seborrheic keratosis. The keratosis has a grayish, waxy appearance.

Occasionally, small examples are pedunculated, especially on the neck and upper chest, where they resemble soft fibromas (see Chapter 32). Malignant change is rare but has been reported in association with unusual clinical appearances to the seborrhoeic keratoses (71).

Histopathology. Seborrheic keratoses show a considerable variety of histologic appearances. Six types are generally recognized: irritated; adenoid or reticulated; plane; clonal; melanoacanthoma; inverted follicular keratosis; and benign squamous keratosis (Figs. 29-5 to 29-13). Often more than one type is found in the same lesion. In addition, two clinical variants of seborrheic keratosis will be described—dermatosis papulosa nigra and stucco keratosis (Fig. 29-14).

All types of seborrheic keratosis have in common hyperkeratosis, acanthosis, and papillomatosis. The acanthosis in most instances is due entirely to upward extension of the tumor. Thus the lower border of the tumor is even and generally lies on a straight line that may be drawn from the normal



FIGURE 29-6. Seborrheic keratosis. Two keratoses lie close together and show variable pigmentation.



FIGURE 29-7. Seborrheic keratosis. Low magnification. The keratosis is radially symmetric, contains several horn cysts, and has a flat base.

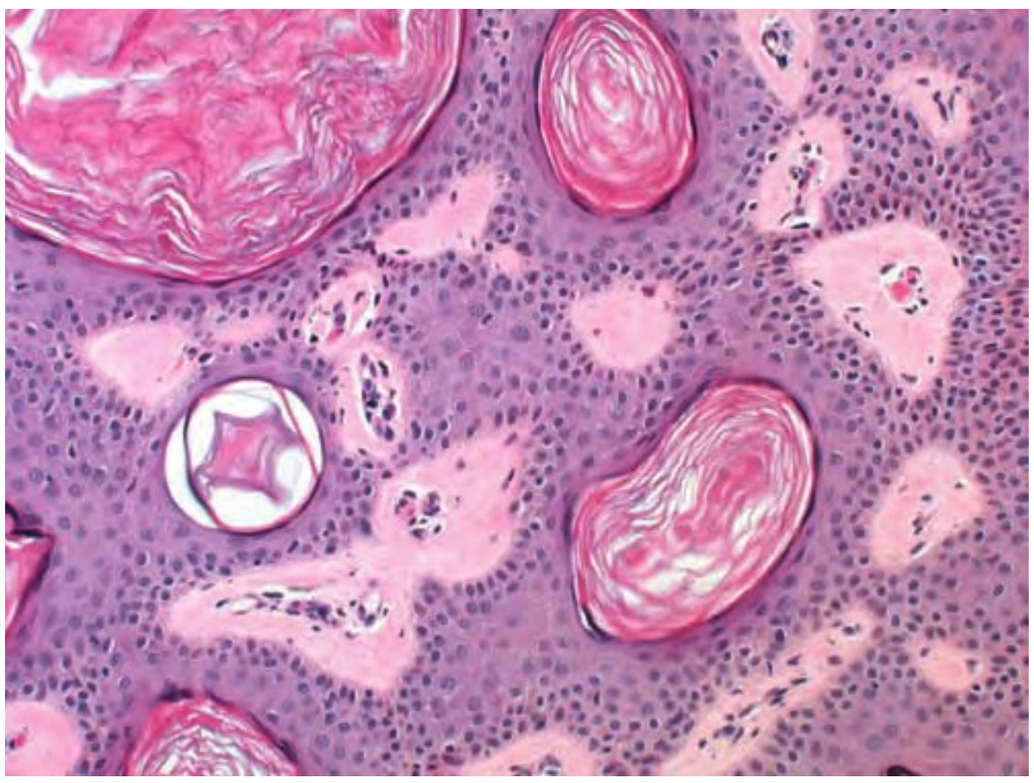


FIGURE 29-8. Seborrheic keratosis. High magnification. Most of the cells have a basaloid appearance, with interspersed horn cysts filled with keratin.

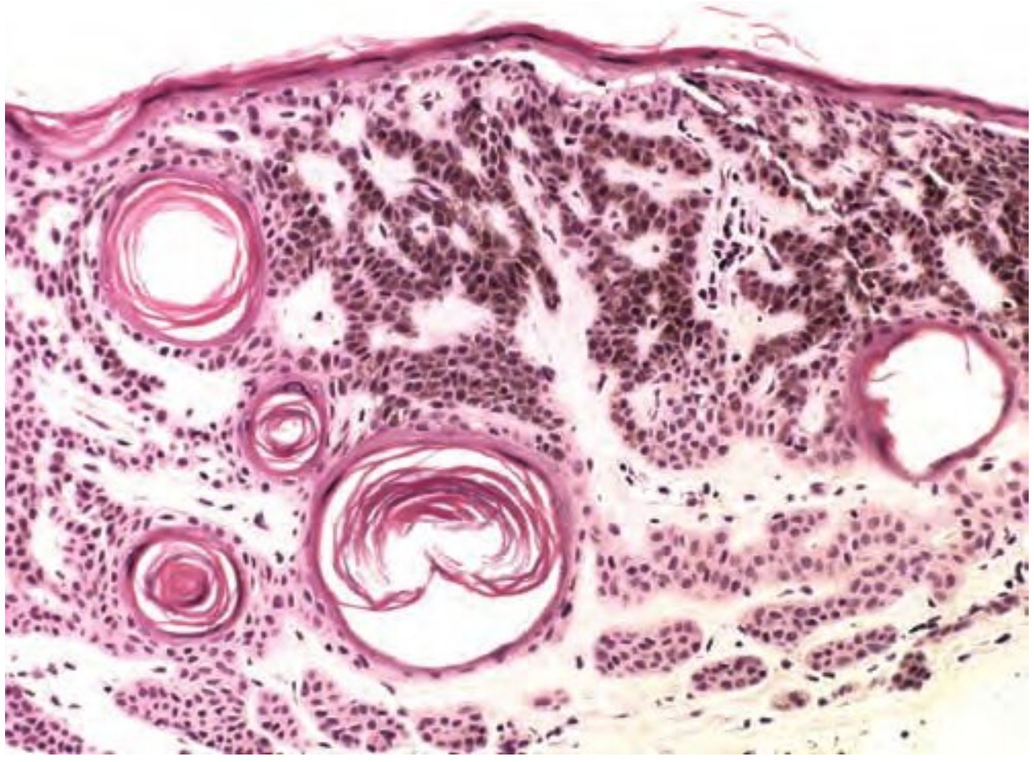


FIGURE 29-9. Pigmented seborrheic keratosis. Thin interwoven cords of basaloid cells show cytoplasmic melanin pigmentation and horn cysts.



FIGURE 29-10. Clonal seborrheic keratosis, showing focal variation in pigmentation.

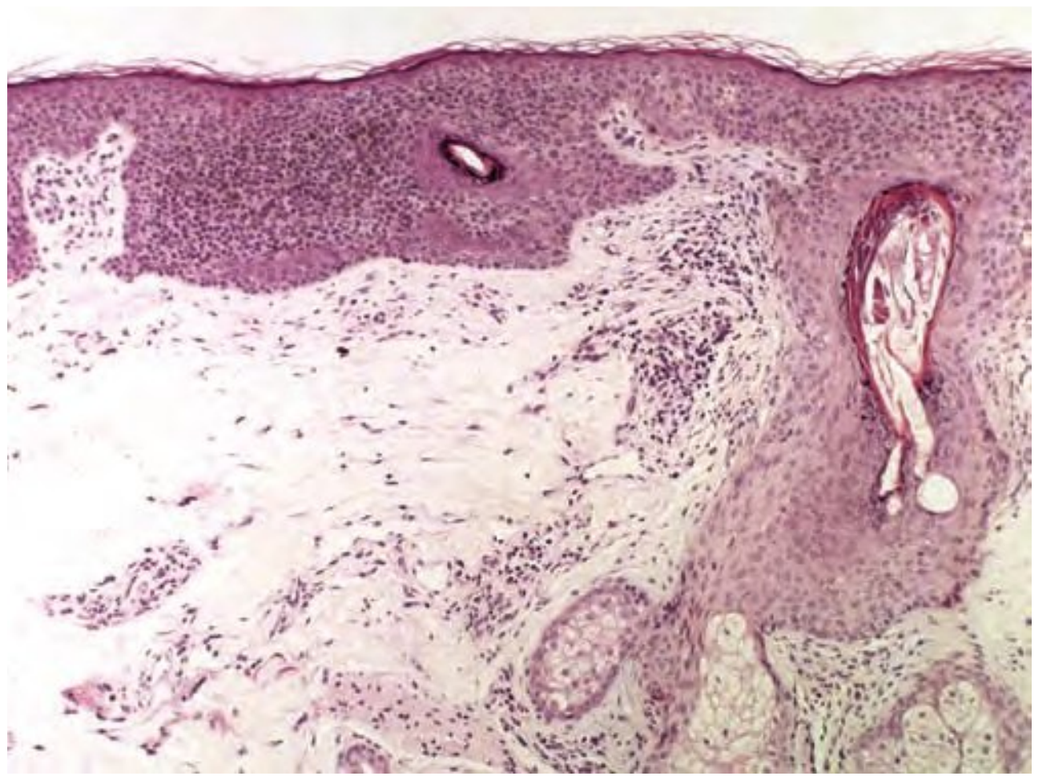


FIGURE 29-11. Clonal seborrheic keratosis showing foci of basaloid cells surrounded by more eosinophilic squamous cells.



FIGURE 29-12. Irritated seborrheic keratosis showing inflammation of the adjacent skin.

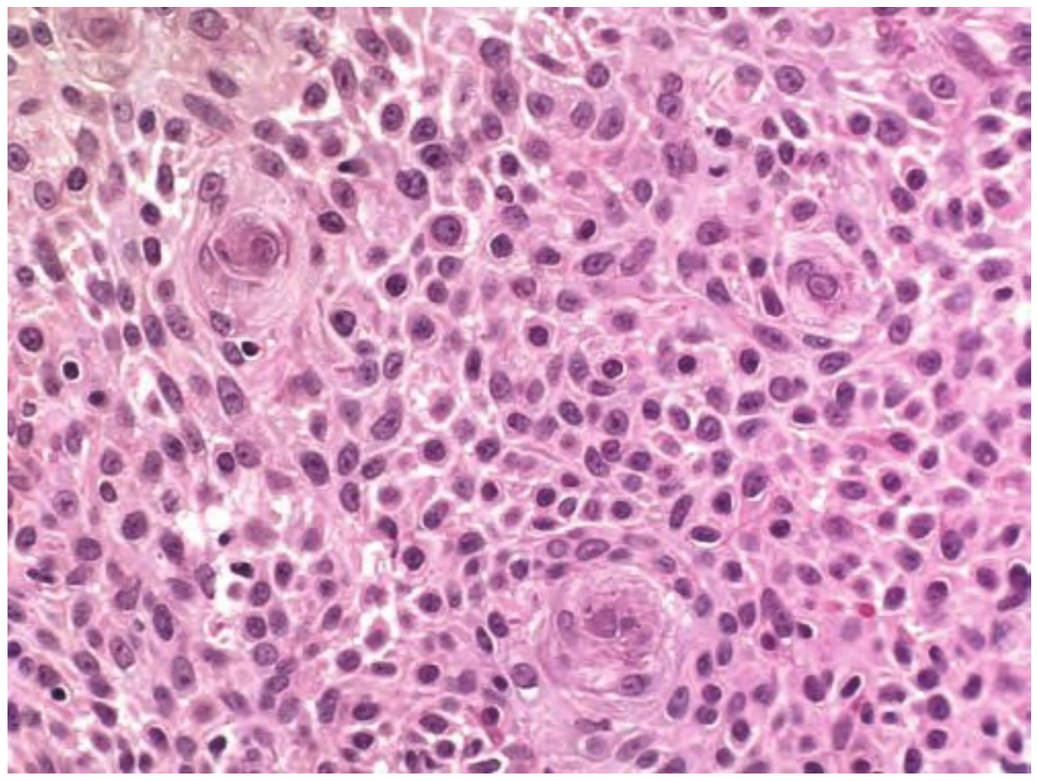


FIGURE 29-13. Inverted follicular keratosis. Squamous eddies are present, composed of whorls of squamous cells. There is no substantial cytologic atypia.

epidermis at one end of the tumor to the normal epidermis at the other end (see Fig. 29-7). Two types of cells are usually seen in the acanthotic epidermis: squamous cells and basaloid cells. The former have the appearance of squamous cells normally found in the epidermis; the basaloid cells are small and uniform in appearance and have a relatively large nucleus. In areas of slight intercellular edema, intercellular bridges can be easily recognized (72). Thus they resemble the basal cells found normally in the basal layer of the epidermis.

Irritated Type and Inverted Follicular Keratosis

In the irritated, or activated, type of seborrheic keratosis, squamous cells outnumber basaloid cells. The characteristic feature is the presence of numerous whorls or eddies composed of eosinophilic, flattened squamous cells arranged in an onion-peel fashion, resembling poorly differentiated horn pearls (Figs. 29-12 and 29-13). These "squamous eddies" are easily differentiated from the horn pearls of squamous cell carcinoma by their large number, small size, and circumscribed configuration. Irritated seborrheic keratoses, in addition, may show areas of downward proliferation breaking through the horizontal demarcation generally present in nonirritated seborrheic keratoses (73,74). Frequently, some of these proliferations are seen to originate from the walls of keratin-filled invaginations. Inflammation beneath irritated seborrheic keratoses usually is mild or absent, indicating that irritated seborrheic keratoses are different from inflamed seborrheic keratoses.

In a few instances, acantholysis has been observed within tumor nests composed of squamous cells (75). These acantholytic changes differ from those occurring in incidental focal acantholytic dyskeratosis by not showing suprabasal location or dyskeratotic cells resembling corps ronds (76).

Pathogenesis. The formation of numerous squamous eddies is the result of the "activation" of resting basaloid cells into squamous cells. This unique and highly diagnostic feature of irritated or activated seborrheic keratoses, as well as their downward proliferation, is the result of irritation. This has been proved experimentally by the excision of seborrheic keratoses either after a previous biopsy (77) or after irritation with croton oil (78).

The identical histologic picture as seen in irritated seborrheic keratosis has been described under the designations of *inverted follicular keratosis* (79,80) and *follicular poroma* (81,82). As these terms indicate, the authors regard the keratin-filled invaginations as follicular infundibula and the proliferations arising from them as composed of cells of the follicular infundibulum. The follicular infundibulum consists of cells with the same type of keratinization as the surface epidermis, and there is evidence that seborrheic keratoses incorporate cells of the infundibular portion of the hair follicle and are partially derived from these cells. Seborrheic keratoses, like inverted follicular keratoses, occur exclusively on hair-bearing skin. Some seborrheic keratoses even contain aggregates of vellus hairs within the keratinous invaginations, an occurrence analogous to trichostasis spinulosa (see Chapter 18) (83). Although some authors merely concede that irritated seborrheic keratoses and inverted follicular keratoses may be histologically indistinguishable (74,84,85), others regard the two disorders as identical (73,83,86). Because of their histologic similarity and particularly because of the highly specific appearance of the squamous eddies that occur in these two conditions, they are best regarded as identical.



FIGURE 29-14. Stucco keratoses: multiple small, white and gray-white seborrheic keratoses.

Adenoid or Reticulated Type

In the adenoid or reticulated type of seborrheic keratosis, numerous thin tracts of epidermal cells extend from the epidermis and show branching and interweaving in the dermis. Many tracts are composed of only a double row of basaloid cells. Horn cysts and pseudo–horn cysts are absent in purely reticulated lesions; however, the reticulated type often also shows areas of the acanthotic type, and horn cysts and

pseudo–horn cysts are commonly seen in these areas. The basaloid cells of the reticulated type of seborrheic keratosis usually show marked hyperpigmentation.

There is both clinical and histologic evidence of a close relationship between solar or senile lentigo senilis and the reticulated type of seborrheic keratosis. A lesion of solar lentigo may even become a reticulated seborrheic keratosis through exaggeration of the process of downward budding of pigmented basaloid cells (see Chapter 28) (87).

Acanthotic Type

In the acanthotic type, the most common type of seborrheic keratosis, hyperkeratosis and papillomatosis often are slight, but the epidermis is greatly thickened. Although only narrow papillae are included in the thickened epidermis in some cases, one can see in other lesions a retiform pattern composed of thick, interwoven tracts of epithelial cells surrounding islands of connective tissue. Horny invaginations that on cross sections appear as pseudo–horn cysts are numerous. In addition, there also are true horn cysts, which, like the pseudo–horn cysts, show sudden and complete keratinization with only a very thin granular layer.

The true horn cysts begin as foci of orthokeratosis within the substance of the lesion (88). In time, they enlarge and are carried by the current of epidermal cells toward the surface of the lesion, where they unite with the invaginations of surface keratin. In the greatly thickened epidermis, basaloid cells usually outnumber squamous cells.

The amount of melanin in seborrheic keratoses of the acanthotic type is often greater than normal. Excess amounts of melanin are seen in about one third of the specimens stained with hematoxylin-eosin (89); staining with silver reveals excess amounts in about two thirds of the cases (90). In dopa-stained sections, melanocytes are limited to the dermal–epidermal junctional layer present at the base of the tumor and at the interfaces between the tumor tracts and the islands of dermal stroma (78). The melanin, largely present in keratinocytes, is in most instances also limited to keratinocytes located at the dermal–epidermal junction. Only deeply pigmented lesions show melanin widely distributed throughout the tumor within basaloid cells (91).

A mononuclear inflammatory infiltrate is seen quite frequently in the dermis underlying a seborrheic keratosis. The inflammation may impinge on the tumor in a lichenoid or eczematous pattern. In the lichenoid pattern, a bandlike infiltrate is seen hugging the basal cell layer of the tumor. In the eczematous pattern, there is exocytosis leading to spongiosis. Squamous eddies, typical of irritated seborrheic keratoses, are only rarely seen in inflamed seborrheic keratoses (92).

Formation of an *in situ* carcinoma within an acanthotic seborrheic keratosis, so-called bowenoid transformation, is seen occasionally (93,94). It seems to occur predominantly in lesions located in sun-exposed areas of the skin, so that sun damage may be a factor (95). In one reported case, a metastasis in a regional lymph node was found (96). On rare occasions, a basal cell epithelioma may form within an acanthotic seborrheic keratosis and may extend from there into the underlying dermis (97,98).

Pathogenesis. Electron microscopic examination has confirmed the light microscopic impression that the small basaloid cells seen in the acanthotic type of seborrheic keratosis are related to cells of the epidermal basal cell layer rather than to the basaloma cells of basal cell epithelioma. They possess a fair number of desmosomes and a moderate number of tonofilaments that differ from those present in cells of the epidermal basal cell layer only by showing less orientation (99).

Hyperkeratotic Type

In the hyperkeratotic type, also referred to as the digitate or serrated type, hyperkeratosis and papillomatosis are pronounced, whereas acanthosis is not very conspicuous. The numerous digitate upward extensions of epidermis-lined papillae often resemble church spires. The histologic picture then resembles that seen in acrokeratosis verruciformis of Hopf (see Chapter 6). The epidermis consists largely of squamous cells, although small aggregates of basaloid cells may be seen here and there. As a rule, no excess amounts of melanin are found.

Clonal Type

In the clonal, or nesting, type of seborrheic keratosis, well-defined nests of cells are located within the epidermis. In some instances, the nests resemble foci of basal cell epithelioma because the nuclei appear small and dark-staining and intercellular bridges are seen in only a few areas (see Figs. 29-10 and 29-11) (100). The histologic picture in such cases has been erroneously interpreted by some authors as representing an intraepidermal epithelioma of Borst-Jadassohn (see Chapter 30) (101). In other instances of clonal seborrheic keratosis, the nests are composed of fairly large cells showing distinct intercellular bridges, with the nests separated from one another by strands of cells exhibiting small, dark nuclei.

Melanoacanthoma

This rather rare variant of pigmented seborrheic keratosis (91) differs from the usual type of pigmented seborrheic keratosis by showing a marked increase in the concentration of melanocytes. Rather than being confined to the basal layer of the tumor lobules, many melanocytes are scattered throughout the tumor lobules (91,102). In some instances, well-defined islands of basaloid cells intermingled with many melanocytes are distributed through the tumor (103). The melanocytes are large and richly dendritic and contain variable amounts of melanin. The block in transfer of melanin from melanocytes to keratinocytes often is only partial (102), although in some instances nearly all the melanin is retained in the melanocytes (104).

Pathogenesis. Melanoacanthoma is a benign mixed tumor of melanocytes and keratinocytes (91).

DERMATOSIS PAPULOSA NIGRA

Dermatosis papulosa nigra is found in about 35% of all adult blacks, often has its onset during adolescence (105), and has been described in a 3-year-old child (106). The lesions are located predominantly on the face, especially in the malar regions, but they also may occur on the neck and upper trunk. They usually consist of small, smooth, pigmented papules, except on the neck and trunk, where some of them may be pedunculated.

Histopathology. The lesions have the histologic appearance of seborrheic keratoses but are smaller. Most lesions are of the acanthotic type and show thick interwoven tracts of epithelial cells. The cells are largely squamous in appearance, with only a few basaloid cells (105). Horn cysts are quite common. An occasional lesion shows a reticulated pattern in which the tracts are composed of a double row of basaloid cells. Melanin pigmentation is pronounced in all lesions.

STUCCO KERATOSIS

Stucco keratoses are small, gray-white seborrheic keratoses 1 to 3 mm in diameter located in symmetric arrangement on the distal portions of the extremities, especially the ankles (Fig. 29-14). They can easily be scraped off without any resultant bleeding.

Histopathology. Stucco keratoses have the appearance of the hyperkeratotic type of seborrheic keratosis, showing the church-spire pattern of upward-extending papillae (96,97). Horn cysts and basaloid cells are usually absent (109).

LESER-TRÉLAT SIGN

The Leser-Trélat sign is characterized by the sudden appearance of numerous seborrheic keratoses in association with a malignant tumor. Although many reports have appeared in recent years concerning this sign and although its existence is accepted, it is not always easy to decide which cases should be included. In some instances, numerous seborrheic keratoses develop on inflamed skin, but this does not represent the Leser-Trélat sign (92). A review of 40 cases that were accepted as representing the Leser-Trélat sign (110) showed that 30% had "malignant" acanthosis nigricans (see Chapter 17) either accompanying (111) or following the sign (112). Thus the Leser-Trélat sign has been interpreted as "an incomplete form of acanthosis nigricans" (113) or as "potentially representing an early stage of acanthosis nigricans" (112).

Although the malignant tumor in 67% of the reported cases consisted of an abdominal adenocarcinoma (110,114), the remaining 33% included many different types of malignancies, including leukemia (115) and mycosis fungoides (116). More controversially, a case–control study failed to demonstrate a specific association between eruptive seborrheic keratoses and internal cancer risk (117).

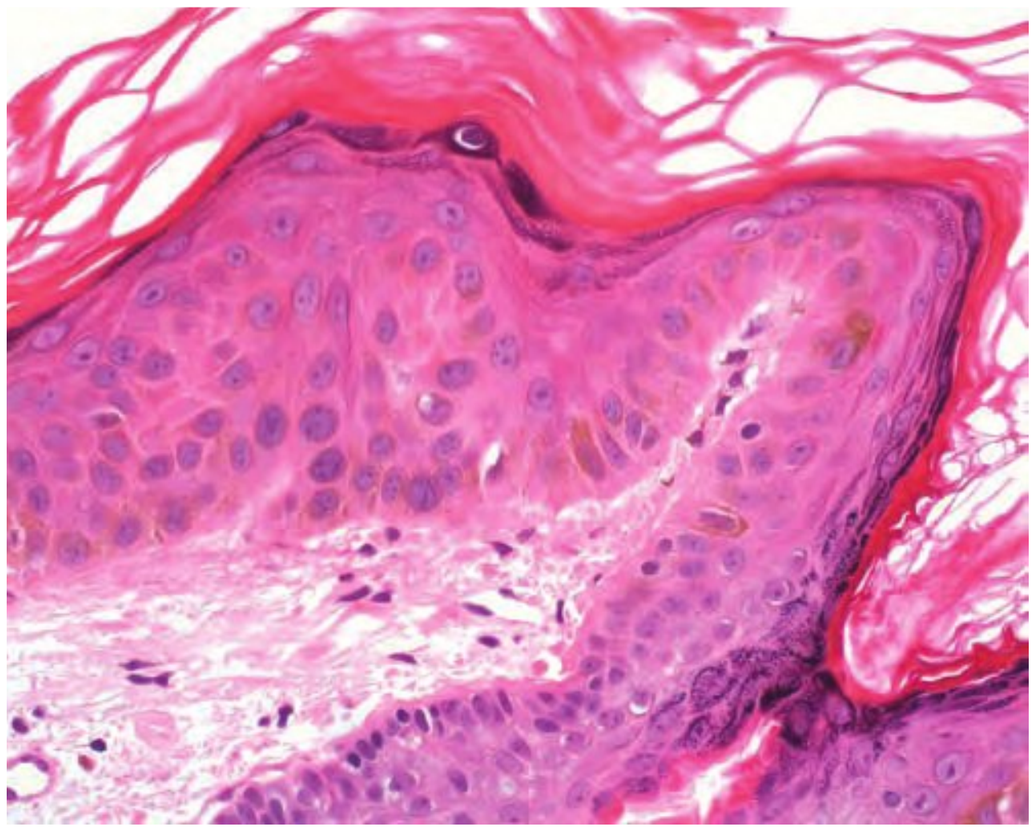


FIGURE 29-15. Large cell acanthoma. Keratinocytes are increased in size and arranged in a disorderly manner.

Histopathology. The seborrheic keratoses in the Leser-Trélat sign are the same as other seborrheic keratoses. The hyperkeratotic form is indistinguishable from malignant acanthosis nigricans (110,118).

LARGE CELL ACANTHOMA

Large cell acanthoma occurs as a slightly hyperkeratotic, sharply demarcated patch, usually on sun-exposed skin of the head or extremities. As a rule, it measures less than 1 cm in size. Generally, it is a solitary lesion; occasionally multiple lesions are observed (119–121).

Histopathology. Within a well-demarcated area of the epidermis, the scattered large keratinocytes are about twice the normal size and have proportionally large nuclei. There may be a disordered arrangement of the keratinocytes (Fig. 29-15).

Pathogenesis. The lesion is aneuploid, with various stages of development, and is probably related to stucco keratosis (119,121).

CLEAR CELL ACANTHOMA

Clear cell acanthoma, a tumor that is clinically and histologically quite distinct, was first described in 1962 (122). It is not rare. Typically the lesions are solitary and occur on the legs. They are slowly growing, sharply delineated, red nodules or plaques 1 to 2 cm in diameter and usually covered with a thin crust and exuding some moisture. A collarette is often seen at the periphery. It has been said that the lesion appears stuck on, like a seborrheic keratosis, and is vascular, like a granuloma pyogenicum (Fig. 29-16) (123,124).



FIGURE 29-16. Clear cell acanthoma. A raised, sharply demarcated patch.

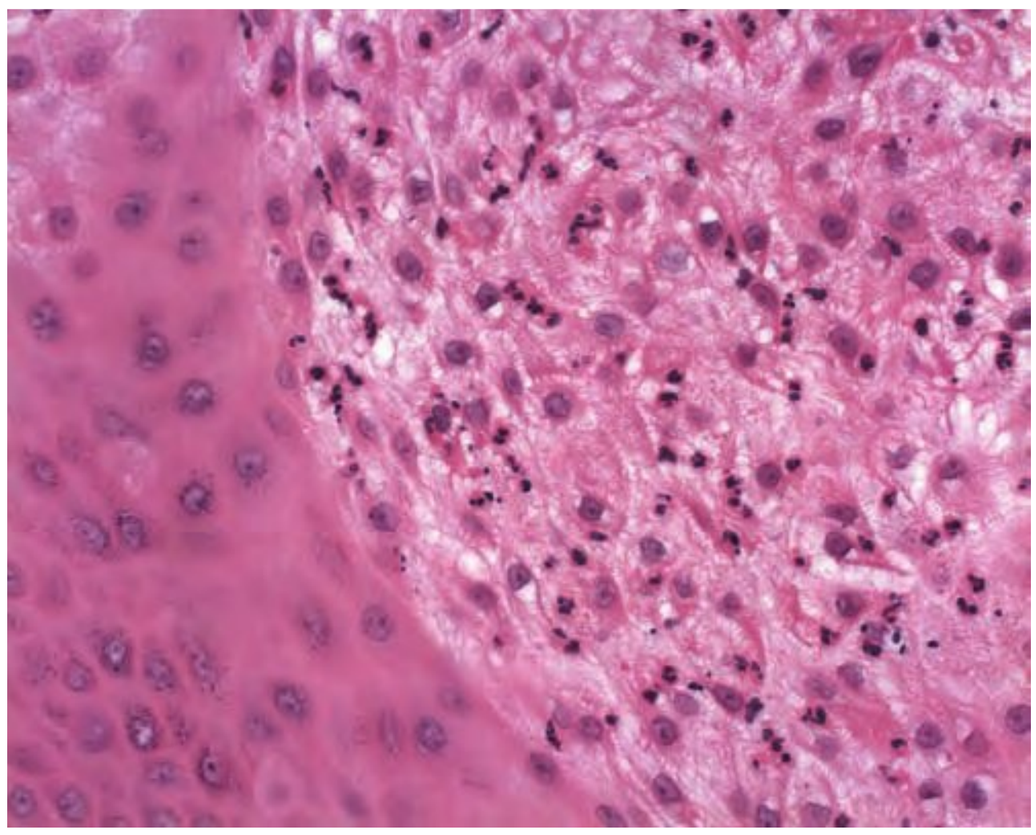


FIGURE 29-18. Clear cell acanthoma. High magnification. Neutrophils and nuclear dust are scattered through the clear cells of the lesion.

Histopathology. Within a sharply demarcated area of the epidermis, all epidermal cells, with the exception of cells of the basal cell layer, appear strikingly clear and slightly enlarged (Figs. 29-17 and 29-18). The nuclei of the clear epidermal cells appear normal. When staining is carried out with the periodic acid-Schiff (PAS) reaction, the presence of large amounts of glycogen is revealed within the cells (122,125).

Slight spongiosis is present between the clear cells. The rete ridges are elongated and may show intertwining (126). The surface shows parakeratosis with few or no granular cells. The acrosyringia and acrotrichia within the tumor retain their normal stainability (125). There is an absence of melanin within the tumor cells, but dendritic melanocytes containing melanin are occasionally seen interspersed between the clear cells (125,128).

A conspicuous feature in most lesions is the presence throughout the epidermis of numerous neutrophils, many of which show fragmentation of their nuclei (Fig. 29-18). The neutrophils often form microabscesses in the parakeratotic horny layer (129,130). Dilated capillaries are seen in the elongated papillae and often also in the dermis underlying the tumor (125). In addition, a mild to moderately severe cellular infiltrate composed largely of lymphoid cells is present in the dermis. Some clear cell acanthomas appear papillomatous, so that they have the configuration of a seborrheic keratosis (131).

Beneath the tumor, some cases have shown hyperplasia of sweat ducts (129) or syringoma-like proliferations (132).

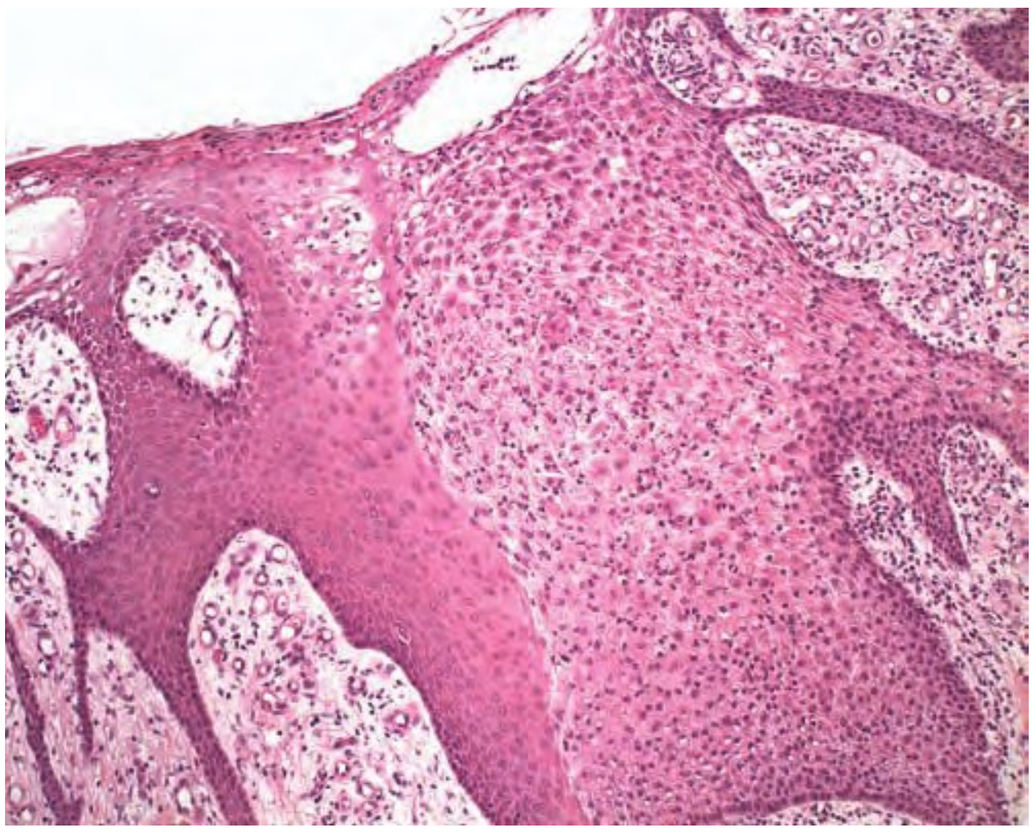


FIGURE 29-17. Clear cell acanthoma. The cells within the lesion appear pale by comparison with the adjacent normal epidermis.

Pathogenesis. On histochemical examination, phosphorylase is absent in clear cell acanthoma except for the basal cell layer. This enzyme normally is present in the epidermis and is necessary for the degradation of glycogen (133).

Electron microscopy reveals glycogen granules in the tumor cells, except in the cells of the basal cell layer. In the lower portion of the tumor, the glycogen granules are seen largely around the nuclei. In the upper portion, however, the amount of glycogen is increased, and the granules are seen to infiltrate between the tonofilaments (133).

Although the melanocytes, including their dendrites, contain melanosomes, hardly any melanosomes are present within the tumor cells, indicating a blockage in the transfer of melanosomes from the melanocytes to the tumor cells (134).

EPIDERMAL OR INFUNDIBULAR CYST

Epidermal cysts are slowly growing, elevated, round, firm, intradermal or subcutaneous tumors that cease growing after



FIGURE 29-19. Epidermal cyst. The cyst distends the overlying skin of the cheek.

having reached 1 to 5 cm in diameter. They occur most commonly on the face, scalp, neck, and trunk (Fig. 29-19). Although most epidermal cysts arise spontaneously in hair-bearing areas, occasionally they occur on the palms or soles (135,136) or form as the result of trauma (137). Usually a patient has only one or a few epidermal cysts, rarely many. In Gardner's syndrome, however, numerous epidermal cysts occur, especially on the scalp and face (see Chapter 32).

Histopathology. Epidermal cysts have a wall composed of true epidermis, as seen on the skin surface and in the infundibulum of hair follicles, the infundibulum being the uppermost part of the hair follicle that extends down to the entry of the sebaceous duct. In young epidermal cysts, several layers of squamous and granular cells can usually be recognized (Fig. 29-20). In older epidermal cysts, the wall often is markedly atrophic, either in some areas or in the entire cyst, and may consist of only one or two

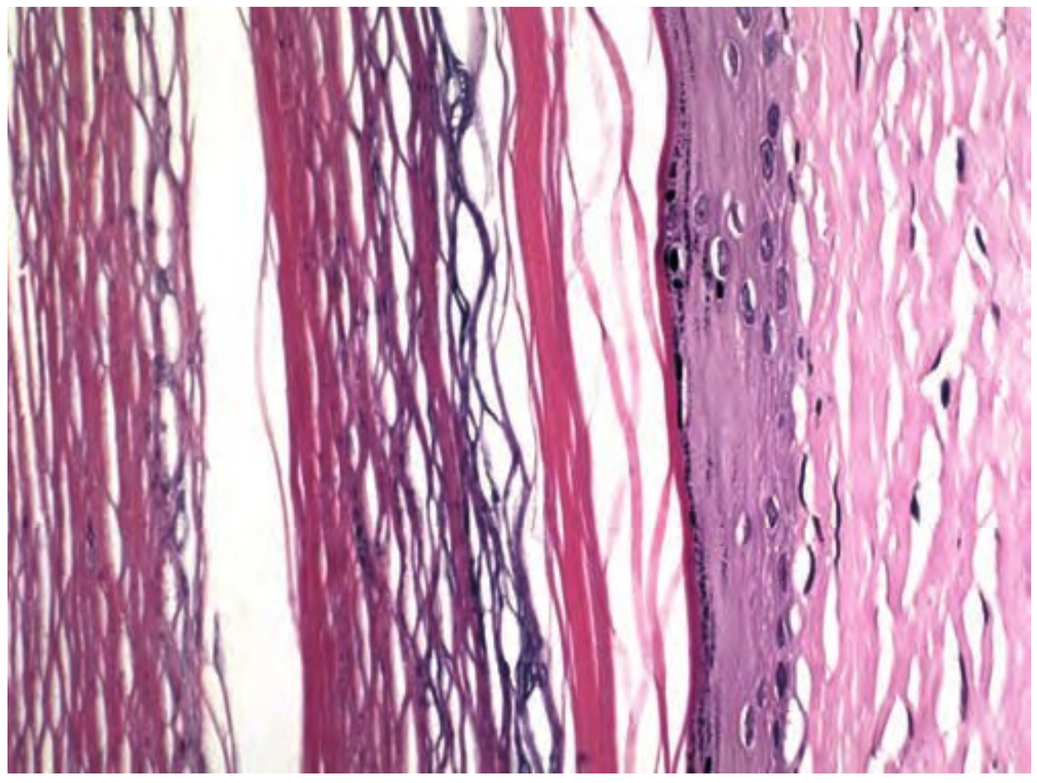


FIGURE 29-20. Epidermal cyst. The cyst is lined by stratified squamous epithelium with a granular layer. The cyst is filled with keratin flakes.

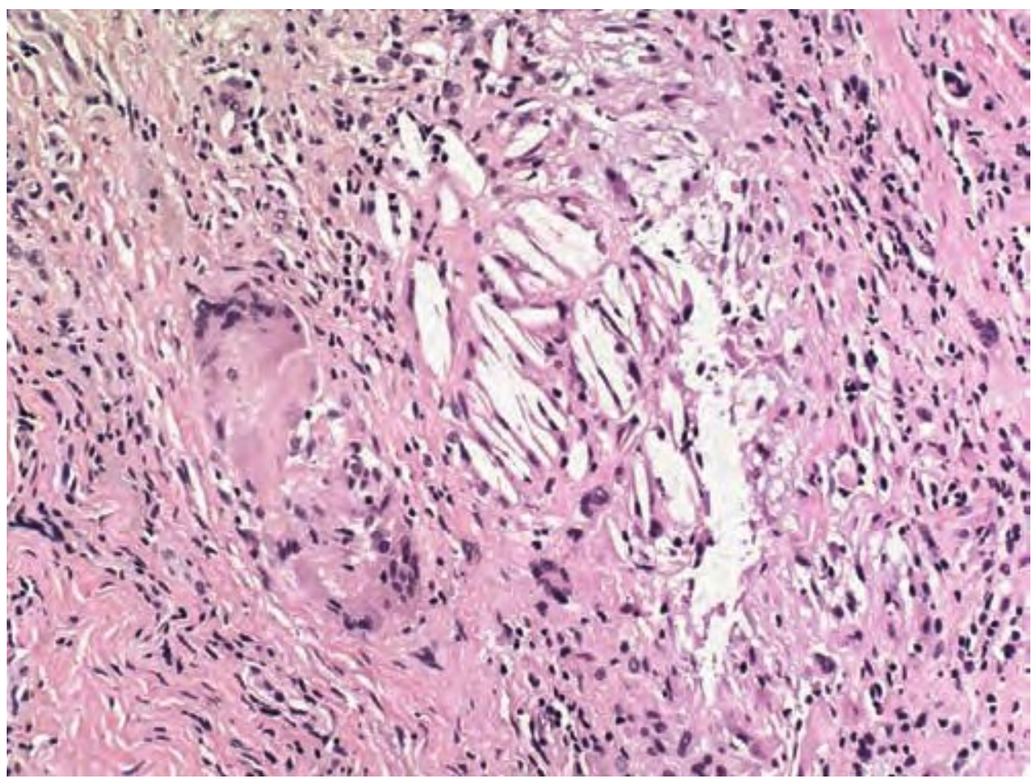


FIGURE 29-21. Keratin granuloma. At the edge of a partially ruptured cyst, cholesterol clefts form part of a keratin granuloma.

rows of greatly flattened cells. The cyst is filled with horny material arranged in laminated layers. In sections stained with hematoxylin-eosin, melanocytes and melanin pigmentation of keratinocytes can be seen only rarely in epidermal cysts of whites but frequently in epidermal cysts of blacks. Silver stains reveal that most of the melanin is located in the basal layer of the cyst lining, but some melanin is seen also in the contents of the cyst (138).

When an epidermal cyst ruptures and the contents of the cyst are released into the dermis, a considerable foreign-body reaction with numerous multinucleated giant cells results, forming a *keratin granuloma* (Figs. 29-21 and 29-22). The foreign-body reaction usually causes disintegration of the cyst wall. However, it may lead to a pseudocarcinomatous proliferation in remnants of the cyst wall, simulating a squamous cell carcinoma (139). Melanocytes, melanin, and melanophages

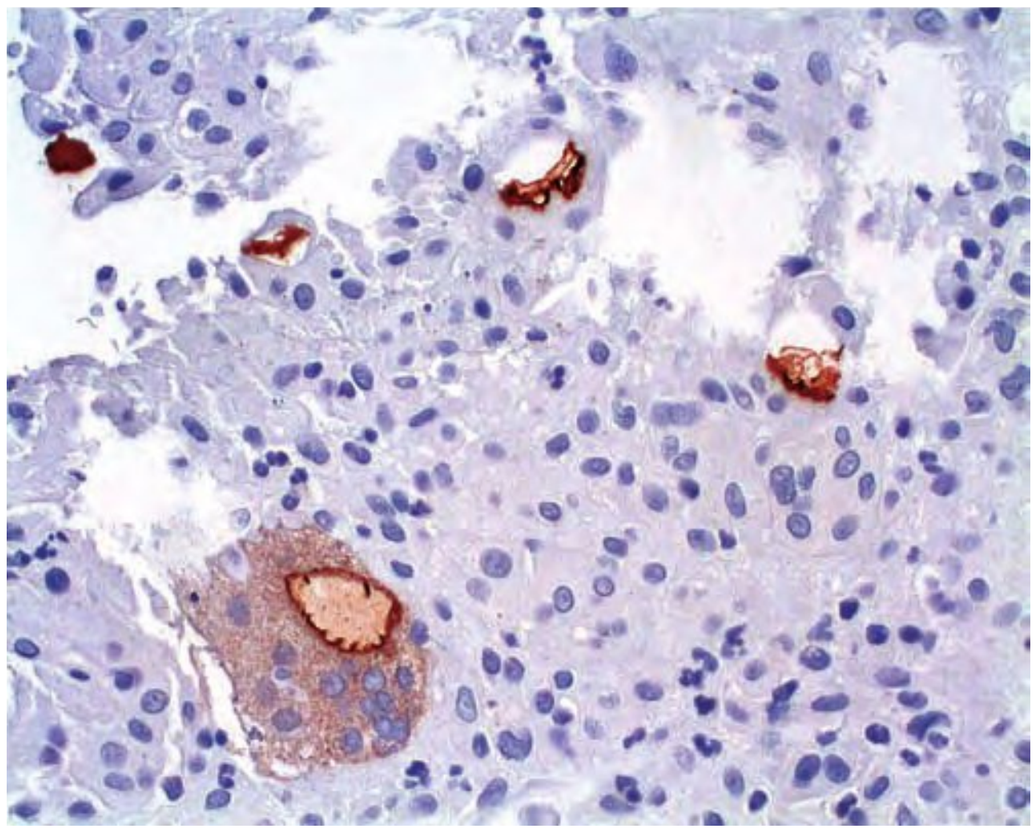


FIGURE 29-22. Keratin granuloma. Cytokeratin staining highlights keratin flakes in giant cells within a keratin granuloma.

have been reported in the walls of epidermal cysts in some Indians (140) and a Japanese patient (141).

Development of a basal cell epithelioma (142), a lesion of Bowen's disease (143), or a squamous cell carcinoma (144) in epidermal cysts is a rare event. In cases of squamous cell carcinoma, the tumor is apt to be of low malignancy and does not metastasize. It is likely that some cases that were regarded in the past as malignant degeneration of epidermal cysts now are interpreted either as pseudocarcinomatous hyperplasia in a ruptured epidermal cyst (139) or as proliferating trichilemmal tumor (see Chapter 30) (145).

Pathogenesis. It is widely assumed that most spontaneously arising epidermal cysts are related to the follicular infundibulum. The occurrence of hybrid cysts with partially epidermal and partially trichilemmal lining favors this assumption (146). Epidermal cysts in nonfollicular regions, such as the palms or soles, probably form as a result of the traumatic implantation of epidermis into the dermis or subcutis (135,136).

As seen by electron microscopy, the keratinization in epidermal cysts is identical to that in the surface epidermis and in the pilosebaceous infundibulum because the keratin located within the keratinized cells consists of relatively electron-lucent tonofilaments embedded in an electron-dense interfilamentous substance derived from keratohyaline granules. The keratinized cells of the cyst content have a markedly flattened, elongated appearance and are surrounded by a thick marginal band rather than by a plasma membrane. Desmosomes are no longer present (147).

MILIA

Milia are multiple, superficially located, white, globoid, firm lesions generally only 1 to 2 mm in diameter. A distinction is made between primary milia, which arise spontaneously on the face in predisposed individuals, and secondary milia, which occur either in diseases associated with subepidermal bullae, such as bullous pemphigoid, dystrophic epidermolysis bullosa (148,149), and porphyria cutanea tarda, or after dermabrasion (150) and other trauma.

Histopathology. *Primary milia* of the face are derived from the lowest portion of the infundibulum of vellus hairs at about the level of the sebaceous duct. The milia often are still connected with the vellus hair follicle by an epithelial pedicle. Primary milia are small cysts differing from epidermal cysts only in size. They are lined by a stratified epithelium a few cell layers thick and contain concentric lamellae of keratin (150).

Secondary milia have the same histologic appearance as primary milia (150). They may develop from any epithelial structure and on serial sections may still show a connection to the parent structure, whether a hair follicle, sweat duct, sebaceous duct, or epidermis (151). Secondary milia that follow blistering arise in most instances from the eccrine sweat duct and very rarely from a hair follicle. In a certain percentage of cases, however, no connection is found with any skin appendage, suggesting that the milia have developed from aberrant epidermis (152). In milia derived from eccrine sweat ducts, the sweat ducts are frequently seen to enter the cyst wall at the bottom of the milium (150,152).



FIGURE 29-23. Pilar cyst. Clinically similar to an epidermal cyst, but more frequently seen on the scalp.

Pathogenesis. Primary milia of the face represent a keratinizing type of benign tumor (150). In contrast, secondary milia represent retention cysts caused by proliferative tendencies of the epithelium after injury (153).

PILAR OR TRICHILEMMAL CYST

Pilar or trichilemmal cysts are clinically indistinguishable from epidermal cysts but differ from them in frequency and distribution. They are less common than epidermal cysts, constituting only about 25% of the combined material; about 90% occur on the scalp (Fig. 29-23). Pilar cysts often show an autosomal dominant inheritance pattern and are solitary in only 30% of the cases, with 10% of patients having more than 10 cysts (154). Furthermore, in contrast to epidermal cysts, pilar cysts are easily enucleated and appear as firm, smooth, white-walled cysts (Fig. 29-24) (155).



FIGURE 29-24. Pilar cyst. The cyst has a well-defined margin, as seen at the time of excision.

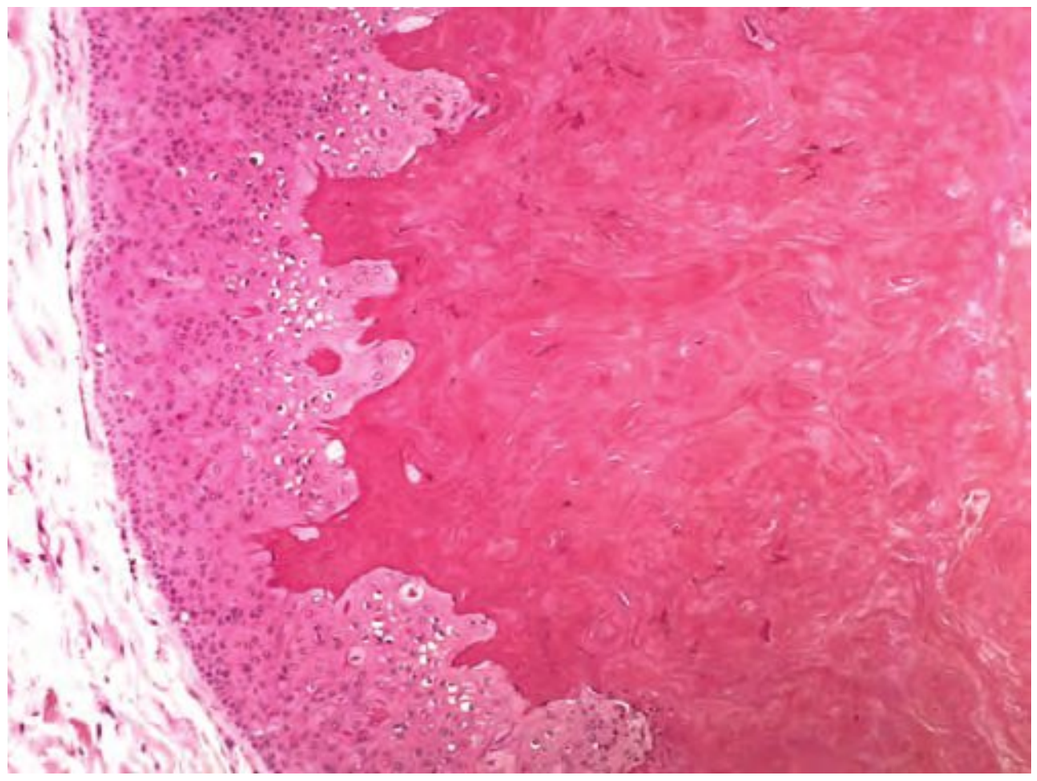


FIGURE 29-25. Pilar cyst. The cyst is lined by a squamous epithelium without a granular layer and with swelling of the cells close to the cyst cavity that is filled with homogeneous keratin.

Histopathology. The wall of trichilemmal cysts is composed of epithelial cells possessing no clearly visible intercellular bridges. The peripheral layer of cells shows a distinct palisade arrangement not seen in epidermal cysts. The epithelial cells close to the cystic cavity appear swollen and are filled with pale cytoplasm (Fig. 29-25). These swollen cells do not produce a granular layer but generally undergo abrupt keratinization, although nuclear remnants are occasionally retained in a few cells. The content of the cysts consists of homogeneous eosinophilic material (147).

Whereas focal calcification of the cyst content does not occur in epidermal cysts, foci of calcification are seen in approximately one fourth of trichilemmal cysts (140). A considerable foreign-body reaction results when the wall of a trichilemmal cyst ruptures, and the cyst may then undergo partial or complete disintegration.

Trichilemmal cysts frequently disclose small, acanthotic foci in their walls that are indistinguishable from solid areas, as seen in a proliferating trichilemmal cyst (156). The association of a trichilemmal cyst with tumor lobules of a proliferating trichilemmal cyst is also seen occasionally (see Chapter 30) (154).

Pathogenesis. Pilar cysts were originally called sebaceous cysts. The name was changed when it became apparent that the keratinization in them is analogous to the keratinization that takes place in the outer root sheath of the hair, or trichilemma (157). The outer root sheath of the hair does not keratinize wherever it covers the inner root sheath. It keratinizes normally in two areas—the follicular isthmus of anagen hairs and the sac surrounding catagen and telogen hairs—because in these two regions the inner root sheath has disappeared. The follicular isthmus of anagen hairs is the short, middle portion of the hair follicle, extending upward from the attachment of the arrector pili muscle to the entrance of the sebaceous duct. At the lower end of the follicular isthmus, the inner root sheath sloughs off, exposing the outer root sheath, which, in its exposed portion, undergoes a specific type of homogeneous keratinization without the interposition of a granular layer. This type of trichilemmal keratinization also takes place in the sac surrounding catagen and telogen hairs because hairs in these stages have lost their inner root sheath. The differentiation toward hair keratin in trichilemmal cysts has been confirmed by immunohistochemical staining because they stain with antikeratin antibodies derived from human hair, in contrast to epidermal cysts, which stain with antikeratin antibodies obtained from human callus (158).

Electron microscopic examination of the epithelial lining of trichilemmal cysts shows that, on their way from the peripheral layer toward the center, the epithelial cells have an increasing number of filaments in their cytoplasm. The transition from nucleate to anucleate cells is abrupt and is associated with the loss of all cytoplasmic organelles. The junction between the keratinizing and keratinized cells shows interdigitations (159). The keratinized cells are filled with tonofilaments and, unlike those in epidermal cysts, retain their desmosomal connections (147).

Differential Diagnosis. Even though both the pilar cyst and the proliferating trichilemmal cyst show trichilemmal types of keratinization and can occur together, one is essentially a cyst and the other essentially a solid, tumorlike proliferation. The latter is therefore discussed under Tumors With Differentiation Toward Hair Follicle Components in Chapter 30.

STEATOCYSTOMA MULTIPLEX

Steatocystoma multiplex is inherited in an autosomal dominant pattern. One observes numerous small, rounded, moderately firm, cystic nodules that are adherent to the overlying skin and usually measure 1 to 3 cm in diameter (Fig. 29-26). When punctured, the cysts discharge an oily or creamy fluid and, in some instances, also small hairs (160–163). They are found most commonly in the axillae, in the sternal region, and



FIGURE 29-26. Steatocystoma multiplex. Multiple small, rounded cysts are present in the axilla.

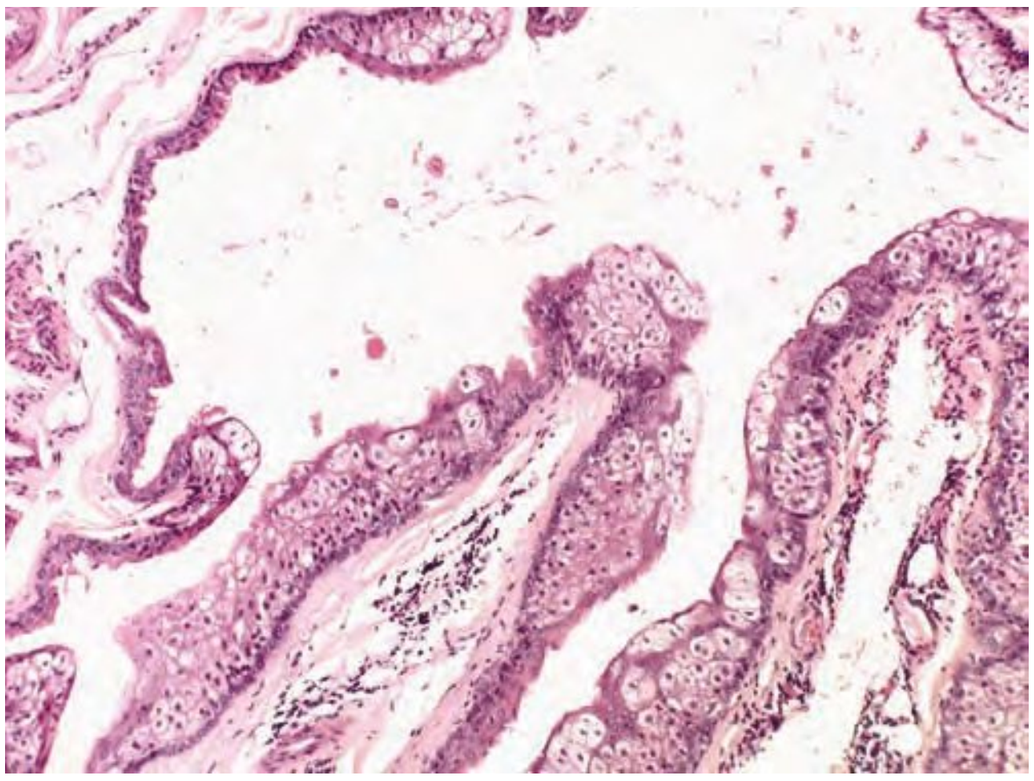


FIGURE 29-27. Steatocystoma multiplex. The cyst wall shows intricate folding. The lining stratified squamous epithelium has sebaceous gland lobules within and close to it.

on the arms. Steatocystoma also occurs occasionally as a solitary, noninherited tumor in adults, where it is referred to as *steatocystoma simplex* (164).

Histopathology. The cysts have walls that are intricately folded with several layers of epithelial cells, although in atrophic areas only two or three layers of flat cells may be present. Elsewhere there is a basal layer in palisade arrangement, above which are two or three layers of swollen cells without recognizable intercellular bridges. Central to these cells there is a thick, homogeneous, eosinophilic horny layer that forms without an intervening granular layer. It protrudes irregularly into the lumen in a fashion simulating the decapitation secretion of apocrine glands (Fig. 29-27) (165).

A characteristic feature seen in most lesions of steatocystoma is the presence of flattened sebaceous gland lobules either within or close to the cyst wall (166). In some cysts, invaginations resembling hair follicles extend from the cyst wall into the surrounding stroma, and in rare instances true hair shafts are seen within them, indicating that the invaginations represent the outer root sheath of hairs. In a few cysts, the lumen contains clusters of hair, mainly of lanugo size but partially of intermediate character (167). When stained with the PAS reaction, the cells of the cyst wall are found to be rich in glycogen.

Pathogenesis. Electron microscopic examination has shown that the cyst wall consists of keratinizing cells. Nearest to the lumen, the cyst wall consists of several layers of flattened, very elongated horny cells interconnected by desmosomes.

It appears likely that differentiation in the cyst wall of steatocystoma multiplex is to a large extent in the direction of the sebaceous duct (168,169). The sebaceous duct and the outer root sheath are composed of similar cells, but undulation and thinning of the horny layer and the existence of sebaceous cells in the cyst wall are characteristic features of the sebaceous gland side of the sebaceous duct (169). Sebaceous duct cells, like outer root sheath cells, contain abundant glycogen and amylophosphorylase, keratinize without the interposition of keratohyaline granules, and, on electron microscopic examination, retain their desmosomes after keratinization (165).

PIGMENTED FOLLICULAR CYST

This is an uncommon pigmented lesion resembling a nevus.

Histopathology. The cyst wall consists of infundibular epidermis. The cyst contains, in addition to laminated keratin, numerous large pigmented hair shafts. One or two growing hair follicles are seen in the wall of the cyst (170).

DERMOID CYST

Dermoid cysts are subcutaneous cysts that usually are present at birth. They occur most commonly on the head, mainly around the eyes, and occasionally on the neck. When located on the head, they often are adherent to the periosteum. Usually they measure between 1 and 4 cm in diameter.

Histopathology. Dermoid cysts, in contrast to epidermal cysts, are lined by an epidermis that possesses various epidermal appendages that are usually fully matured (Figs. 29-28 and 29-29). Hair follicles containing hairs that project into the lumen of the cyst are often present. In addition, the dermis of dermoid cysts usually contains sebaceous glands, often eccrine glands, and, in about 20% of the cases, apocrine glands that have matured (171).

Pathogenesis. Dermoid cysts are a result of the sequestration of skin along lines of embryonic closure.

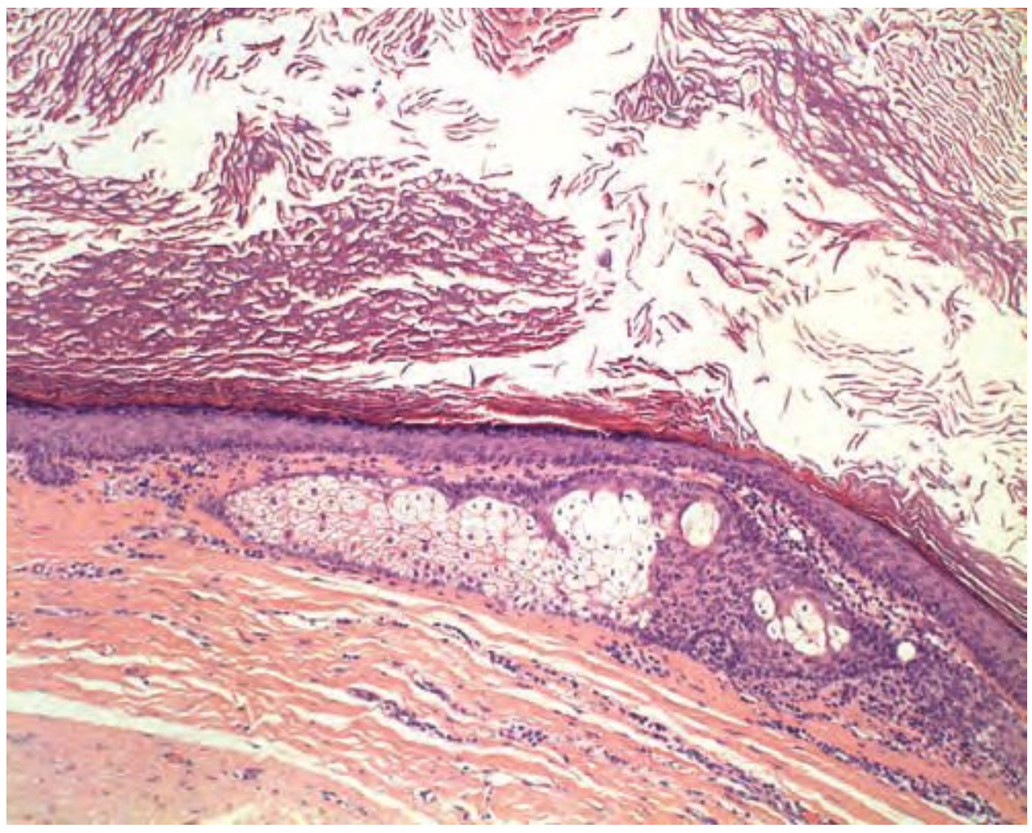


FIGURE 29-28. External angular dermoid cyst. The cyst is lined by stratified squamous epithelium, with adnexal structures in the wall.

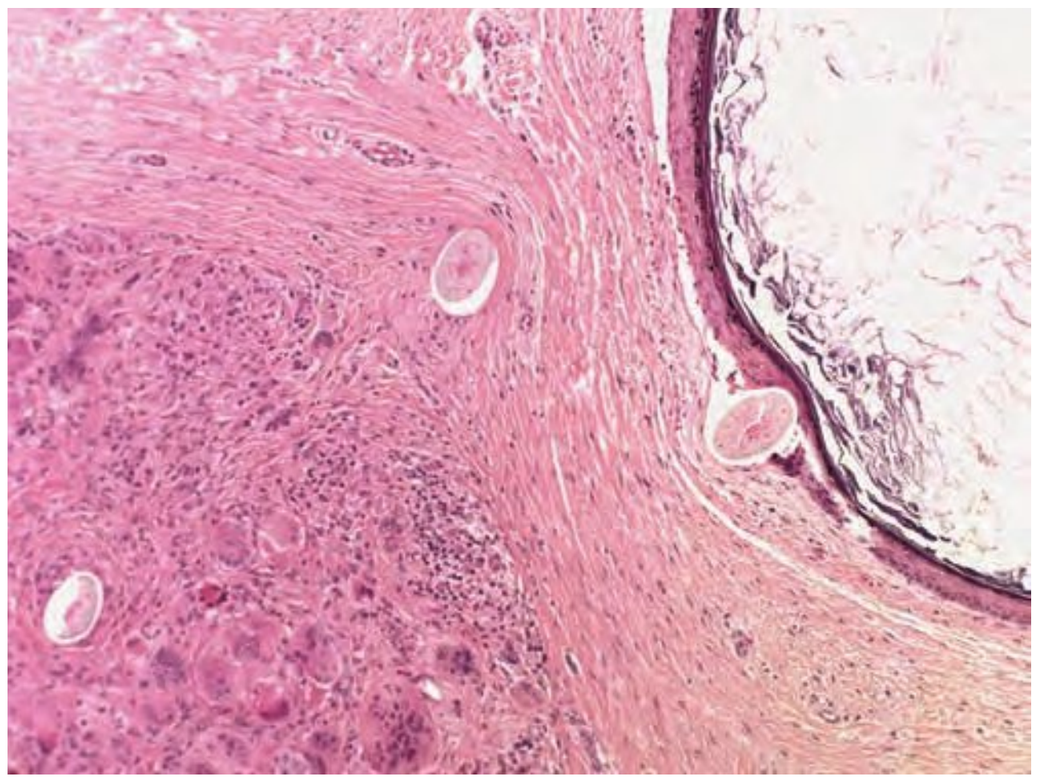


FIGURE 29-29. External angular dermoid cyst. In this example the cyst has ruptured, producing an adjacent granuloma containing hair shafts derived from the cyst.

BRONCHOGENIC AND THYROGLOSSAL DUCT CYSTS

Bronchogenic cysts are rare. They are small, solitary lesions seen most commonly in the skin or subcutaneous tissue just above the sternal notch. Rarely, they are located on the anterior aspect of the neck or on the chin. As a rule, they are discovered shortly after birth. They may show a draining sinus.

Thyroglossal duct cysts are clinically indistinguishable from bronchogenic cysts, except that they are usually located on the anterior aspect of the neck.

Histopathology. *Bronchogenic cysts* are lined by a mucosa consisting of ciliated pseudostratified columnar epithelium (Fig. 29-30). Goblet cells may be interspersed. The wall frequently contains smooth muscle and mucous glands but only rarely contains cartilage (153).

Thyroglossal duct cysts differ from bronchogenic cysts in that they do not contain smooth muscle and they frequently contain thyroid follicles (172).

Pathogenesis. On electron microscopy the cilia show two central microtubules surrounded by nine paired microtubules (173).

CUTANEOUS CILIATED CYST

Cutaneous ciliated cysts are found very rarely in females as a single lesion, largely on the lower extremities, and even more rarely in males and on the back (174–176,178). They usually measure several centimeters in diameter. They are either unilocular or multilocular and are filled with clear or amber fluid. The finding of one on the perineum led the authors to suggest a primitive tailgut origin to this cyst, probably from the embryonic remnants of cloacal membrane (177).

Histopathology. Cutaneous ciliated cysts show numerous papillary projections lined by a simple cuboidal or columnar ciliated epithelium. Mucin-secreting cells are absent (176).

Pathogenesis. The epithelial lining of the cysts resembles that seen in the fallopian tube. On electron microscopy, the cilia show two central filaments encircled by nine pairs of filaments (179).

MEDIAN RAPHE CYST OF THE PENIS

Median raphe cysts of the penis occur usually in young adults. They are located on the ventral aspect of the penis, most commonly on the glans. They are solitary and measure only a few millimeters in diameter (180). However, they may extend over several centimeters in a linear fashion (181). It seems that, in some instances, median raphe cysts have been erroneously reported as apocrine cystadenoma of the penis (Fig. 29-31; see also Chapter 31) (182,183).

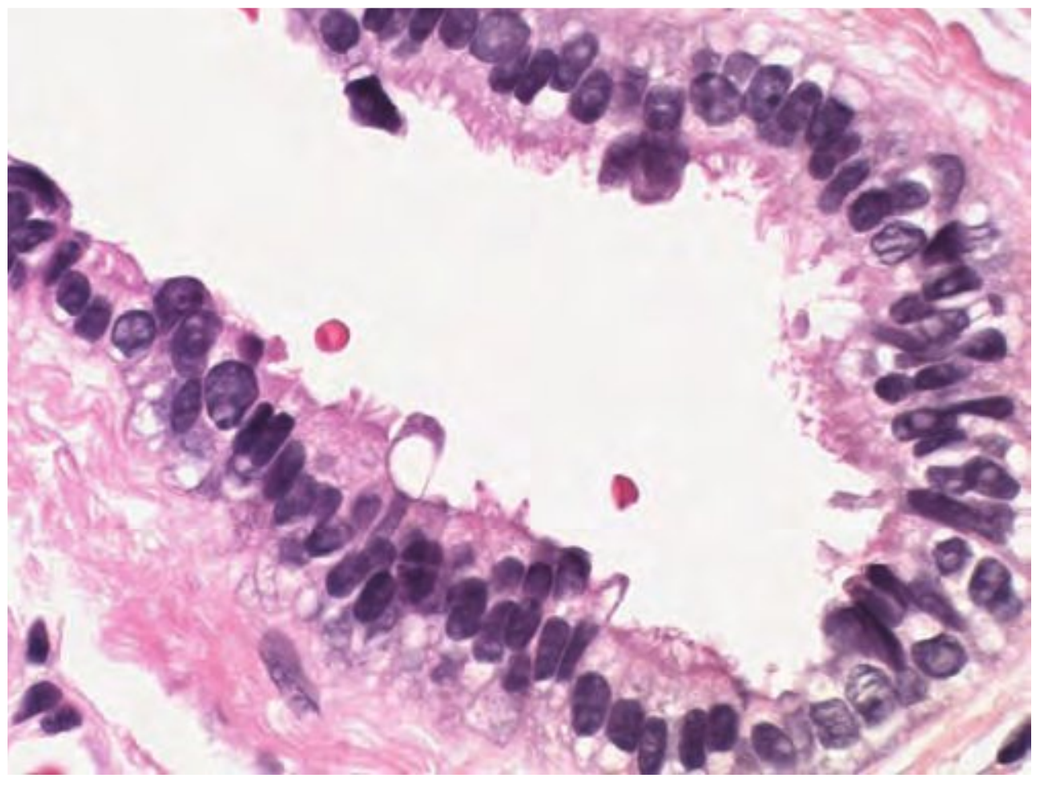


FIGURE 29-30. Bronchogenic cyst. High magnification. The lining epithelium is columnar, with a ciliated surface.



FIGURE 29-31. Apocrine cyst. In this small dermal cyst the lining epithelium forms a single layer with apocrine snouting secretion.

Histopathology. The cysts are lined by pseudostratified columnar epithelium varying from one to four cells in thickness, mimicking the transitional epithelium of the urethra. Some of the epithelial cells have clear cytoplasm, mucin-containing cells are uncommon, and a case lined by ciliated epithelium has been described (184).

Pathogenesis. It is likely that median raphe cysts do not represent a defective closure of the median raphe but rather the anomalous budding and separation of urethral columnar epithelium from the urethra (185).

ERUPTIVE VELLUS HAIR CYSTS

In eruptive vellus hair cysts, a condition first described in 1977 (186), asymptomatic follicular papules 1 to 2 mm in diameter occur, most commonly on the chest but in some instances elsewhere. Some of the papules have a crusted or umbilicated surface. The condition is usually seen in children and young adults but can develop at any age. Spontaneous clearing may take place in a few years. Autosomal dominant inheritance has been described (187,188). Cytokeratin studies have shown that epidermoid cysts expressed cytokeratin 10 and eruptive vellus hair cysts expressed cytokeratin 17, whereas trichilemmal cysts and steatocystoma multiplex showed expression of both cytokeratin 10 and cytokeratin 17, supporting the opinion that eruptive vellus hair cysts, which stained negative for cytokeratin 10, and steatocystoma multiplex are distinct entities and not variants of one disorder (189).

Histopathology. A cystic structure is usually seen in the middermis lined by squamous epithelium. It contains laminated keratinous material and varying numbers of transversely and obliquely cut vellus hairs (186). In some cysts, vellus hairs are seen emerging from follicle-like invaginations of the cyst wall (190). In other cysts, a telogen hair follicle is seen extending from the lower surface toward the subcutis (186). Crusted or umbilicated lesions show either a cyst communicating with the surface and extruding its contents (188,191) or partial destruction of a cyst by a granulomatous infiltrate and elimination of vellus hairs to the surface of the skin (192).

Pathogenesis. Eruptive vellus hair cysts represent a developmental abnormality of vellus hair follicles that predisposes them to occlusion at their infundibular level. This results in retention of hairs, cystic dilation of the proximal part of the follicle, and secondary atrophy of the hair bulbs (186,191). There is a close relationship with steatocystoma multiplex (193). Both processes could be described as multiple pilosebaceous cysts (194).

WARTY DYSKERATOMA

Warty dyskeratoma, first described in 1957 (195), usually occurs as a solitary lesion, most commonly on the scalp, face, or neck, although a case with multiple lesions has been described (196). It has also been reported in non–sun-exposed skin,

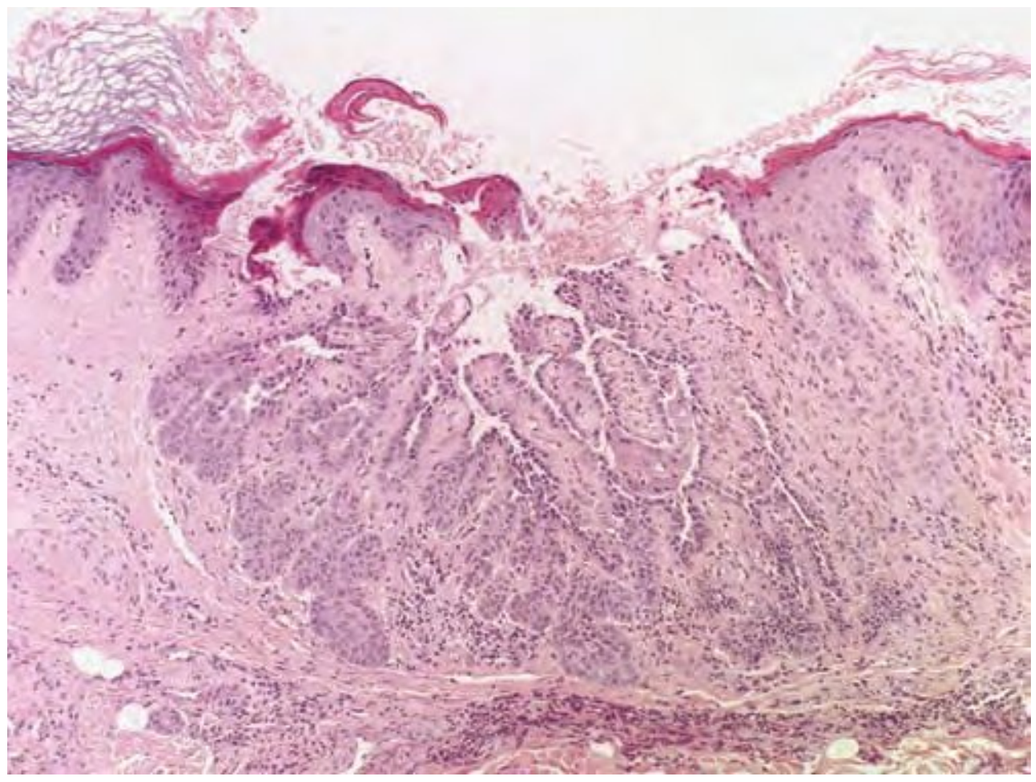


FIGURE 29-32. Warty dyskeratoma. Low magnification. A large invagination is connected to the surface by a channel.

including the oral mucosa, usually on the hard palate or an alveolar ridge (197,198). Although its clinical appearance is not always distinctive, it often occurs as a slightly elevated papule or nodule with a keratotic umbilicated center (199). The lesion, after having reached a certain size, persists indefinitely.

Histopathology. The center of the lesion is occupied by a large, cup-shaped invagination connected with the surface by a channel filled with keratinous material (Figs. 29-32 to 29-34). The large invagination contains numerous acantholytic, dyskeratotic cells in its upper portion. The lower portion of the invagination is occupied by numerous villi, that is, markedly elongated dermal papillae that are often lined with only a single layer of basal cells and project upward from the base of the cup-shaped invagination (Fig. 29-32) (195,200–202). Typical corps ronds can

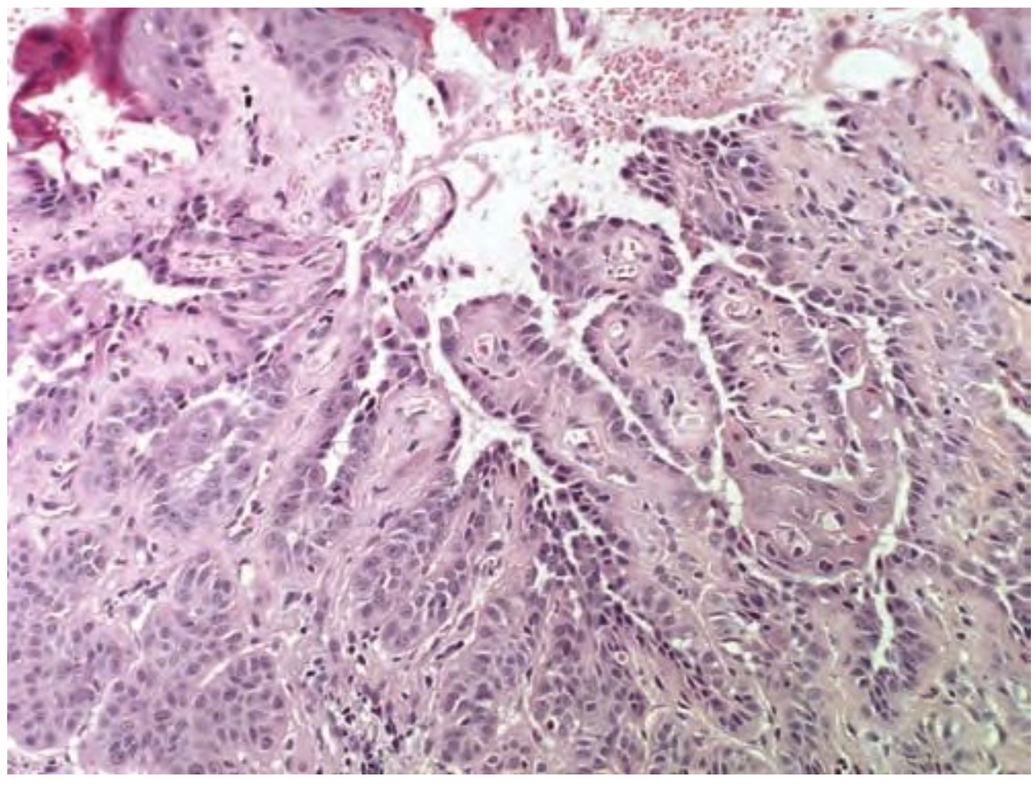


FIGURE 29-33. Warty dyskeratoma. The villi at the base of the invagination are covered with a single layer of cells. Acantholytic, dyskeratotic cells lie above the villi.

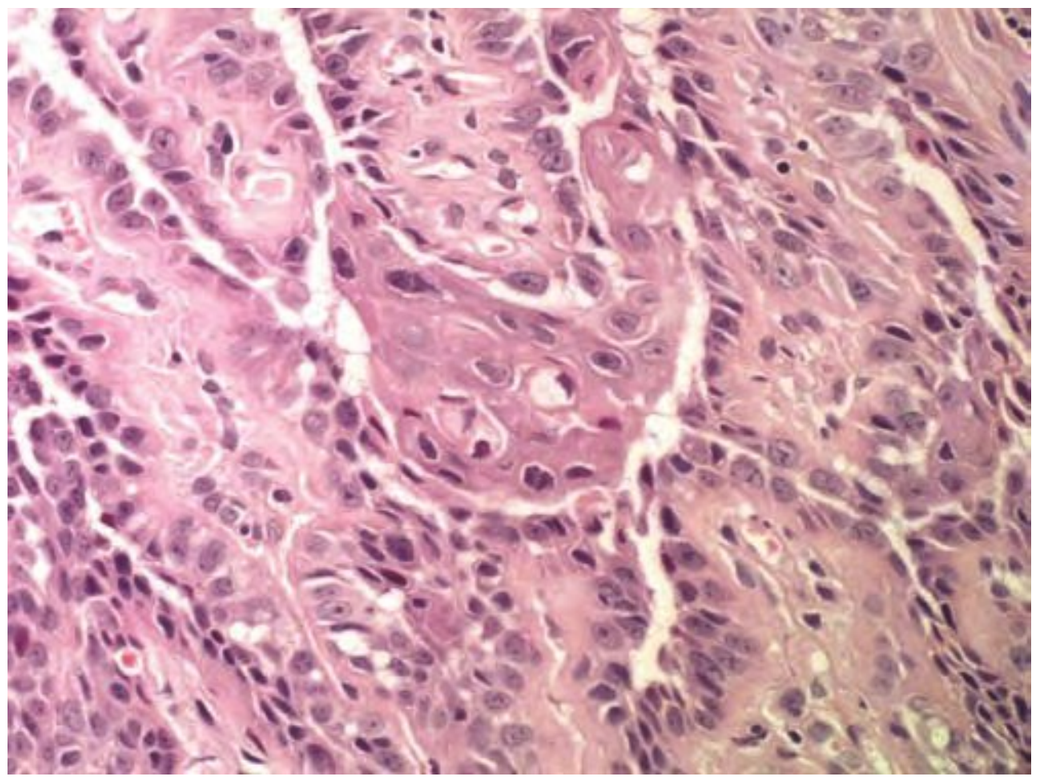


FIGURE 29-34. Warty dyskeratoma. High magnification. Acantholytic and dyskeratotic cells lie above the basal layer of epithelial cells.

usually be seen in the thickened granular layer lining the channel at the entrance to the invagination (Fig. 29-33) (199,203).

Pathogenesis. The central cup-shaped invagination has been interpreted by several observers as a greatly dilated hair follicle because in early lesions a hair follicle or sebaceous gland is often connected with the invagination (200). Occasionally, two or three adjoining follicles seem to be involved (199). The fact, however, that warty dyskeratoma can arise on the oral mucosa indicates that, as in Darier's disease, the dyskeratotic, acantholytic process is not always derived from a pilosebaceous structure.

Although attempts were made at first to correlate warty dyskeratoma with Darier's disease, it is now generally agreed that warty dyskeratoma represents an entity—"a benign cutaneous tumor that resembles Darier's disease microscopically" (195).

ACTINIC KERATOSIS

Solar keratoses are also known as actinic keratoses. The adjective *solar* is more specific because it refers to the sun as the cause, whereas the adjective *actinic* refers to a variety of rays (204). Even among the sun's rays, action spectrum evaluations indicate that the ultraviolet B (UVB) rays (290 to 320 nm) are the most damaging ("carcinogenic") rays, although UVA rays (320 to 400 nm) can augment the damaging effects of UVB rays (205).

Actinic keratoses are usually seen as multiple lesions in sun-exposed areas of the skin in persons in or past middle life who have fair complexions (Figs. 29-35 and 29-36). Excessive exposure to sunlight over many years and inadequate protection against it are the essential predisposing factors. Actinic keratoses are seen most commonly on the face and the dorsa of the hands and in the bald portions of the scalp in men (206).



FIGURE 29-35. Actinic keratosis. The lesion on the forehead is crusted and erythematous.

Usually, the lesions measure less than 1 cm in diameter. They are erythematous, are often covered by adherent scales, and, except in their hypertrophic form, show little or no infiltration. Some actinic keratoses are pigmented and show peripheral spreading, making clinical differentiation from lentigo maligna difficult (207). Occasionally, lesions show marked hyperkeratosis and then have the clinical aspect of cutaneous horns. A lesion analogous to actinic keratosis occurs on the vermilion border of the lower lip as *solar cheilitis* and may show areas of erosion and hyperkeratosis (208–210).

Actinic keratosis and solar cheilitis can develop into squamous cell carcinoma. However, the incidence of this transformation is difficult to determine because the borderline between actinic keratosis and squamous cell carcinoma is not clear-cut (see Histopathology). It has been estimated that in 20% of patients with actinic keratoses squamous cell carcinoma develops in one or more of the lesions (211). Usually, squamous cell carcinomas arising either in actinic keratoses or *de novo* in sun-damaged skin do not metastasize. The incidence of metastasis in different series varies from 0.5% (212) to 3%

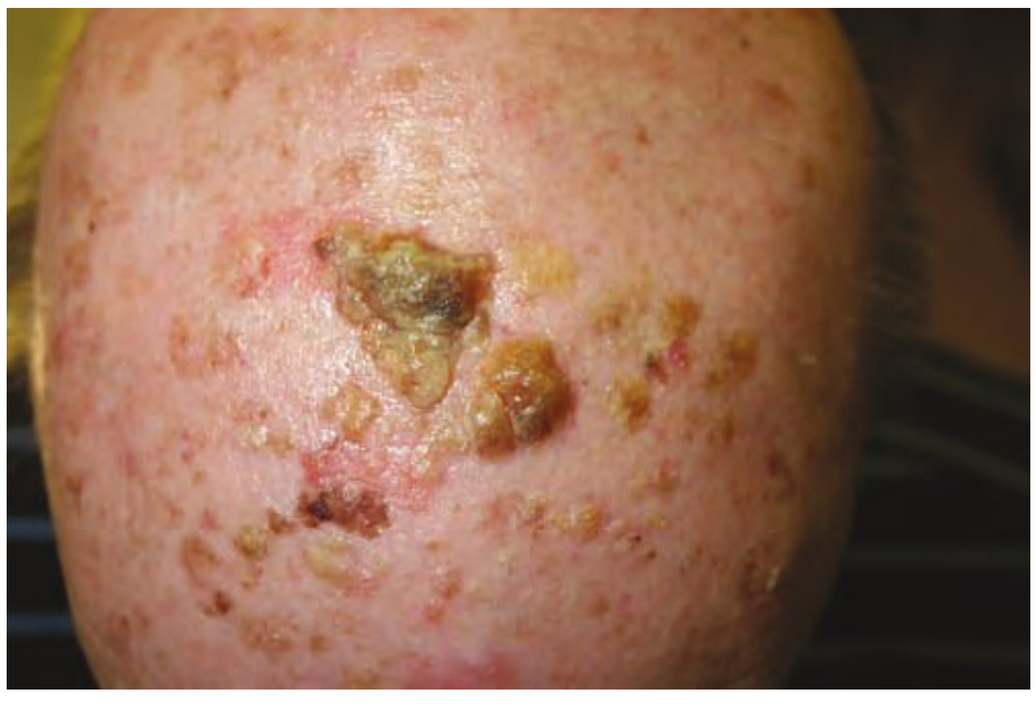


FIGURE 29-36. Actinic keratosis. Multiple lesions on this sun-damaged scalp.

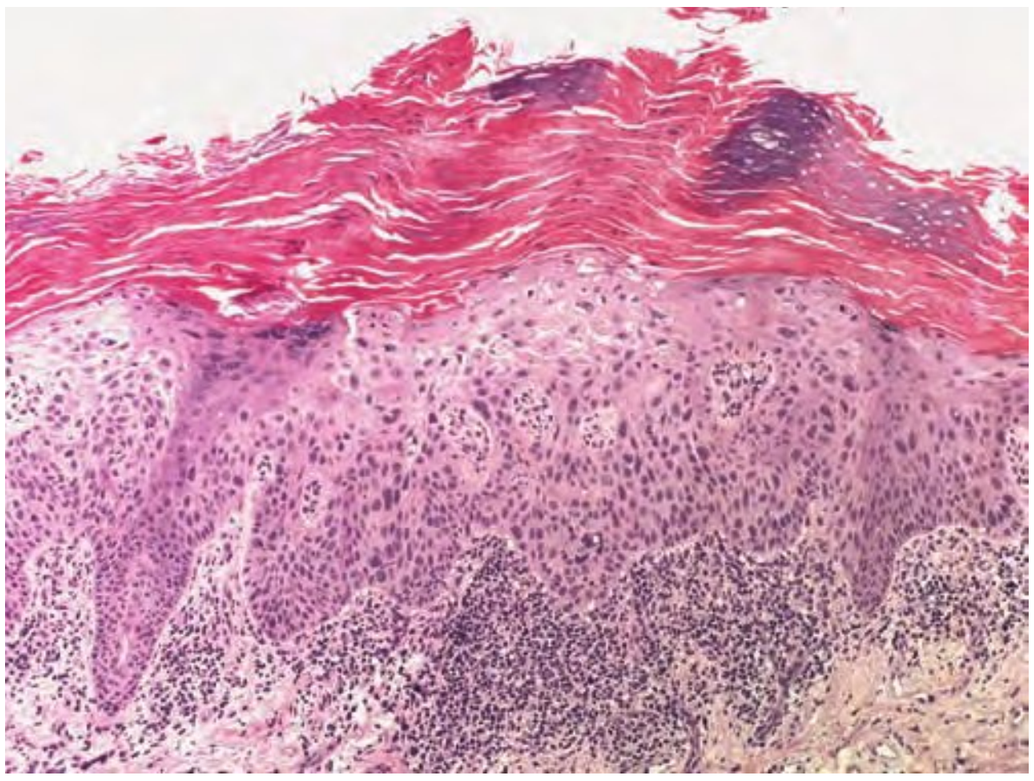


FIGURE 29-37. Actinic keratosis. Tall columns of parakeratotic keratin alternate with bands of orthokeratotic keratin with moderate atypia of the underlying keratinocytes.

(213). In carcinoma of the vermilion border of the lip, however, metastases have been found in 11% of the cases (213).

Histopathology. Actinic keratoses are keratinocytic dysplasias or squamous cell carcinomas *in situ*. This definition is preferable to their designation as precancerous because most of them never progress to cancers. Biologically, the lesions are still benign; invasion into the dermis, if present at all, is limited to the most superficial portion, the papillary dermis (see Differential Diagnosis) (214–227).

Five types of actinic keratosis can be recognized histologically: hypertrophic, atrophic, bowenoid, acantholytic, and pigmented (Figs. 29-37 to 29-46). Transitions and combinations among these five types occur. In addition, many cutaneous horns prove on histologic examination to be actinic keratoses.

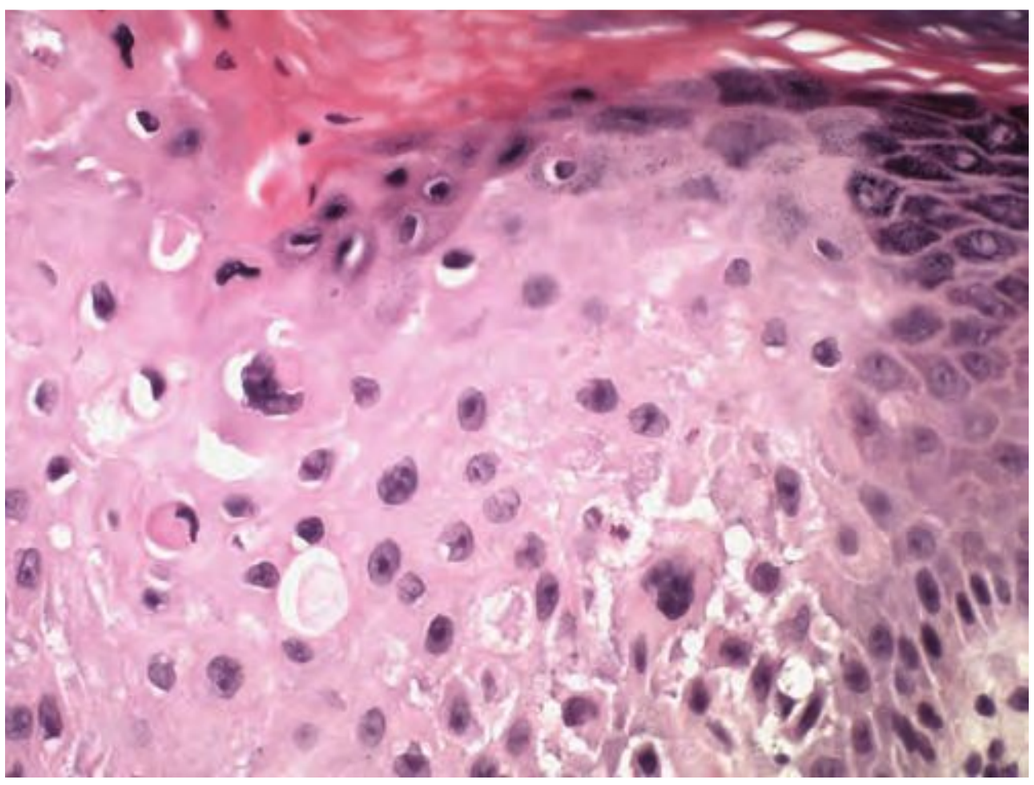


FIGURE 29-38. Actinic keratosis. Beneath a thick layer of parakeratotic keratin the epidermis shows cytologic atypia.

In the *hypertrophic type* of actinic keratosis, hyperkeratosis is pronounced and is usually intermingled with areas of parakeratosis (214). This variety of keratosis, sometimes referred to as *florid keratosis*, may easily be overdiagnosed as invasive squamous cell carcinoma by the unwary. Mild or moderate papillomatosis may be present. The epidermis is thickened in most areas and shows irregular downward proliferation that is limited to the uppermost dermis and does not represent frank invasion (Fig. 29-39). A varying proportion of the keratinocytes in the stratum malpighii show a loss of polarity and thus a disorderly arrangement. Some of these cells show pleomorphism and atypicality ("anaplasia") of their nuclei, which appear large, irregular, and hyperchromatic. Often the nuclei in the basal layer are closely crowded together. Some of the cells in the midportion of the epidermis show premature keratinization, resulting in dyskeratotic cells or apoptotic bodies characterized by homogeneous, eosinophilic cytoplasm with or without a nucleus. In contrast to the epidermal keratinocytes, the cells of the hair follicles and eccrine ducts that penetrate the epidermis within actinic keratoses retain their normal appearance and keratinize normally (215,216). Occasionally, cells of the normal adnexal epithelium extend over the atypical cells of the epidermis in an umbrella-like fashion. In some cases, abnormal keratinocytes extend downward on the outside of the follicular infundibulum to the level of the sebaceous duct and, less commonly, along the eccrine duct (216).

A variant of the hypertrophic type of actinic keratosis is the lichenoid actinic keratosis, which demonstrates nuclear atypia, irregular acanthosis and hyperkeratosis, the presence of basal cell liquefaction, degeneration of the basal cell layer, and a bandlike "lichenoid" infiltrate in close apposition to the epidermis (217). Fairly numerous eosinophilic, homogeneous apoptotic bodies are seen in the upper dermis as so-called Civatte bodies. Aside from the presence of nuclear atypicality,

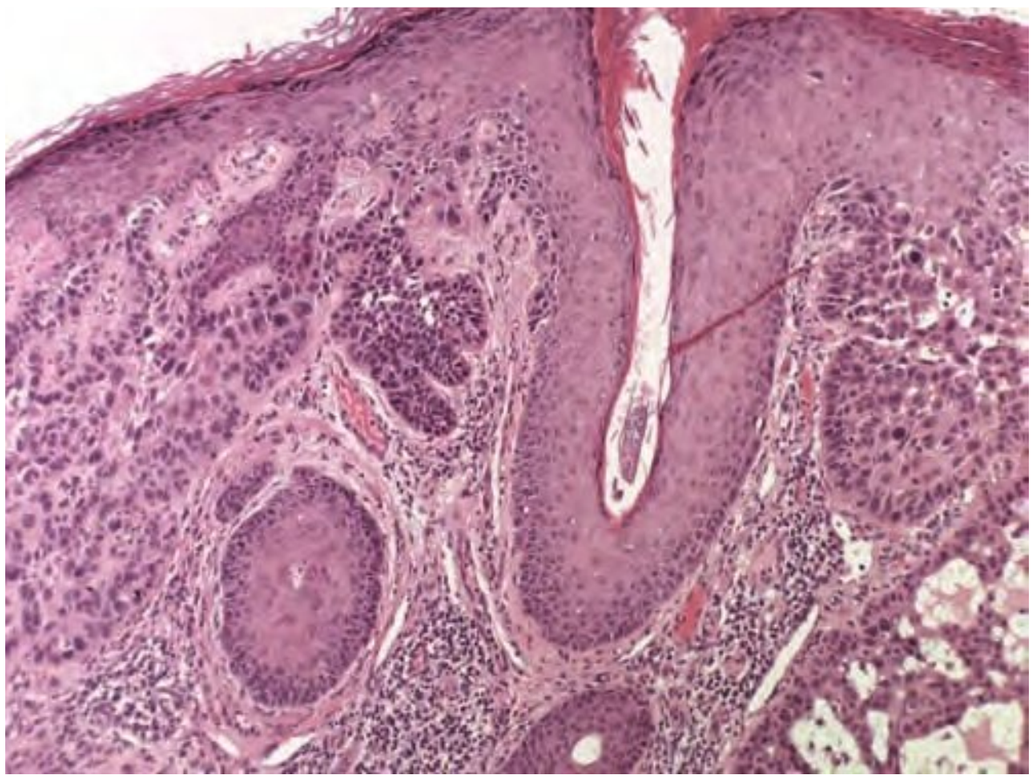


FIGURE 29-39. Actinic keratosis, hypertrophic type. The lesion shows hyperkeratosis and papillomatosis with prominent cytologic atypia. There is a moderate lymphocytic infiltrate in the underlying papillary dermis.



FIGURE 29-40. Bowenoid actinic keratosis. A crusted lesion on the ear helix.

there is considerable resemblance to lichen planus and benign lichenoid keratosis. An additional distinguishing feature may be the presence of plasma cells in the lichenoid infiltrate (see Chapter 7).

In rare instances of actinic keratosis of the hypertrophic type, in addition to finding anaplastic nuclei in the lower epidermis, one finds areas of epidermolytic hyperkeratosis in the upper epidermis. These changes are like those seen in bullous congenital ichthyosiform erythroderma, in linear epidermal nevus, and as incidental epidermolytic hyperkeratosis in a variety of lesions. In areas of epidermolytic hyperkeratosis, one observes in the upper epidermis clear spaces around the nuclei and a thickened granular layer with large, irregularly shaped keratohyaline granules (39). Epidermolytic hyperkeratosis may occur also in lesions of solar cheilitis (218).

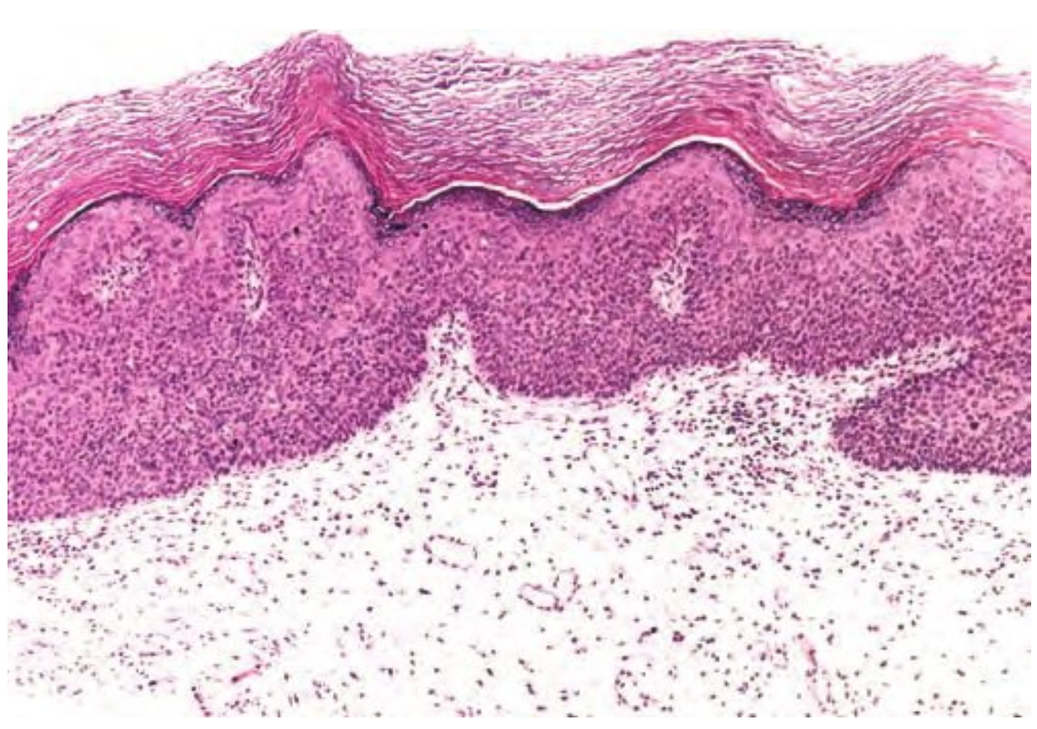


FIGURE 29-41. Bowenoid actinic keratosis. Low magnification. Beneath a thick layer of parakeratotic keratin the epidermis shows cytologic atypia.

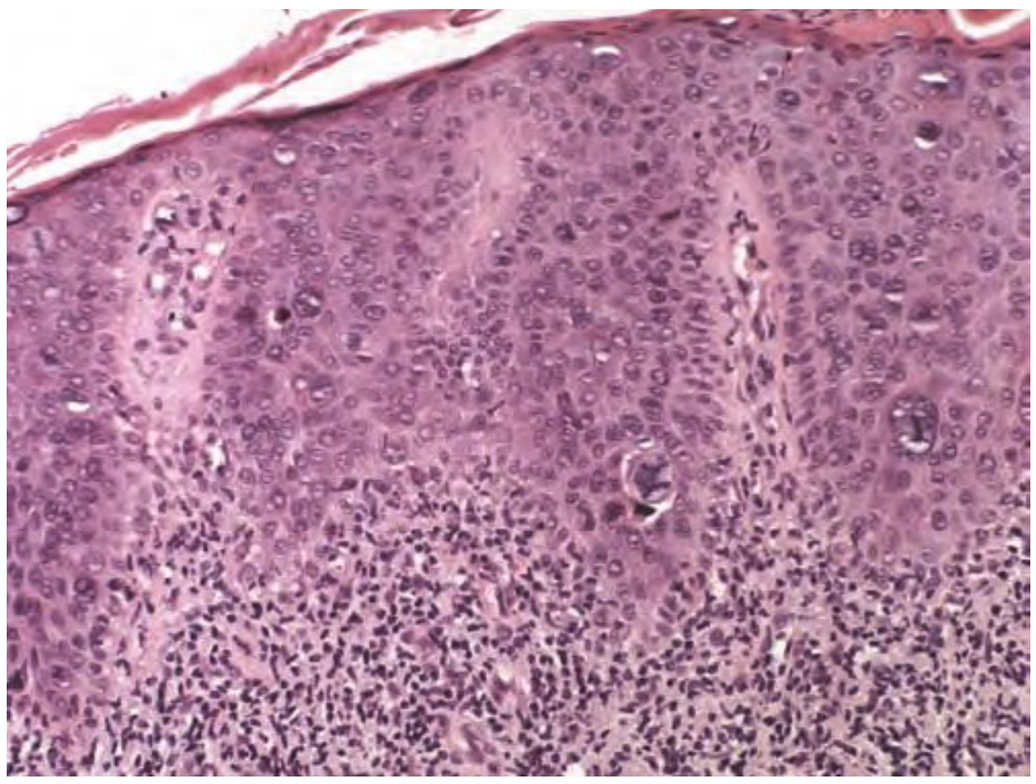


FIGURE 29-42. Bowenoid actinic keratosis. Medium magnification. Marked cellular and nuclear pleomorphisms are present together with frequent and atypical mitoses in a bowenoid actinic keratosis (squamous cell carcinoma in situ).

In the *atrophic type* of actinic keratosis, hyperkeratosis usually is slight. The epidermis is thinned and devoid of rete ridges. Atypicality of the cells is found predominantly in the basal cell layer, which consists of cells with large hyperchromatic nuclei that lie close together. The atypical basal layer may proliferate into the dermis as buds and ductlike structures. It may also surround as cell mantles the upper portion of pilosebaceous follicles and sweat ducts, the epithelium of which otherwise appears normal (196).

The *bowenoid type* of actinic keratosis is histologically indistinguishable from Bowen's disease and may also be referred to as squamous cell carcinoma *in situ*. As in Bowen's disease, within the epidermis there is considerable disorder in the arrangement of the nuclei, as well as clumping of nuclei and dyskeratosis (Figs. 29-40 to 29-43).

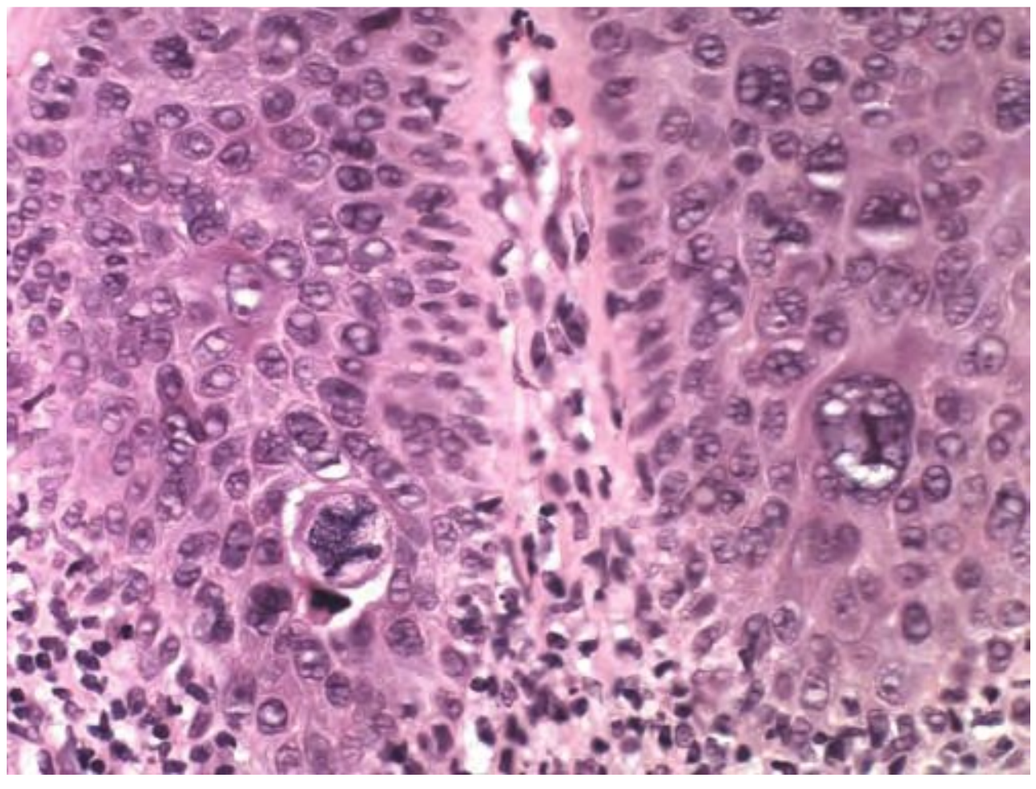


FIGURE 29-43. Bowenoid actinic keratosis. High magnification. Large atypical mitoses are prominent in this bowenoid actinic keratosis.

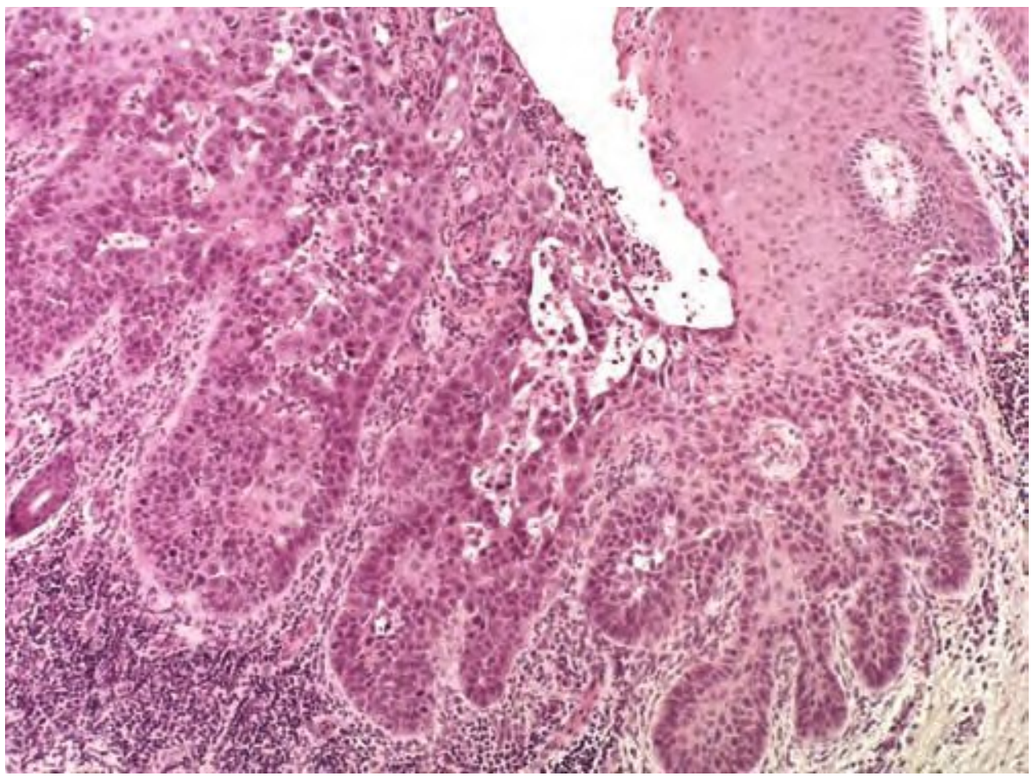


FIGURE 29-44. Actinic keratosis, acantholytic type. Low magnification. The epidermis is markedly hyperkeratotic. In the dermis, there is a dense, lichenoid inflammatory infiltrate. The keratosis shows focal acantholytic change.

In the *acantholytic type* of actinic keratosis, immediately above the atypical cells composing the basal cell layer there are clefts or lacunae similar to those seen in Darier's disease (see Chapter 6) (219). These clefts form as a result of anaplastic changes in the lowermost epidermis, resulting in dyskeratosis and loss of the intercellular bridges (Fig. 29-44). A few acantholytic cells may be present within the clefts (Fig. 29-45). Because the acantholysis is preceded by cellular changes, it is referred to as *secondary acantholysis*, in contrast to the primary acantholysis seen in the "acantholytic" diseases, such as pemphigus vulgaris and Darier's disease. Above the acantholytic clefts, the epidermis shows varying degrees of atypicality but generally less atypicality than is seen in the basal cell layer. The anaplastic cells of the basal cell layer frequently show extensions into the upper dermis as buds or short, ductlike structures. Suprabasal acantholysis may be seen also around hair follicles and sweat ducts in the upper dermis. When atypia is full thickness or high grade, the term *acantholytic squamous cell carcinoma in situ* may be applied.

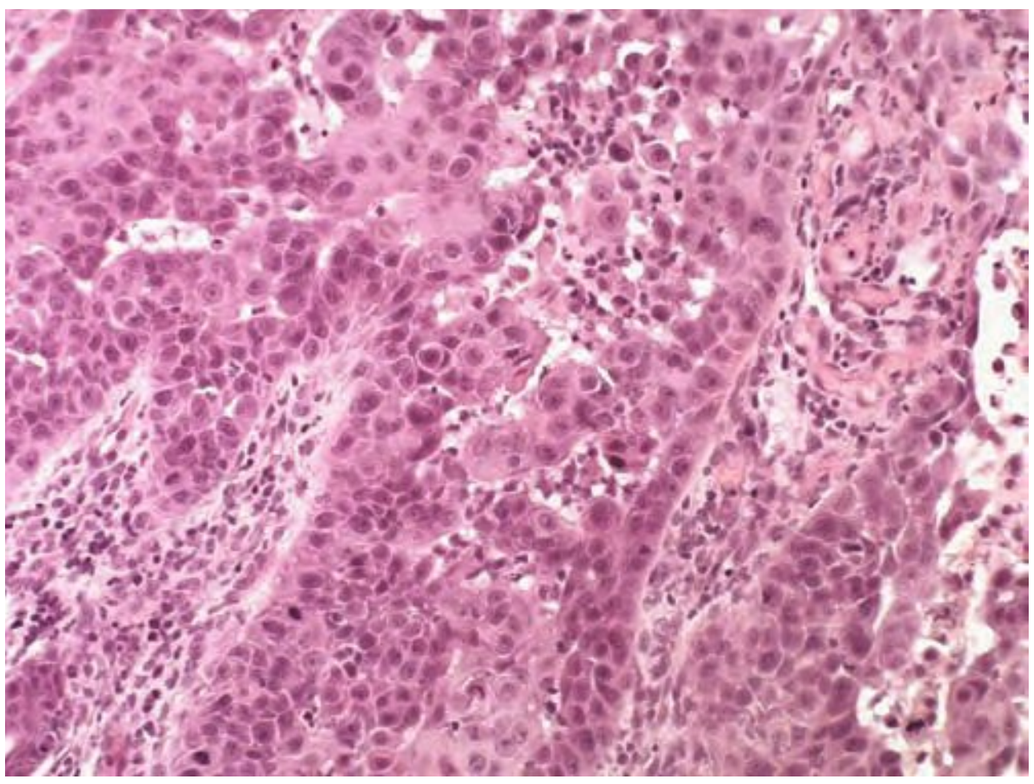


FIGURE 29-45. Actinic keratosis, acantholytic type. High magnification. Keratinocytes in the basal layer are crowded, with an increased nuclear–cytoplasmic ratio. They tend to become separated from one another and adopt a rounded configuration. This process of "secondary acantholysis" may in some instances result in the formation of pseudoglandular spaces that may mimic a glandular pattern of differentiation.

In the *pigmented type* of actinic keratosis, excessive amounts of melanin are present, especially in the basal cell layer. In some cases, the atypical keratinocytes are well melanized (220). In others, almost all of the melanin is retained within the cell bodies and dendrites of the melanocytes, indicating some block in melanin transfer. Numerous melanophages are seen in most cases in the superficial dermis (207).

In all five types of actinic keratosis, the upper dermis usually shows a fairly dense, chronic inflammatory infiltrate composed predominantly of lymphoid cells but often also containing plasma cells. Solar cheilitis, more frequently than actinic keratosis of the skin, shows an inflammatory infiltrate in which plasma cells predominate (208). Although the upper dermis usually shows solar or basophilic degeneration, this may be absent in areas with a pronounced inflammatory reaction, probably because the inflammation has resulted in a regeneration of collagen.

In instances in which the histologic diagnosis is actinic keratosis but the clinical diagnosis is squamous cell carcinoma, it is advisable to section more deeply into the block of tissue because progression into squamous cell carcinoma may have taken place in another area. Because no sharp line of demarcation exists between the two conditions, it is not always possible to decide whether a lesion can still be regarded as actinic keratosis or should be classified as early squamous cell carcinoma. Thus, some authors regard squamous cell carcinoma as a lesion in which irregular aggregates of atypical keratinocytes are found in the papillary dermis, not in continuity with the overlying epidermis (221). Others call a lesion that does not extend downward to the level of the reticular dermis an actinic keratosis without qualification (222). This decision is rarely a vital one because early squamous cell carcinoma arising in an actinic keratosis rarely causes metastases, although it may become deeply invasive and destructive through further growth. Because carcinomas arising in solar cheilitis have a significantly higher tendency to metastasize than carcinomas arising in actinic keratosis, and because invasion of the dermis in solar cheilitis may be focal, lesions of solar cheilitis require thorough examination by means of step sections (209).

Pathogenesis. On electron microscopic examination, only a difference in degree was found to exist between actinic keratosis and squamous cell carcinoma (223). With the use of blood group antigens as indicators of malignancy to sections of actinic keratosis, areas of positive staining alternate with areas showing no staining, the lack of staining being indicative of anaplasia. Areas of irregular downward proliferation or early invasion are consistently negative (224).

Differential Diagnosis. In actinic keratoses showing relatively slight atypicality, or anaplasia, of the tumor cells, diagnosis

may be difficult. Thus a hypertrophic actinic keratosis with a lichenoid inflammatory infiltrate may show a close histologic resemblance to the lesion known as *benign lichenoid keratosis*. In fact, this lesion was at one time believed to be a variant of actinic keratosis (225). Benign lichenoid keratosis differs from actinic keratosis by showing dissolution rather than atypicality of the basal cell layer, analogous to lichen planus (see Chapter 7) (226,227).

An atrophic actinic keratosis may closely resemble lupus erythematosus because both types of lesions show flattening of the epidermis. Although lupus erythematosus shows vacuolization and actinic keratosis shows atypicality of the cells in the basal layer, these two changes are not always easily distinguished from one another. Therefore, other findings, such as follicular plugging and a patchy, periappendageal infiltrate in lupus erythematosus, are necessary for differentiation (see Chapter 10).

A pigmented actinic keratosis may resemble lentigo maligna, particularly if the melanin is seen largely within the melanocytes (227). Usually, however, lentigo maligna shows more flattening of the epidermis than pigmented actinic keratosis and, more important, a great increase in the number of melanocytes, together with atypicality in the melanocytes but not in the basal keratinocytes (see Chapter 28).

CUTANEOUS HORN

Cutaneous horn, or *cornu cutaneum,* is the clinical term for a circumscribed, conical, markedly hyperkeratotic lesion in which the height of the keratotic mass amounts to at least half of its largest diameter (228) (Fig. 29-46). The term refers to a reaction pattern and not to a specific lesion (229).

Histopathology. On histologic examination, different types of lesions can be seen at the base of the conical hyperkeratosis of a cornu cutaneum. Most commonly, an actinic keratosis is



FIGURE 29-46. Cutaneous horn. The horn consists of a column of keratin arising on the sun-exposed skin of the ear.

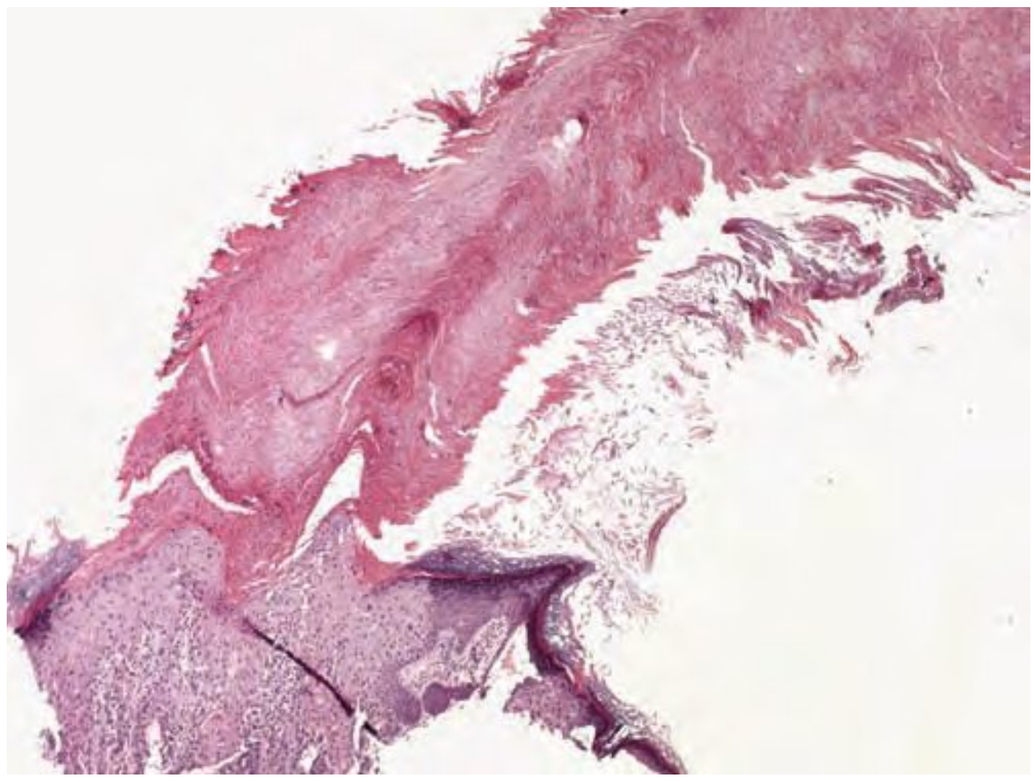


FIGURE 29-47. Cutaneous horn. The horn consists of a column of keratin arising in an actinic keratosis.

encountered (Fig. 29-47) (230). In some instances, a filiform verruca, a seborrheic keratosis, or a squamous cell carcinoma is found (228). On rare occasions, a trichilemmoma (229) or a basal cell epithelioma is seen (231). For a description of trichilemmal horn, see Chapter 30.

ORAL LEUKOPLAKIA

The term *leukoplakia* was used in the past by dermatologists and gynecologists (232) to designate white patches of the oral mucosa or the vulva that showed early, *in situ*, anaplastic changes; the term *leukokeratosis* was used for patches with a histologically benign appearance. However, leukoplakia has been redefined on the basis of the concept proposed by oral pathologists (233), and this concept has been accepted by the World Health Association (234).

According to this concept, the term *leukoplakia* carries no histologic connotation and is used only as a clinical description. It is defined as a white patch or plaque that will not rub off and that cannot be characterized clinically or histologically as any specific disease (e.g., lichen planus, lupus erythematosus, candidiasis, white sponge nevus) (235). The reason for using the term *leukoplakia* as a purely clinical designation is that a distinction between benign leukoplakia and leukoplakia with dysplastic changes cannot be made on clinical grounds. It is therefore essential that all white plaques that either are idiopathic in origin or persist for 3 to 4 weeks after any existing irritation has been eliminated be examined histologically (236). In many cases of oral leukoplakia, either chemical irritation through tobacco use or mechanical irritation through dental stumps or ill-fitting dentures plays a role. Although the leukoplakia clears in some instances after the irritation has been removed, it persists in others. However, the transformation of a benign leukoplakia into a malignant leukoplakia is regarded as rare (237). Still, any leukoplakia that is growing or altering its appearance requires a repeat biopsy (32).

Clinically, lesions of leukoplakia on the oral mucosa consist of one or several white patches that may not be raised and that appear ill defined. However, if they are slightly elevated, they appear sharply demarcated, with an irregular outline.

Erythroplakia of the oral mucosa consists of red, sharply delineated patches that vary greatly in size. Some of these lesions are sprinkled or intermingled with patches of leukoplakia and are then referred to as *speckled erythroplakia* (238).

On examination by histology, scraping, or culture, both leukoplakia and erythroplakia frequently show *Candida albicans* as a secondary invader, a finding that may give rise to an incorrect diagnosis of candidiasis (239). However, infection with *C. albicans* may cause oral lesions that are clinically indistinguishable from leukoplakia (240).

The analysis of oral leukoplakias and oral invasive carcinomas for human papillomavirus–related DNA has shown that a significant percentage of these lesions are reactive with papillomavirus antibodies, allowing the conclusion that they are induced by papillomaviruses, especially by HPV-11 and HPV-16 (see Chapter 25) (241,242).

For a discussion of leukoplakia of the vulva, see page 816, and of oral hairy leukoplakia, see Chapter 25.

Histopathology. The whiteness of leukoplakia is the result of hydration of a thickened horny layer. On histologic examination, about 80% of the lesions of oral leukoplakia are found to be benign (235,239). Such lesions show hyperkeratotic or parakeratotic thickening of the horny layer, acanthosis, and a chronic inflammatory infiltrate (Fig. 29-48). Of the remaining 20% of the cases, 17% show varying degrees of dysplasia or *in situ* carcinoma, and 3% show infiltrating squamous cell carcinoma (235). Ultimate development of carcinoma has been observed in 7% to 13% of all cases of leukoplakia (234). Localization of the leukoplakia seems to play an important role in the presence of malignancy. Leukoplakias on the buccal mucosa were found to be benign in 96% of the cases, whereas on the floor of the mouth, only 32% of the leukoplakias were benign, and 31% showed a carcinoma *in situ* and 37% an invasive carcinoma (243).

In situ carcinoma, also referred to as precancerous leukoplakia, may have a similar histologic appearance to the hypertrophic type of actinic keratosis. Thus the most important features observed within a moderately acanthotic epithelium are, first, pleomorphism and atypicality of the nuclei, which appear large, irregular, and hyperchromatic, and, second, loss of polarity, resulting in a disorderly arrangement of the cells. In some instances, one finds as additional features premature keratinization resulting in dyskeratotic cells in the midportion of the epithelium, crowding of nuclei in the basal cell layer, and irregular downward proliferations of the epithelium. There is considerable histologic, philosophical, and biological overlap among lesions categorized as high-grade dysplasia and carcinoma *in situ* in oral as in other mucous membranes.

Erythroplakia of the oral mucosa, in contrast to leukoplakia, invariably shows nuclear atypicality. One observes *in situ* carcinoma in half of the cases and invasive carcinoma in the other half (238). The red appearance is explained by the absence of the normal surface covering of orthokeratin or parakeratin.

Differential Diagnosis. A decision as to whether *in situ* carcinoma exists in a leukoplakia can be difficult because some pleomorphism of nuclei and some loss of polarity of the cells can be seen occasionally also in various inflammatory conditions, including benign leukoplakia (236). In cases of doubt, step sections throughout the biopsy specimen are required, as well as, possibly, examination of additional biopsy specimens. The decision as to whether a leukoplakia is benign or low grade or is a high-grade dysplasia or a carcinoma *in situ* is of great importance. In comparison with squamous cell carcinoma of the skin developing in an actinic keratosis, squamous cell carcinoma of the oral mucosa developing in a leukoplakia with *in situ* carcinoma has a much greater tendency to metastasize.

Differentiation of leukoplakia from oral lichen planus also may cause difficulties both clinically and histologically. In lichen planus no atypia is seen and there often is partial absence of basal cells. In addition, the prevalence of Langerhans cells in lesions of lichen planus may aid in the differentiation (244).

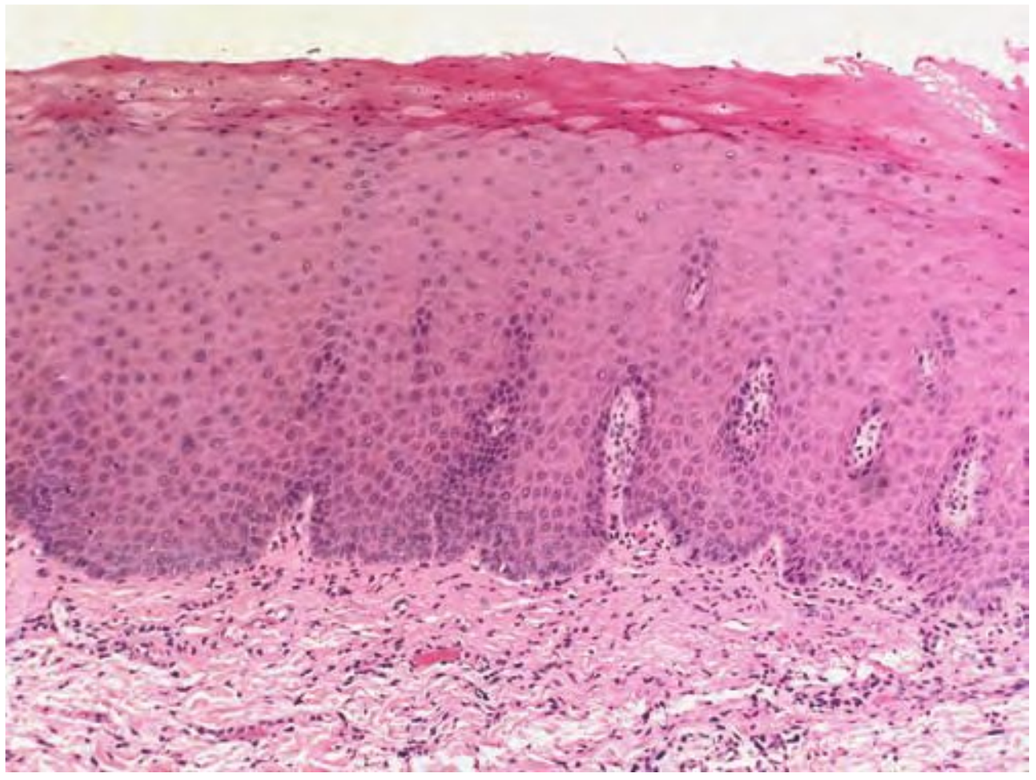


FIGURE 29-48. Oral leukoplakia. In this example the squamous epithelium is hyperkeratotic and acanthotic but shows no evidence of dysplasia.

VERRUCOUS HYPERPLASIA, VERRUCOUS CARCINOMA OF THE ORAL MUCOSA

Verrucous hyperplasia of the oral mucosa consists of extensive verrucous, white patches that may arise as such or develop from lesions of leukoplakia. Verrucous hyperplasia and verrucous carcinoma are indistinguishable clinically. They may coexist, or verrucous carcinoma may develop from verrucous hyperplasia. In some instances, verrucous hyperplasia develops into frank squamous cell carcinoma rather than into verrucous carcinoma (245).

Verrucous carcinoma of the oral mucosa is also known as *oral florid papillomatosis*. Clinically, one observes white, cauliflower-like lesions that may involve large areas of the oral mucosa and that gradually extend and coalesce. Extensive local tissue destruction may occur. However, metastases are rare, and, if they occur, they remain limited to the regional lymph nodes (246–248).

Histopathology. *Verrucous hyperplasia* shows a hyperplastic epithelium with upward extension of verrucous projections located predominantly superficial to the adjacent epithelium (245).

Verrucous carcinoma (oral florid papillomatosis) differs in its early stage from verrucous hyperplasia by showing, in addition to the surface verrucous projections, extension of the lesion into the underlying connective tissue (245). The downward extensions of the epithelium are round and club shaped and appear well demarcated from the surrounding stroma. Nuclear pleomorphism or hyperchromasia and formation of horn pearls are absent.

Some lesions of verrucous carcinoma persist in this stage for many years, although ultimately they show, in the areas of deepest extension, a moderate loss of polarity, increased cytoplasmic basophilia, nuclear hyperchromasia, and frequent mitotic figures. These features, however, do not suffice for a diagnosis of squamous cell carcinoma (249). Other lesions show sufficient nuclear atypicality and loss of polarity in the downward proliferations to indicate the presence of a well-differentiated squamous cell carcinoma (250). In about 10% of the cases of verrucous carcinoma, transformation into a classic squamous cell carcinoma takes place (247,248). (For a more detailed discussion of verrucous carcinoma, see page 822.)

NECROTIZING SIALOMETAPLASIA

One or occasionally two ulcers showing a rolled border and measuring 1 to 2 cm in diameter are found usually on the hard palate and occasionally on the soft palate. If they are located on the hard palate, bone may be exposed at the base of the ulcer. Spontaneous healing takes place within 6 to 12 weeks. The importance of necrotizing sialometaplasia, a rare condition first reported in 1973 (251), lies in its clinical and histologic resemblance to carcinoma (186).

Histopathology. Histologic examination shows coagulative necrosis of salivary gland lobules and squamous metaplasia within adjacent viable lobules. The connective tissue framework of the necrotic glands remains intact, thereby preserving the lobular architecture of the salivary gland. Faintly basophilic material representing sialomucin is seen within the necrotic glands. This is both PAS positive and Alcian blue positive. Adjacent to the necrotic glands, one may see normal-appearing salivary gland acini. Other salivary gland structures show either partial squamous metaplasia, with a peripheral rim of squamous cells, or complete replacement by squamous epithelium. The squamous metaplasia also involves the salivary ducts (252,253).

Pathogenesis. The abrupt clinical onset and rapid spontaneous healing suggest that an acute vascular insult results in infarction and coagulation necrosis of the salivary acini (252).

Differential Diagnosis. To pathologists not familiar with this condition, the apparent irregular proliferation and deep extension of squamous epithelium may suggest a diagnosis of carcinoma. However, the confinement of cytologically benign squamous epithelium to the preexisting lobular pattern of salivary glands should permit the correct diagnosis (254).

EOSINOPHILIC ULCER OF THE TONGUE

One or two asymptomatic ulcers measuring 0.8 to 2.0 cm in diameter arise suddenly on the tongue. Spontaneous healing takes place within a few weeks.

Histopathology. A dense cellular infiltrate is present at the base of the ulcer, extending through the submucosa into the striated muscle bundles of the tongue. Most of the cells are eosinophils, but there are also lymphocytes and histiocytes (255,256). In one case, focal leukocytoclastic vasculitis was present (257).

Differential Diagnosis. This lesion differs from eosinophilic granuloma of histiocytosis X (see Chapter 26) clinically by its tendency to arise and heal rapidly and histologically by the smaller number and smaller size of the histiocytes (255).

BOWEN'S DISEASE

Bowen's disease usually consists of a solitary lesion. It may occur on exposed or on unexposed skin. It may be caused on exposed skin by exposure to the sun and on unexposed skin by the ingestion of arsenic (see Pathogenesis, following, and Arsenical Keratosis and Carcinoma). Lesions of Bowen's disease can form in lesions of epidermodysplasia verruciformis caused by HPV-5 (see Chapter 25). Not infrequently the fingers, including the nail fold or nail bed, are involved (258).

Bowen's disease manifests as a slowly enlarging erythematous patch of sharp but irregular outline showing little or no infiltration. Within the patch are generally areas of scaling and crusting. Although Bowen's disease may resemble a superficial basal cell epithelioma, it differs from it by the absence of a fine, pearly border and lack of a tendency to heal with central atrophy. Lesions of Bowen's disease can occur on the glans penis, where they are referred to also as erythroplasia of Queyrat.

Bowenoid papulosis of the genitalia, because of its probable relationship to genital warts, is discussed in Chapter 25.

Histopathology. Bowen's disease is an intraepidermal squamous cell carcinoma referred to also as squamous cell carcinoma *in situ*. Thus it represents biologically but not morphologically a *precancerous dermatosis*, under which designation it was described originally in 1912 (259).



FIGURE 29-49. Bowen's disease. The lesion is crusted and erythematous, with a poorly defined margin.

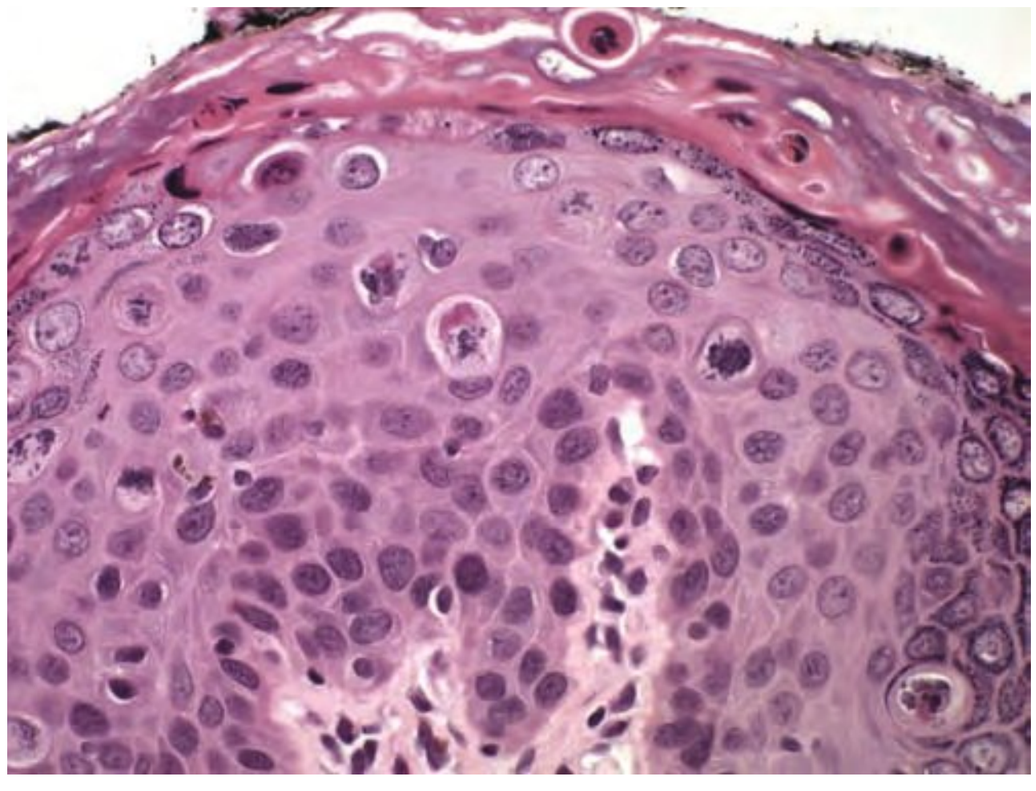


FIGURE 29-51. Bowen's disease. Throughout the epidermis, the cells lie in disarray, with frequent large atypical mitoses.

The epidermis shows acanthosis with elongation and thickening of the rete ridges, often to such a degree that the papillae located between the rete ridges are reduced to thin strands (Fig. 29-49). Throughout the epidermis, the cells lie in complete disorder, resulting in a "windblown" appearance (Figs. 29-50 and 29-51). Many cells appear highly atypical, showing large, hyperchromatic nuclei. Multinucleated epidermal cells containing clusters of nuclei are often present. The horny layer usually is thickened and consists largely of parakeratotic cells with atypical, hyperchromatic nuclei (260).

A common and rather characteristic feature is the presence of cells showing atypical individual cell keratinization. Such dyskeratotic cells are large and round and have a homogeneous, strongly eosinophilic cytoplasm and a hyperchromatic nucleus. The infiltrate of atypical cells in Bowen's disease frequently extends into follicular infundibula and causes replacement of the follicular epithelium by atypical cells down to the entrance of the sebaceous duct (204).

Even though the marked atypicality of the epidermal cells includes the cells of the basal layer, the border between the epidermis and dermis everywhere appears sharp, and the basement membrane remains intact. The upper dermis usually shows a moderate amount of a chronic inflammatory infiltrate.

An occasional finding in Bowen's disease is vacuolization of the cells, especially in the upper portion of the epidermis (261). In addition, in exceptional cases, multiple nests of atypical cells are scattered through a normal epidermis, sometimes with sparing of the basal cell layer. This results in a histologic picture that used to be interpreted as intraepidermal epithelioma of Borst-Jadassohn (see Chapter 31) (204,262).

In a small percentage of cases of Bowen's disease, an invasive squamous cell carcinoma develops. The usual figure quoted is 3% to 5% (263). The highest incidence given is 11% (264). On the opposite end is a statement that, in the vast majority of cases, Bowen's disease remains a carcinoma *in situ* during the lives of those affected (265). If invasion happens, it usually takes place after many years' duration of the disease. The invasive tumor retains the cytologic characteristics of the intraepidermal tumor, and invasion may occur at first in only a limited area. To avoid missing such an area, it is advisable to examine representative sections throughout the entire tissue block. As soon as invasion has taken place, the prognosis changes. So long as Bowen's disease remains in its intraepidermal stage, metastases do not occur. However, once invasion of the dermis has occurred, there exists the possibility of regional and even visceral metastases (264).

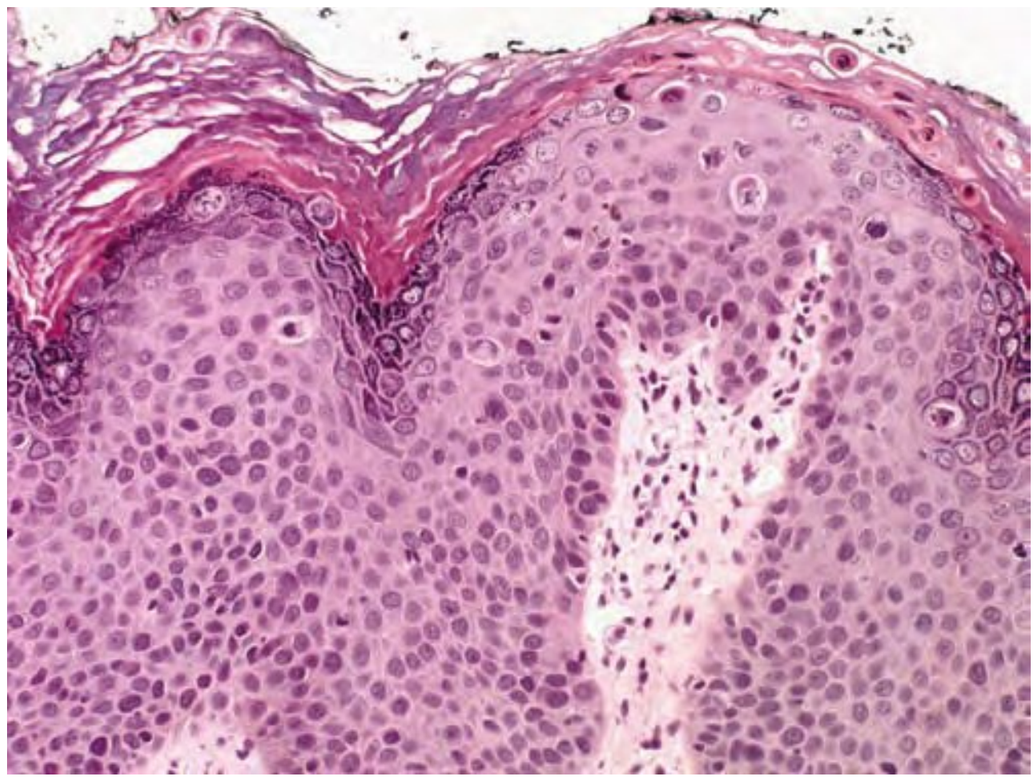


FIGURE 29-50. Bowen's disease. The epidermis is irregularly thickened. The normal maturation pattern is effaced.

Pathogenesis. No agreement exists about the frequency with which visceral carcinoma develops in patients with Bowen's disease. The first authors to point out an association between Bowen's disease and visceral cancer found that, of 35 patients

with Bowen's disease who were known to have died, 20 (57%) had an associated internal cancer (264). In a subsequent series, however, a significant increase in the incidence of associated internal cancer was observed only in patients in whom the lesions of Bowen's disease were located in areas not exposed to the sun (33%); in patients in whom the lesions were in exposed areas, the incidence of visceral cancer was low (5%) (246). Subsequent studies, with one exception (267), have not demonstrated a significantly increased risk of internal malignancy in patients with Bowen's disease (204,268–270).

Electron microscopic examination of lesions of Bowen's disease has demonstrated the presence of many dyskeratotic cells. The perinuclear aggregation and condensation of tonofilaments in these dyskeratotic cells are similar to but more pronounced than in the dyskeratotic cells of Darier's disease (271). Some of the markedly dyskeratotic cells in Bowen's disease disintegrate, and portions of such cells are phagocytized by other epidermal cells, which may contain, in addition to the phagocytized dyskeratotic material, phagocytized desmosomes in their cytoplasm (271,272). In other instances, the intracellularly located desmosomes are not phagocytized but are drawn into the dyskeratotic cells of Bowen's disease together with aggregating tonofilaments (273). The phenomenon of intracytoplasmic desmosomes, however, is not specific for Bowen's disease, although it is found most commonly in this condition. Thus intracytoplasmic desmosomes have been observed within dyskeratotic keratinocytes in Darier's disease (274), squamous cell carcinoma (275), and keratoacanthoma (276); within nondyskeratotic keratinocytes in extramammary Paget's disease (277), and malignant melanoma (278); and even within normal keratinocytes in both the epidermis (279) and the oral mucosa (280). It can be assumed that the occasional occurrence of invaginations of the plasma membrane is a normal event in keratinocytes and that the invaginated plasma membrane can contain desmosomal structures. These structures are more resistant to enzymatic destruction than the plasma membrane and thus may be found free in the cytoplasm (280).

Two types of epidermal giant cells can be recognized in Bowen's disease. In one type, an entire dyskeratotic cell has been "cannibalized" by another keratinocyte and is located within the cytoplasm of the phagocytizing cell (281). In the second type, multiple nuclei lie in the center of the giant cell surrounded by dyskeratotic tonofilaments. It seems that, by becoming entangled with the spindles of the mitotic apparatus, the dyskeratotic tonofilaments interfere with the normal division of the cell so that nuclear division can take place but cellular division cannot (271,272).

Differential Diagnosis. No histologic difference exists between bowenoid actinic keratosis and Bowen's disease. They may differ merely in size, with the bowenoid actinic keratosis usually being smaller than Bowen's disease.

In some cases of Bowen's disease, there are single atypical cells scattered among benign keratinocytes in a pattern of "pagetoid Bowen's disease" or "pagetoid squamous cell carcinoma *in situ*" that must be differentiated from superficial spreading melanoma *in situ*, if necessary with the use of immunostaining for keratin markers and S100 and/or Melan-A/MART1 (see Chapter 28). Paget's disease may similarly share with Bowen's disease the presence of vacuolated cells in a "pagetoid" pattern, but, in contrast with Bowen's disease, it shows no dyskeratosis. In addition, immunostaining for the aforementioned melanoma markers and for carcinoembryonic antigen and keratins may be used to aid in making this distinction, and furthermore the material contained in Paget cells is often PAS positive and diastase resistant, whereas the PAS-positive material that is sometimes present in the vacuolated cells of Bowen's disease is glycogen and therefore diastase labile (282).

ERYTHROPLASIA OF QUEYRAT (BOWEN'S DISEASE OF THE GLANS PENIS, CARCINOMA IN SITU)

Erythroplasia of Queyrat is the term often used for carcinoma *in situ* located on the glans penis. Clinically and histologically, it is identical to Bowen's disease, and this designation would seem preferable for simplicity's sake. The only reason for keeping the term *erythroplasia of Queyrat* alive is that it was introduced in 1911 (283), 1 year before the description of Bowen's disease (259).

Erythroplasia or Bowen's disease of the glans penis is seen almost exclusively in uncircumcised men. It manifests itself as an asymptomatic, sharply demarcated, bright-red, shiny, very slightly infiltrated plaque on the glans penis or, less often, in the coronal sulcus or on the inner surface of the prepuce (284).

Histopathology. Erythroplasia of Queyrat of the glans penis has the same histologic appearance as Bowen's disease. Progression into an invasive squamous cell carcinoma has been observed in up to 30% of the patients (285), with metastases in about 20% of the patients with invasive erythroplasia (286). It thus has a greater tendency toward invasion and metastasis than Bowen's disease of the skin (285).

Differential Diagnosis. A clinical diagnosis of erythroplasia of Queyrat requires histologic examination of an adequate biopsy for confirmation because differentiation from balanitis circumscripta plasmacellularis is not possible on a clinical basis.

BALANITIS CIRCUMSCRIPTA PLASMACELLULARIS

A disorder first described by Zoon in 1952 (287), balanitis circumscripta plasmacellularis has the same clinical appearance as erythroplasia of Queyrat or Bowen's disease of the glans penis. In some instances, erosions with a tendency to bleed are present (288). Like erythroplasia, this disorder is seen almost exclusively in uncircumcised males (289). On rare occasions, an analogous lesion referred to as *vulvitis circumscripta plasmacellularis* is observed on the vulva (290,291).

Histopathology. The epidermis appears thinned and often shows absence of its upper layers (292). It may be partially detached as a result of subepidermal cleavage or even absent (288,293). If present, the epidermis often has a rather distinctive appearance; in addition to being thinned and flattened, it is composed of diamond- or lozenge-shaped, flattened keratinocytes that are separated from each other by uniform intercellular edema (289). Erythrocytes may be seen permeating the epidermis. In some cases, the keratinocytes appear degenerated or necrotic (292).

The upper dermis shows a bandlike infiltrate in which numerous plasma cells are often seen (287,292). In some cases, however, their number is only moderate (289) or even small (293). In addition, the capillaries are dilated, and there may be extravasations of erythrocytes and deposits of hemosiderin (294).

Pathogenesis. It has been pointed out that plasma cells frequently predominate in the inflammatory response at mucocutaneous junctions in a variety of benign and malignant processes. Thus the term *circumorificial plasmacytosis* was introduced for benign plasma cell infiltrates on the glans penis, vulva, and lips (295–297). However, the combination of histologic and clinical features seen in balanitis circumscripta plasmacellularis, and probably also in vulvitis circumscripta plasmacellularis, is unique and deserves recognition as an entity (289,290,292).

SQUAMOUS INTRAEPITHELIAL NEOPLASIA (DYSPLASIA) OF THE VULVA

The term leukoplakia of the vulva is purely a clinical designation requiring histologic examination for clarification of the diagnosis, especially to decide whether atypicality of the epithelial cells exists. The clinical aspect of leukoplakia of the vulva is more variable than that of oral leukoplakia because it does not always consist just of white patches as in the mouth but may have a papular or verrucous appearance. The reason is that on the vulva, HPV infections can occur as flat papular condylomas (298), often in association with similar lesions on the cervix. In addition, the condition previously described as bowenoid papulosis, in the presence of multiple, coalescing papules, may result in a verrucous aspect of the leukoplakia (see Chapter 25) (299). A clear-cut histologic decision often is not possible unless adequate clinical data are available.

The further investigation of dysplastic lesions in the vulva has shown that there are two types of vulvar intraepithelial neoplasia (VIN) (300). The first of these is *undifferentiated VIN*, which is associated with human papillomavirus infection, occurs mainly in younger women, tends to be multicentric, and is of the undifferentiated or bowenoid type. This is probably what has previously been called bowenoid papulosis. The second type is *differentiated VIN*, which is not associated with human papillomavirus infection, typically occurs in older women, and is often unifocal. It is commonly associated with lichen sclerosus or squamous hyperplasia and carries a substantial risk of progression to invasive squamous cell carcinoma.

Histopathology. Flat condylomas that may be associated with VIN show intracellular vacuolization that may result in a somewhat atypical appearance of the epithelium referred to as *koilocytotic atypia*. This may be difficult to differentiate from true atypia (298). In undifferentiated VIN the changes are those of undifferentiated basaloid or bowenoid dysplasia. In differentiated VIN the epithelium is thickened and parakeratotic with elongated and anastomosing rete ridges. The characteristic feature is the presence of large basal or parabasal eosinophilic keratinocytes with abnormal vesicular nuclei and prominent intercellular bridges. Intraepithelial pearls may be present in the rete ridges. There is little or no atypia above the basal layer of the epidermis.

ARSENICAL KERATOSIS AND CARCINOMA

Inorganic arsenic was a frequently used oral medication for a number of dermatoses until evidence accumulated in the 1930s that, besides its long-known tendency to form arsenical keratoses on the palms and soles, inorganic arsenic quite frequently causes carcinoma of the skin (301). In the 1950s, it became apparent that inorganic arsenic could cause visceral carcinoma. The most common form in which inorganic arsenic has been administered was Fowler's solution containing 1% potassium arsenite.

Careless handling of industrial wastes can introduce arsenic into well water used for domestic consumption, resulting in "epidemic" occurrences of arsenical keratoses and cutaneous carcinomas (302,303).

Arsenical keratoses of the palms and soles, consisting of verrucous papules without surrounding inflammation, are a common manifestation of prolonged arsenic ingestion. Thus, in a follow-up study of 262 patients who had been taking Fowler's solution for 6 to 26 years before this study, arsenical keratoses of the palms and soles were observed in 40% and arsenic-induced carcinomas of the skin in 8% (304). In a study from Taiwan, 80% of the 428 patients with arsenical carcinomas of the skin had arsenical keratoses of the palms and soles (305). The minimal latent period between the beginning of arsenic intake and the onset of arsenical keratoses of the palms and soles was 2.5 years, and the average latent period 6 years (304).

Cutaneous carcinomas following arsenic ingestion are usually multiple, and about three fourths of them are located on the trunk (305). They consist of erythematous, scaling, occasionally crusted patches that slowly increase in size. Carcinomas can also arise in arsenical keratoses of the palms and soles (304,305). The average latency between the beginning of arsenic intake and the onset of carcinoma was 18 years, with a range from 3 to 40 years (306).

Visceral carcinoma can be caused by arsenic intake, but the actual incidence is difficult to determine because of the

long latent period, which may vary from 13 to 50 years, with an average of 24 years (307). The most common locations appear to be bronchi and the genitourinary system (304,307). There are on record at least two incidences of prolonged arsenic intake in which lung cancer occurred in a high percentage of the patients: One report concerned vineyard workers exposed to an arsenic insecticide (308), and the other dealt with villagers exposed to arsenic-containing drinking water (309). In the latter series, the onset of pulmonary cancer started 30 years after the arsenic exposure.

Because Bowen's disease is the most common cutaneous carcinoma produced by arsenic, the possibility of a relationship between Bowen's disease and visceral carcinoma is of interest. This association, first pointed out in 1959 (264), appears to be greatest in those cases of Bowen's disease in which the lesions are located in unexposed areas and thus are not caused by sun exposure. In one report, an association with internal carcinoma was found in about one third of the cases (266). It was suggested that arsenic is the common denominator in such cases, causing both Bowen's disease and internal carcinoma. However, subsequent studies showed no significant relationship between Bowen's disease in covered areas and internal malignancy (268), or, if such a relationship was found, no arsenic ingestion was found in most of the patients (267).

Histopathology. In arsenical keratoses of the palms and soles, one may find, in some instances, only hyperkeratosis and acanthosis without evidence of nuclear atypicality (305). However, when one cuts deeper into the tissue block, atypicality may become apparent. Whereas some arsenical keratoses show only mild nuclear atypicality, the findings in others are those of a squamous cell carcinoma *in situ* and are analogous to Bowen's disease or an actinic keratosis. One observes disorder in the arrangement of the squamous cells and nuclear atypicalities, such as hyperchromasia, clumping, or dyskeratosis (310). Atrophy of the epidermis and basophilic degeneration of the upper dermis, as seen in some actinic keratoses, are absent in arsenical keratoses. Evidence of development into an invasive squamous cell carcinoma may be seen in some arsenical keratoses (304,305,310).

The type of cutaneous carcinoma that follows arsenic ingestion can be either squamous cell carcinoma or basal cell carcinoma, usually as multiple lesions. Squamous cell carcinomas usually occur as *in situ* lesions analogous to Bowen's disease, and basal cell carcinomas occur most commonly as superficial basal cell carcinomas, although invasive squamous cell carcinomas and basal cell carcinomas occur occasionally. Invasive tumors may arise *de novo* or may develop within preexisting lesions of Bowen's disease or superficial basal cell carcinoma.

A matter of controversy has been whether arsenical carcinomas occur more commonly as lesions of Bowen's disease or as superficial basal cell carcinomas. For many years, it was accepted that lesions of Bowen's disease were the usual reaction (261). However, whereas two publications stated that superficial basal cell carcinomas are far more prevalent than lesions of Bowen's disease (304,311), in two other publications, Bowen's disease was found to be much more common (305,310). The most likely explanation for this discrepancy appears to be that, in many instances, lesions of Bowen's disease have been misinterpreted as superficial basal cell carcinoma (310). The distinction can indeed be difficult; one author who found mainly superficial basal cell carcinomas conceded that 25% of them showed "squamous metaplasia" (311), and another author proposed the concept of "combined forms" consisting of a "mixture of superficial basal cell carcinoma and intraepidermal carcinoma" (305). It appears likely that lesions designated as superficial basal cell carcinoma with squamous metaplasia or as combined forms represent lesions of Bowen's disease. (For histologic descriptions of Bowen's disease and superficial basal cell carcinoma, see page 813 and page 831 of this chapter respectively.)

Pathogenesis. *In vitro* experiments concerning the effects of inorganic arsenic on human epidermal cells have shown that arsenic depresses premitotic DNA replication. Furthermore, incubation with inorganic arsenic and subsequent exposure of the cell cultures to ultraviolet light causes interruption of the enzymatic "dark repair mechanism" in the epidermal cells. Among other enzymes, arsenic seems to block predominantly DNA polymerase by attaching itself to sulfhydryl groups. The damaging effect of arsenic on DNA may explain its carcinogenic effect (312).

SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma may occur anywhere on the skin and on mucous membranes with squamous epithelium. It rarely arises from normal-appearing skin. Most commonly, it arises in sun-damaged skin, either as such or from an actinic keratosis. Next to sun-damaged skin, squamous cell carcinomas arise most commonly in scars from burns and in stasis ulcers, termed *Marjolin's ulcers* (313). In regard to metastases, carcinomas arising in sun-damaged skin have a very low propensity to metastasize, the incidence amounting to only about 0.5% (212). This is in contrast to a metastatic rate of 2% to 3% for all patients with squamous cell carcinoma of the skin, with death resulting in about three fourths of the patients with metastases (213,314). Carcinomas of the lower lip, even though in most cases they also are induced by exposure to the sun, have a much higher incidence of metastasis, about 16%, with death occurring in about half of these patients as the result of metastases (315). In addition, the rate of metastases is higher in adenoid and mucin-producing squamous cell carcinomas of the skin than in the common type.

The diameter and thickness of cutaneous squamous cell carcinoma are related to the likelihood of metastasis, which is most often seen in primary tumors with a diameter of at least 15 mm and a vertical (Breslow) tumor thickness of at least 2 mm. Decreasing degrees of differentiation, desmoplasia, and an inflammatory reaction including eosinophils and plasma cells are also more frequently seen in metastasizing tumors (319).



FIGURE 29-52. Squamous cell carcinoma. This unpigmented tumor has a fleshy surface.

Cutaneous squamous cell carcinomas that arise secondary to inflammatory and degenerative processes have a much higher rate of metastasis than those developing in sun-damaged skin. Thus the rate of metastasis was found to be 31% in squamous cell carcinomas arising in osteomyelitic sinuses (316), 20% in radiation-induced skin cancer (317), and 18% in carcinomas developing in burn scars (318). Furthermore, carcinomas arising from modified skin, such as the glans penis and the vulva, and from the oral mucosa have a rather high rate of metastasis unless recognized and adequately treated at an early stage.

The incidence of squamous cell carcinomas, like that of other malignant neoplasms, is significantly increased in immunosuppressed patients (320). The incidence of cutaneous squamous cell carcinoma has been found to be 18 times greater in patients with a renal transplant and immunosuppression than in the general population (321). Squamous cell carcinomas may also show greater aggressiveness in such patients (322).

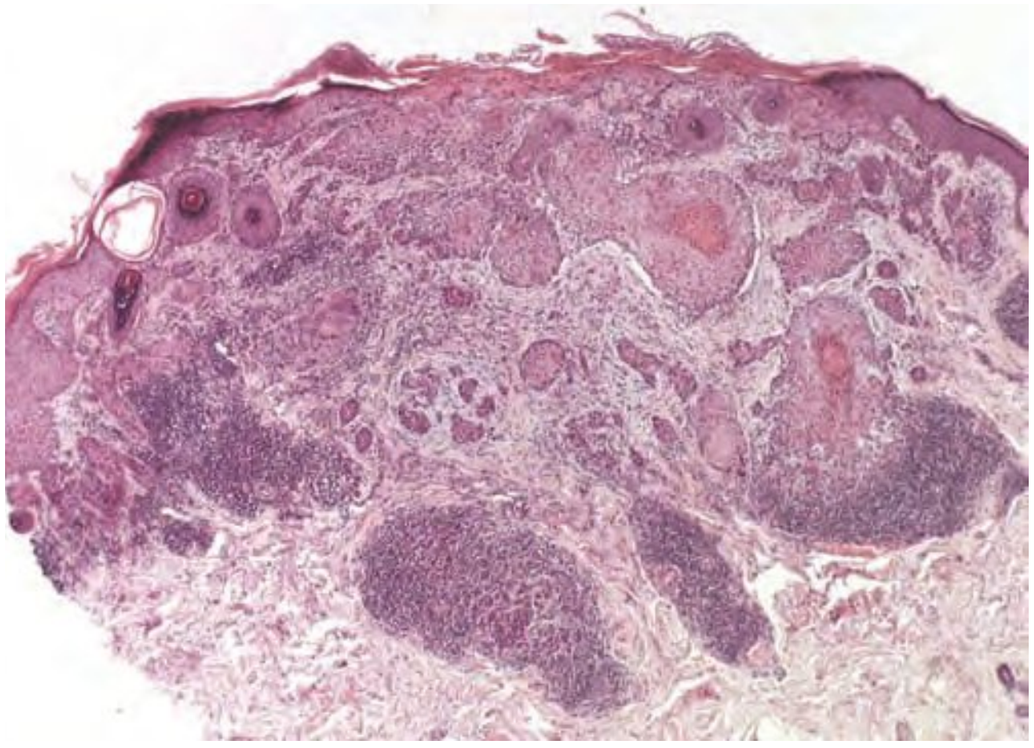


FIGURE 29-53. Squamous cell carcinoma arising in actinic keratosis. Low magnification. The epidermis shows features of an actinic keratosis. There is invasion of the dermis by epidermal masses. The dermis shows a marked inflammatory reaction.

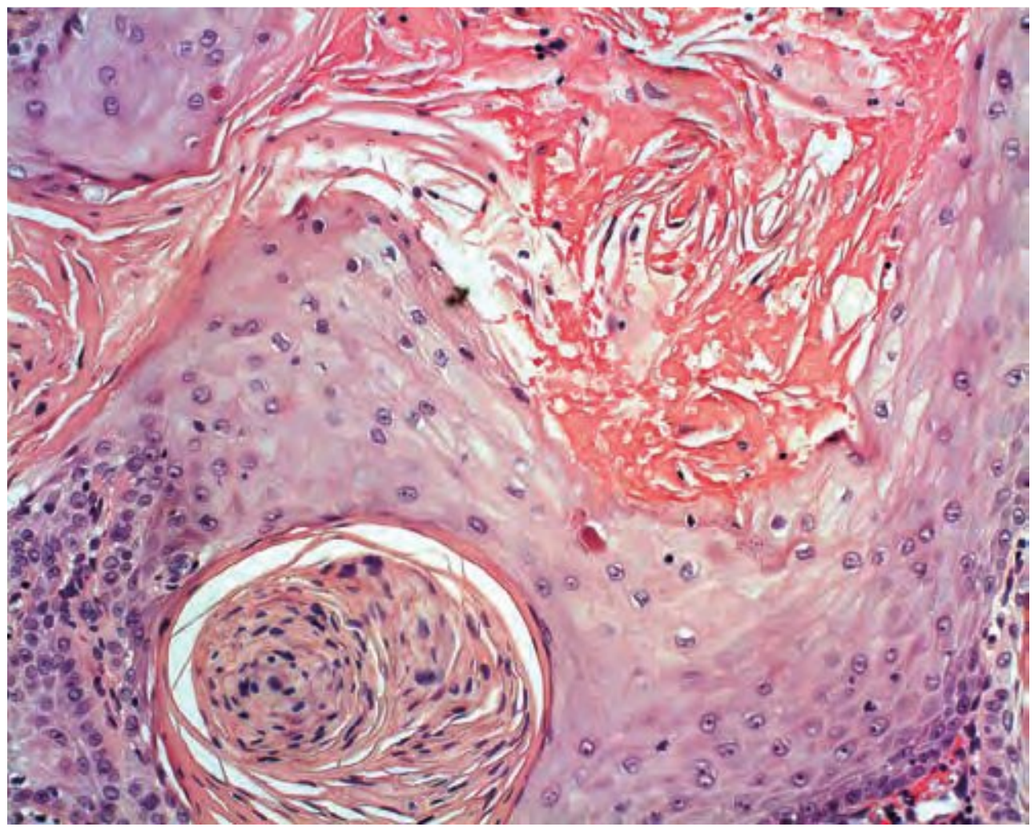


FIGURE 29-54. Squamous cell carcinoma, well differentiated. More than 75% of the tumor is keratinized.

Clinically, squamous cell carcinoma of the skin most commonly consists of a shallow ulcer surrounded by a wide, elevated, indurated border. Often the ulcer is covered by a crust that conceals a red, granular base. Occasionally, raised, fungoid, verrucous lesions without ulceration occur (Fig. 29-52). Multiprofessional guidelines for the management of patients with squamous cell carcinoma have been published (323).

Three variants of squamous cell carcinoma, *adenoid squamous cell carcinoma*, *mucin-producing squamous cell carcinoma*, and *verrucous carcinoma,* are discussed later.

Histopathology. Squamous cell carcinoma of the skin is a true, invasive carcinoma of the surface epidermis. On histologic examination, one finds the tumor to consist of irregular masses of epidermal cells that proliferate downward into the dermis (Figs. 29-53 through 29-61). The invading tumor masses are composed in varying proportions of normal

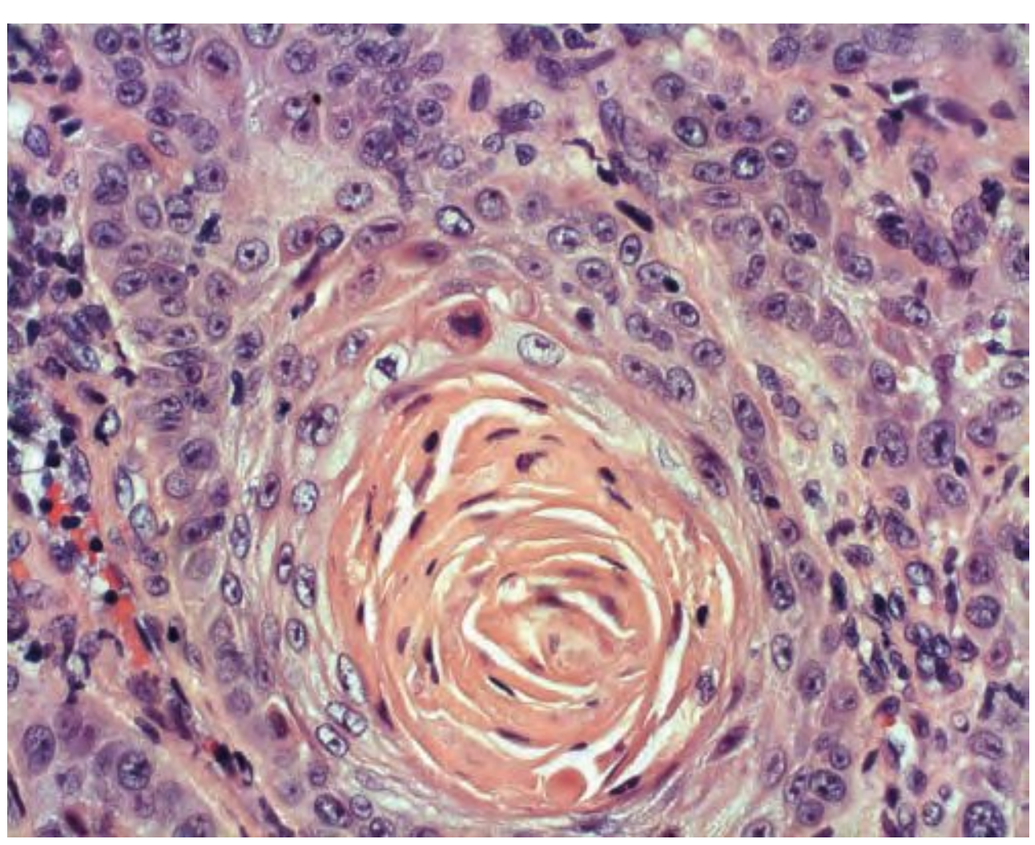


FIGURE 29-55. Squamous cell carcinoma, moderately differentiated. Between 25% and 75% of the tumor is keratinized.

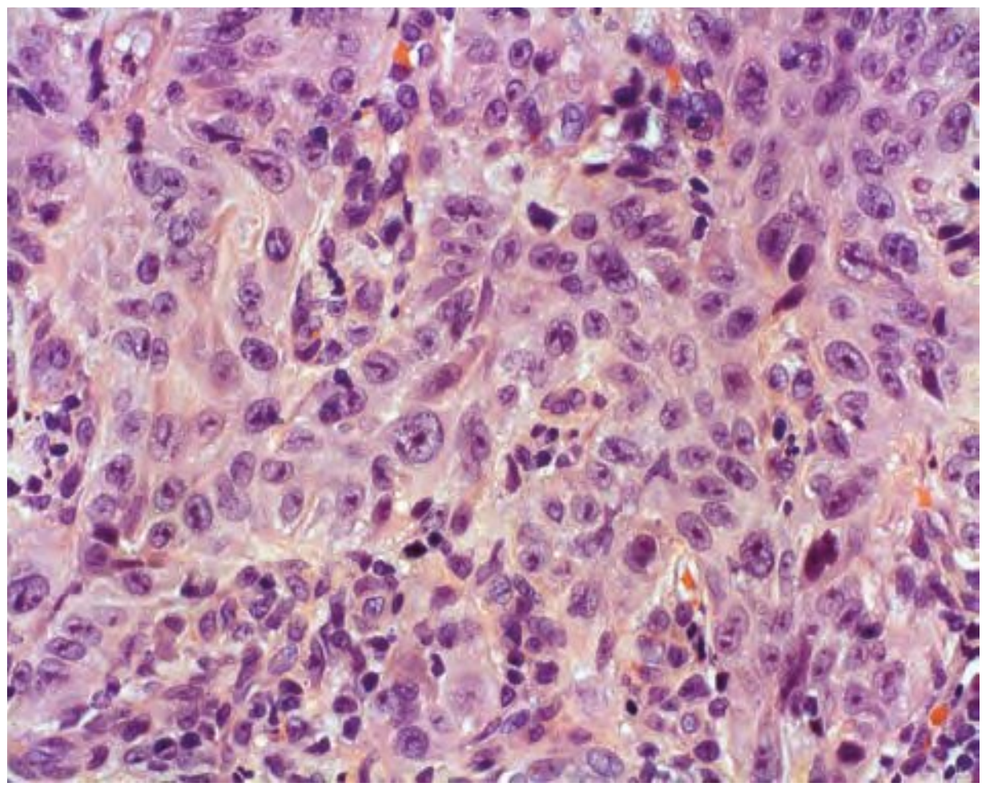


FIGURE 29-56. Squamous cell carcinoma, poorly differentiated. Less than 25% of the tumor is keratinized.

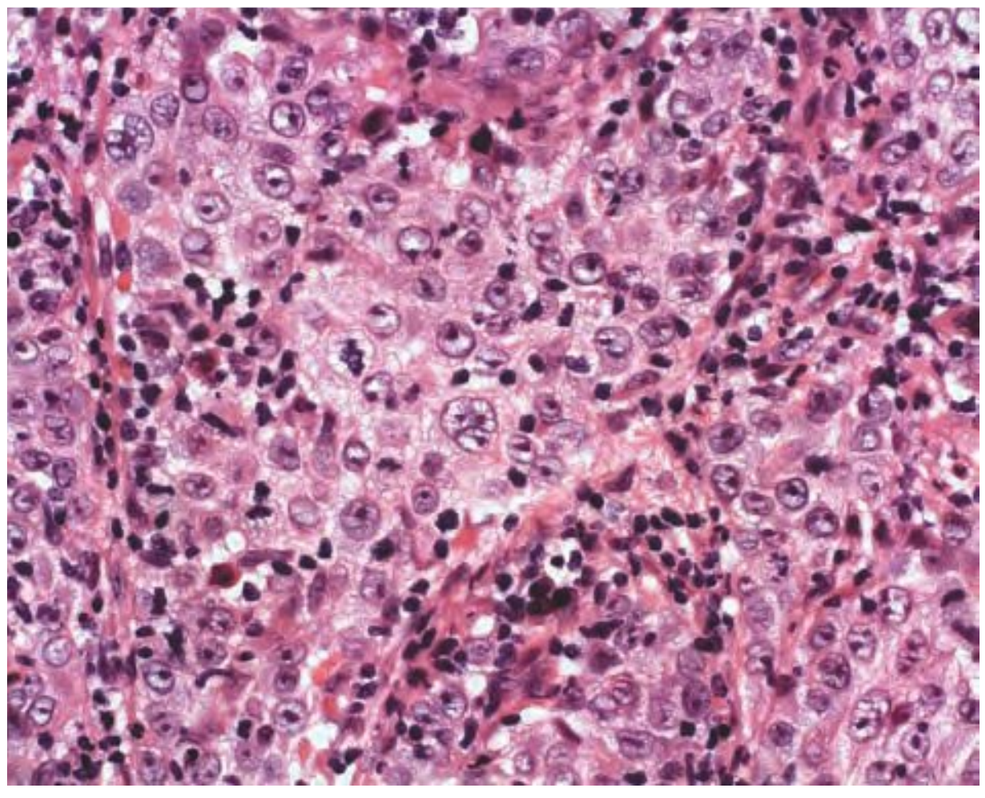


FIGURE 29-57. Lymphoepithelioma-like carcinoma showing similarities to poorly differentiated squamous cell carcinoma but having a more syncytial appearance of tumor epithelial cells and a rich lymphocytic infiltrate.

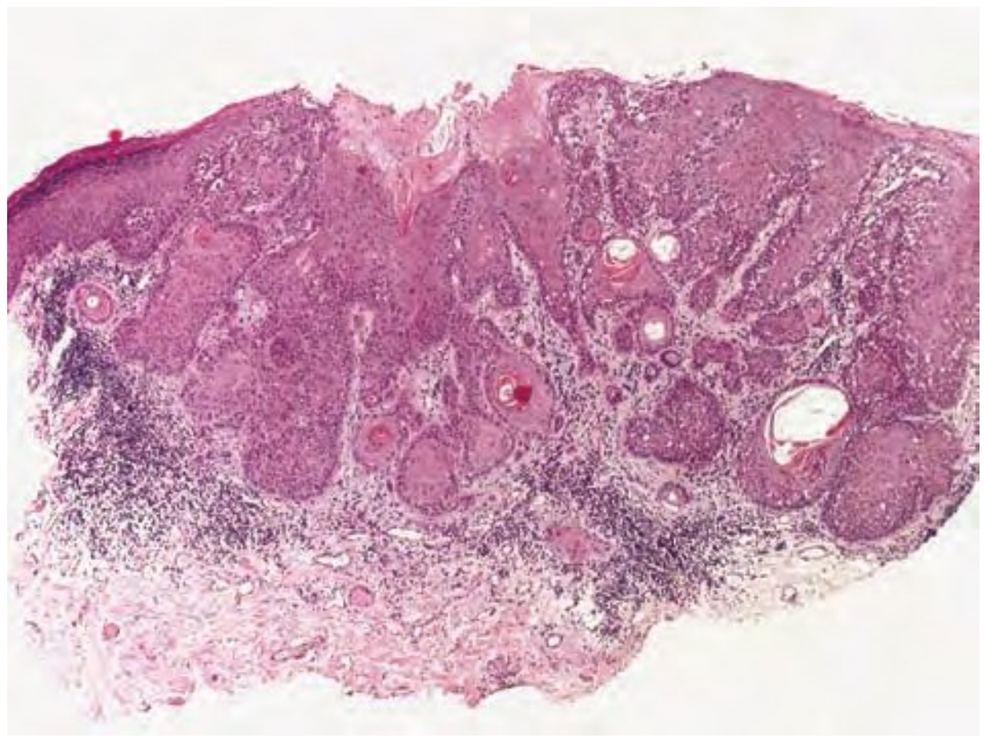


FIGURE 29-58. Squamous cell carcinoma, acantholytic type. In the deep part of the lesion the invasive cell masses show much less keratinization than in a well-differentiated tumor.

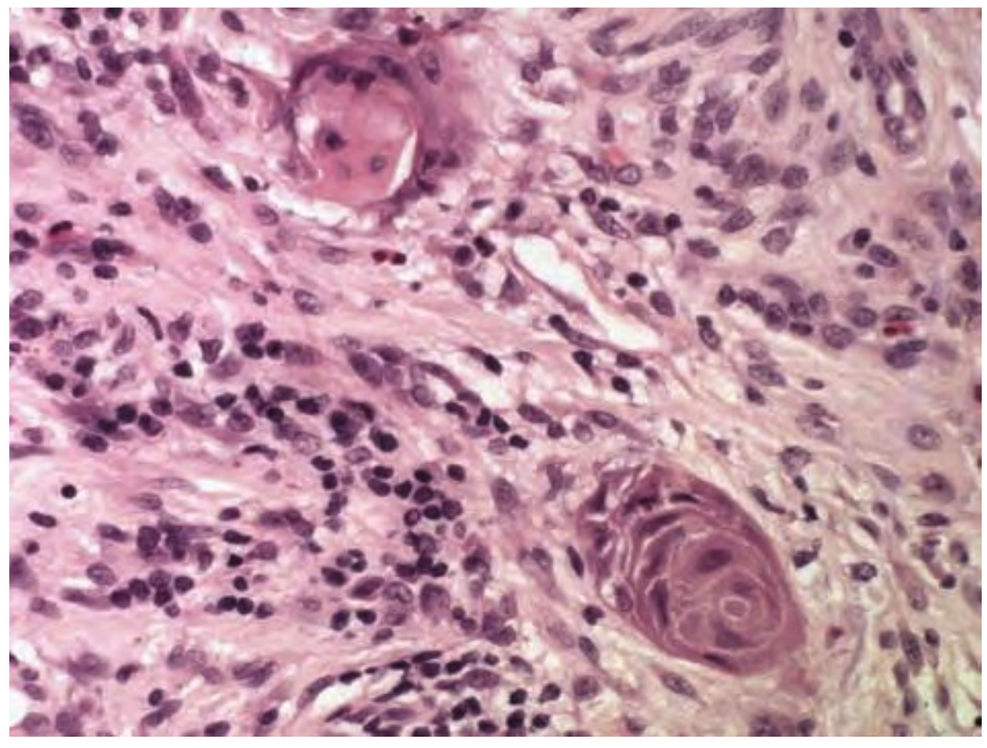


FIGURE 29-59. Squamous cell carcinoma. High magnification. Pleomorphic, hyperchromatic malignant squamous cells infiltrate the dermis.

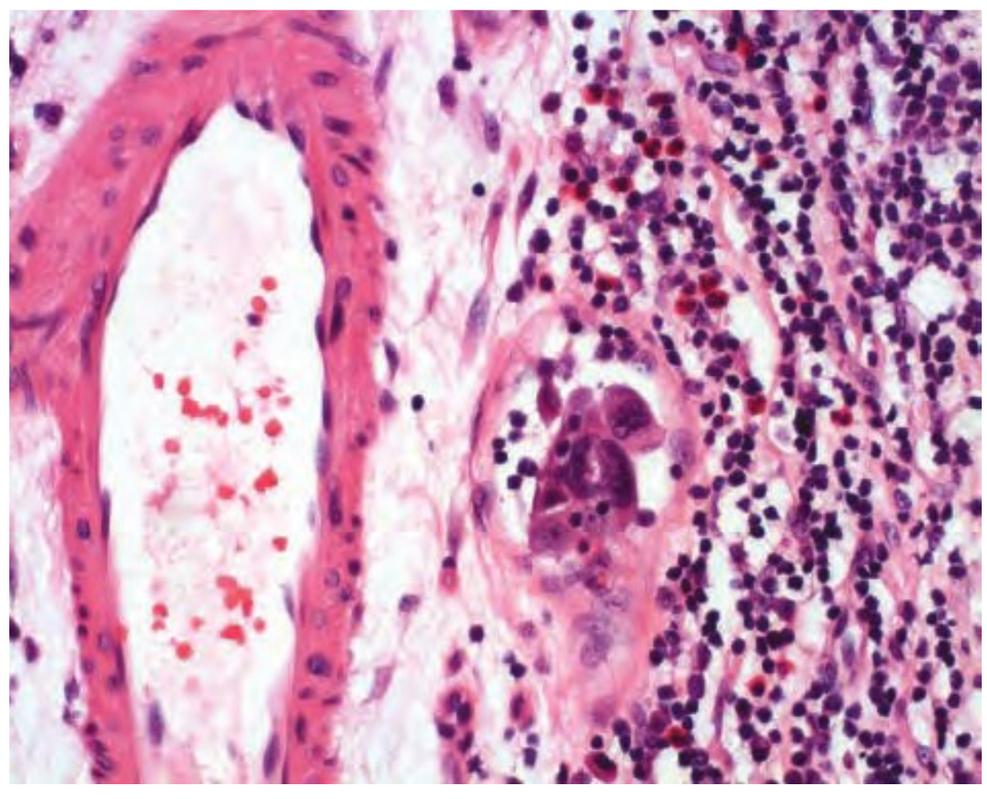


FIGURE 29-60. Squamous cell carcinoma. High magnification. Tumor cells show vascular invasion adjacent to the main tumor mass.

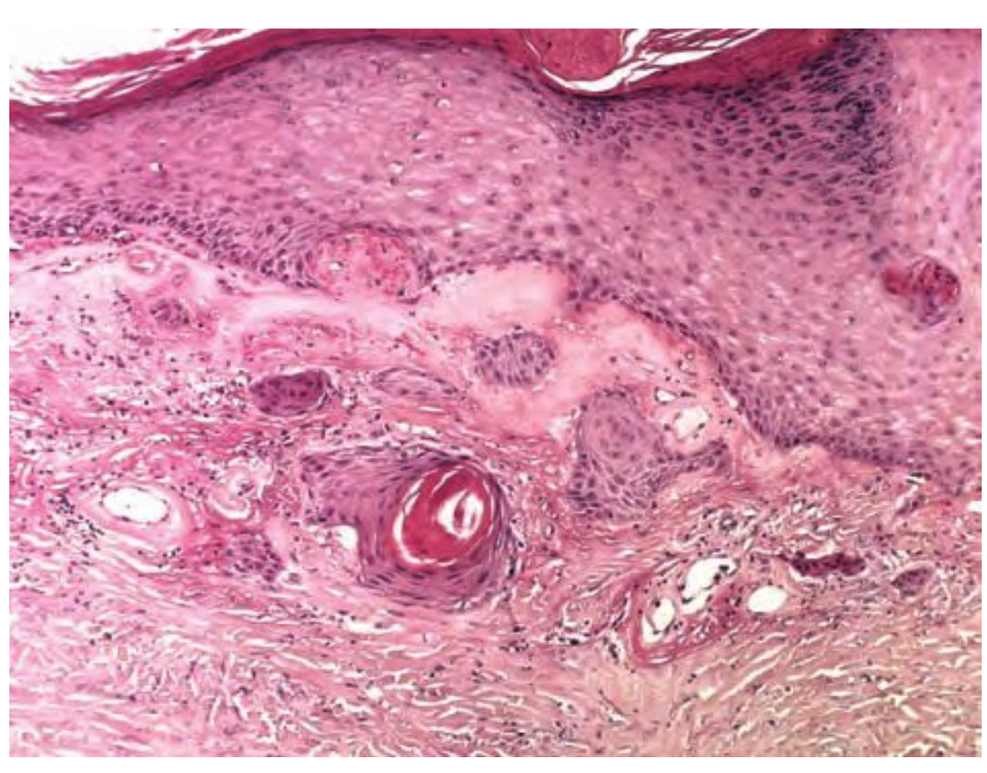


FIGURE 29-61. Postradiotherapy squamous cell carcinoma. This lesion, arising in an area treated many years previously with radiotherapy, shows a combination of invasive keratinizing squamous cell carcinoma and stromal damage secondary to radiotherapy.

squamous cells and of atypical (anaplastic) squamous cells. The number of atypical squamous cells is higher in the more poorly differentiated tumors. Atypicality of squamous cells expresses itself in such changes as great variation in the size and shape of the cells, hyperplasia and hyperchromasia of the nuclei, absence of intercellular bridges, keratinization of individual cells, and the presence of atypical mitotic figures.

Differentiation in squamous cell carcinoma is in the direction of keratinization. Keratinization often takes place in the form of horn pearls, which are very characteristic structures composed of concentric layers of squamous cells showing gradually increasing keratinization toward the center. The center shows usually incomplete and only rarely complete keratinization. Keratohyaline granules within the horn pearls are sparse or absent. There have been attempts to produce grading systems for squamous cell carcinoma, but classification as well-differentiated (Fig. 29-54), moderately differentiated (Fig. 29-55), and poorly differentiated (Fig. 29-56) carcinoma is the most widely adopted and reproducible way of describing the microscopic appearance of the tumors (1).

Marjolin's ulcer is a term applied to tumors that arise at the periphery of a chronic ulcer or a scar (313). The scar may be due to a remote burn or to radiation, or there may be a chronic inflammatory process such as a draining osteomyelitis sinus. The tumors often are well differentiated and may arise in a background of pseudoepitheliomatous (pseudocarcinomatous) hyperplasia, making diagnosis difficult (see discussion on page 822).

Spindle cell squamous cell carcinoma in particular may show a great resemblance to atypical fibroxanthoma (324). In some instances, spindle cell squamous cell carcinomas contain areas in which the cells either show intercellular bridges and beginning keratinization or show evidence of origin from the epidermis. In other cases, however, such areas cannot be detected. The spindle cells are intermingled with collagen and may be arranged in whorls (325). Not infrequently, pleomorphic giant cells are seen (324). In such instances, distinction from atypical fibroxanthoma may be difficult: Differential diagnosis by immunohistochemical examination is required (see Pathogenesis).

Raised, verrucous lesions of squamous cell carcinoma may show a considerable histologic resemblance to keratoacanthoma by having a central keratin-filled crater with peripheral buttresses. Keratoacanthomas typically do not extend into the dermis more deeply than the sweat gland coils, so when a tumor invades into the dermis to a deeper level than this, it can be described with confidence as carcinoma. There has been some reluctance among pathologists to even diagnose keratoacanthoma at all because of the view of some that the entity does not exist. A compromise position is to describe well-circumscribed and well-differentiated tumors as "well-differentiated, keratoacanthoma-like squamous cell carcinomas."

Pathogenesis. Electron microscopy of squamous cell carcinoma, in comparison with normal epidermal squamous cells, shows a reduction in the number of desmosomes on the cell surface. In their place, microvilli extend into the widened intercellular spaces. Desmosomes can be seen within the cytoplasm of some of the tumor cells, either by themselves or attached to bundles of tonofilaments (275). Their intracytoplasmic location may be the result of either phagocytosis or invagination of the plasma membrane. However, it is not a specific finding for squamous cell carcinoma; intracytoplasmic desmosomes also can be found in keratoacanthoma and Bowen's disease, as well as in several unrelated epidermal proliferations and even in normal keratinocytes.

At the dermal–epidermal junction, the basement membrane shows sporadic discontinuities through which long cytoplasmic protrusions penetrate, indicating invasion of the dermis by epidermal keratinocytes (326).

In early squamous cell carcinoma, lymphocytes are often seen in close contact with tumor cells, some of which show degenerative changes such as disruption of the plasma membrane, as well as fragmentation and subsequent release of organelles into the intercellular spaces. This can be interpreted as the cellular expression of an immune reaction against tumor cells (327).

The epithelial nature of the sarcoma-like cells in *spindle cell squamous cell carcinoma* is supported by electron microscopic findings, which have shown that these cells contain tonofilaments and occasional desmosome-like structures (325,328). Electron microscopy has also shown that structures diagnosed by light microscopy as atypical fibroxanthomas represent a heterogeneous group of neoplasms and that some are in actuality spindle cell squamous cell carcinomas (324,329).

Immunohistochemical methods are of considerable value in the differentiation of squamous cell carcinoma from mesodermal tumors, such as atypical fibroxanthoma and malignant fibrous histiocytoma, and from malignant melanoma. For the identification of keratinocytes, primary antibodies directed against high–molecular–weight cytokeratins, such as cytokeratin 13, or a pan-cytokeratin marker may be used. In contrast, atypical fibroxanthoma and malignant fibrous histiocytomas react with vimentin (see Chapter 32) and malignant melanoma with S100 protein and Melan-A/MART-1 (see Chapter 28). At times, even differentiation of a squamous cell carcinoma from a lymphoma may be difficult, in which case a positive reaction with monoclonal antileukocyte antibody (LCA, CD45) would favor lymphoma (330) (see Chapter 31). Immunohistochemistry using keratin markers may also be valuable in identifying tumor cells of a squamous cell carcinoma in the midst of an inflammatory infiltrate and can thus aid in deciding whether the margins of an excised specimen are free of tumor cells (331). The immunohistochemical differential diagnosis of spindle cell neoplasms in the skin is discussed also in Chapters 4, 28, 32, and 34.

Differential Diagnosis. The diagnosis of squamous cell carcinoma, although easily made in typical cases, may sometimes be difficult.

The differences between squamous cell carcinoma *in situ* and actinic keratosis lie in the degree as well as the type of

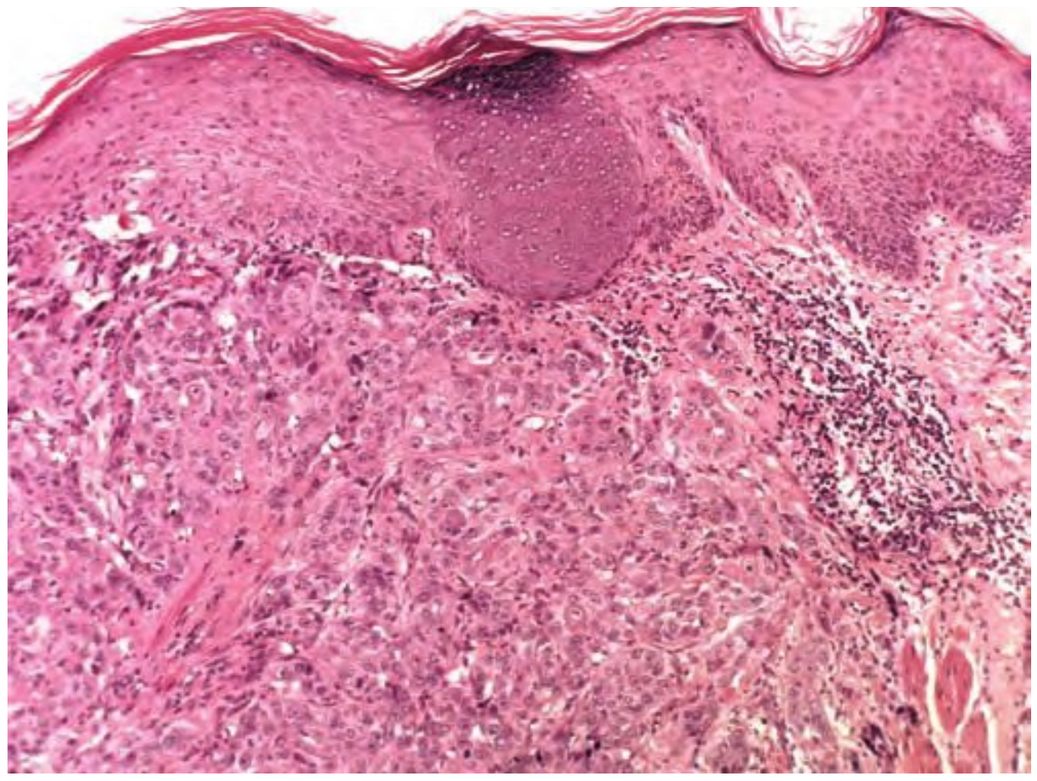


FIGURE 29-62. Metastatic squamous cell. A nodule of squamous cell carcinoma infiltrates the dermis beneath an epidermis devoid of dysplasia. The tumor was metastatic from a bronchial primary.

changes. In both conditions, one finds atypicality of cells, with dyskeratosis of individual cells and downward proliferation of the epidermis. However, only in frank squamous cell carcinoma is there invasion of the reticular dermis. No sharp line of demarcation exists between the two conditions, and not infrequently, on step sectioning for a lesion, the histologic appearance of actinic keratosis reveals one or several areas in which the changes have progressed to squamous cell carcinoma. Metastatic squamous cell carcinoma, for example, from another skin primary or from a mucous membrane or visceral lesion, usually shows a greater degree of cytologic atypia, may be located deeper in the dermis or subcutis, and lacks an overlying *in situ* component (Fig. 29-62).

For discussions of differentiation of squamous cell carcinoma from pseudocarcinomatous hyperplasia, see page 822; from keratoacanthoma, page 837; and from basal cell carcinoma, page 834.

ACANTHOLYTIC (ADENOID) SQUAMOUS CELL CARCINOMA

As a result of dyskeratosis and subsequent acantholysis, squamous cell carcinomas occasionally show what may appear to be tubular and alveolar formations on histologic examination. Such lesions have been termed *adenoid* or *pseudoglandular* squamous cell carcinomas, but they are better termed *acantholytic*. Clinically, they are found almost exclusively in sun-damaged skin of elderly patients, especially on the face and ears (332,333). They have also been seen on the vermilion border of the lower lip (334). Two instances of occurrence on the oral mucosa have been reported, but both were recurrences after radiation therapy (335).

On sun-exposed skin, acantholytic squamous cell carcinomas may arise as such or may develop from an actinic keratosis (333,336). In most instances, they do not differ in clinical appearance from the usual type of squamous cell carcinoma and thus commonly show a central ulceration surrounded by a raised, indurated border. Occasionally, they greatly resemble a keratoacanthoma in clinical appearance (337). The incidence of metastases varies. In one series it was only 2% (333), but in another series 14% of the patients had fatal metastases (338). Tumor size of greater than 15 mm correlates with the risk of an adverse outcome (319).

Histopathology. The adenoid changes may be seen in only a portion of a squamous cell carcinoma or throughout the lesion. Not infrequently, an actinic keratosis of the acantholytic type is seen overlying the lesion. There are tubular and alveolar lumina lined with one or several layers of epithelium (Figs. 29-58 and 29-59). In areas in which the lumina are lined with a single layer of epithelium, the epithelial cells resemble glandular cells, but in areas with several layers of epithelium, squamous and partially keratinized cells usually form the inner layers. The lumina are filled with desquamated acantholytic cells, many of which are partially or fully keratinized (333,337,339). In some cases, the eccrine ducts at the periphery of these tumors show signs of dilatation and proliferation (332,339). These ductal changes probably are induced by the surrounding inflammatory infiltrate.

Pathogenesis. These tumors represent squamous cell carcinomas of lobular growth in which there is considerable dyskeratosis with individual cell keratinization, resulting in acantholysis in the center of the lobular formations. This process is analogous to the suprabasal clefts seen in some actinic keratoses (337). Acantholytic squamous cell carcinomas differ from sweat gland carcinomas (see Chapter 30), in which the single row of cuboidal cells lining the lumina consists of true glandular cells (340,341). In some instances the latter tumors may be highly malignant.

MUCIN-PRODUCING SQUAMOUS CELL CARCINOMA

This rare variant of squamous cell carcinoma is associated with a more aggressive clinical course than are most cutaneous squamous cell carcinomas (342). Eleven cases have been reported under different designations, such as mucoepidermoid carcinoma (343) and adenosquamous carcinoma of the skin (342). The latter designation may lead to confusion with adenoid squamous cell carcinoma.

Histopathology. Varying numbers of mucin-producing cells are found within tumors that have the appearance of a squamous cell carcinoma. These cells generally appear large and pale and stain positively with the PAS method and with mucicarmine (342,344). Treatment of sections with sialidase eliminates the mucicarmine-staining material, whereas treatment with hyaluronidase fails to do so. Thus the material is epithelial mucin (sialomucin) (342). Occasionally, true glandular lumina

are present (342,345). Some of the lumina resemble distorted eccrine ducts and stain positively for carcinoembryonic antigen (345).

VERRUCOUS CARCINOMA

Verrucous carcinoma is a low-grade squamous cell carcinoma first described in 1948 (346) as occurring in the oral cavity. The diagnosis of verrucous carcinoma requires evaluation of the clinical and microscopic appearance and biological behavior of the neoplasm. It is a slowly growing, at first exophytic, verrucous, and fungating tumor that may ultimately penetrate deep into the tissue. However, it causes regional metastases only very late, if at all. Because of its high degree of histologic differentiation, it is often not recognized as a carcinoma for a long time. Three major forms of verrucous carcinoma are recognized, all of them occurring in areas of maceration.

Verrucous carcinoma of the oral cavity, also called oral florid papillomatosis, shows white, cauliflower-like lesions that may involve large areas of the oral mucosa.

Verrucous carcinoma of the genitoanal region, also called giant condyloma acuminatum of Buschke and Loewenstein, most commonly occurs on the glans penis and foreskin of uncircumcised males, where it consists of papillomatous proliferations. Ultimately, it may penetrate into the urethra. It may also occur on the vulva in females and in the anal region (see Chapter 25).

Plantar verrucous carcinoma, also called epithelioma cuniculatum (347), at first shows a striking resemblance to an intractable plantar wart. As the exophytic mass grows, it shows a great tendency toward deep, penetrating growth, resulting in numerous deep crypts filled with horny material and pus. The crypts resemble the burrows of rabbits, hence the name *cuniculatum*. The tumor ultimately penetrates the plantar fascia (348) and may even destroy metatarsal bones and invade the skin of the dorsum of the foot (349).

The occurrence of verrucous carcinoma has been described occasionally in many other areas, such as the face (350) and back (351), as well as in preexisting lesions, such as chronic ulcers and draining sinuses of hidradenitis suppurativa (352).

Histopathology. For the diagnosis of verrucous carcinoma, a large, deep biopsy is essential. The superficial portions generally resemble a verruca by showing hyperkeratosis, parakeratosis, and acanthosis. The keratinocytes appear well differentiated, stain lightly with eosin, and possess a small nucleus. The tumor invades with broad strands that often contain keratin-filled cysts in their center. There are large, bulbous, downward proliferations that compress the collagen bundles and push them aside. Thus the tumor has been said to invade by "bulldozing rather than stabbing" (353). Even in the deep portions of the tumor, nuclear atypia, individual cell keratinization, and horn pearls are absent (354).

However, in some instances, particularly in the oral cavity (247,250), but occasionally also in the genitoanal region (355) and on the plantar surface (356,357), verrucous carcinoma may ultimately show sufficient nuclear atypicality and loss of polarity to indicate the development of a true squamous cell carcinoma. In rare instances, the development of regional lymph node metastases has been observed in verrucous carcinoma of the mouth (248), the genitals (355), and the soles of the feet (357). Radiation therapy has led in some instances of oral verrucous carcinoma to anaplastic transformation and extensive metastases (358).

Pathogenesis. Although a viral cause of verrucous carcinoma has been suspected for a long time, demonstration of viral particles by electron microscopy has been possible in only a few instances. Virus-like particles were demonstrated in 1 case of plantar verrucous carcinoma presumed to be associated with a plantar wart (359), in the superficial epithelium of 5 of 13 cases of plantar verrucous carcinoma (360), and in 1 case of verrucous carcinoma of the vagina. The more sensitive and more specific method of demonstrating various types of human papilloma viruses by means of DNA hybridization has succeeded in proving the presence of HPV-6, and less frequently of HPV-11, in Buschke-Loewenstein tumors of the external genitals in both sexes (361). Similarly, HPV-6 was found in a vulvar tumor of Buschke-Loewenstein through molecular hybridization (362).

PSEUDOCARCINOMATOUS HYPERPLASIA

Pseudocarcinomatous hyperplasia, or *pseudoepitheliomatous hyperplasia,* as it is often called, represents a considerable downward proliferation of the epidermis into the dermis. Clinically and histologically, this downward proliferation may suggest a squamous cell carcinoma. It occurs occasionally (a) in chronic proliferative inflammatory processes, such as bromoderma, blastomycosis, blastomycosis-like pyoderma (pyoderma vegetans) (363), or hidradenitis suppurativa (364), and (b) at the edges of chronic ulcers, as seen in the following conditions: after burns or in stasis dermatitis (365), pyoderma gangrenosum, basal cell epithelioma (366), lupus vulgaris, osteomyelitis, scrofuloderma, gumma, and granuloma inguinale. In addition, granular cell tumor is known to evoke quite frequently a pseudocarcinomatous hyperplasia.

Histopathology. Histologically, pseudocarcinomatous hyperplasia shows an epithelial hyperplasia that often closely resembles moderately or well-differentiated squamous cell carcinoma. Although squamous cell carcinoma may develop at the edges of chronic ulcers, it is likely that some cases that are regarded as such actually represent pseudocarcinomatous hyperplasia. Nevertheless, a lesion starting out as pseudocarcinomatous hyperplasia at the edge of an ulcer may eventually develop into a squamous cell carcinoma and even metastasize (367,368).

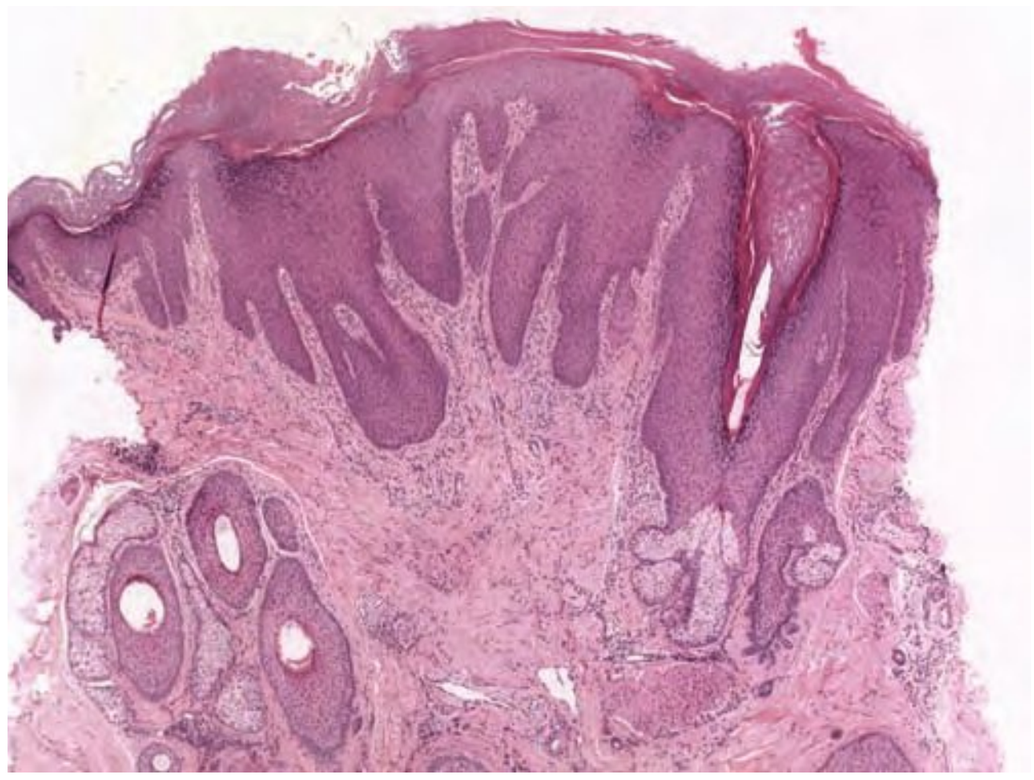


FIGURE 29-63. Lichen simplex chronicus. This punch biopsy specimen shows how epidermal hyperplasia can mainly involve hair follicles to produce a proliferative lesion mimicking an invasive process.

The histologic picture of pseudocarcinomatous hyperplasia shows irregular invasion of the dermis by uneven, jagged, often sharply pointed epidermal cell masses and strands with horn-pearl formation and, often, numerous mitotic figures (Figs. 29-63 and 29-64). These irregular proliferations of the epidermis may extend below the level of the sweat glands, where they appear in sections as isolated islands of epidermal tissue (364). However, the squamous cells usually are well differentiated, and atypicalities, such as individual cell keratinization and nuclear hyperplasia and hyperchromasia, are minimal or absent. Furthermore, one often sees invasion of the epithelial proliferations by leukocytes and disintegration of some of the epidermal cells in pseudocarcinomatous hyperplasia, findings that usually are absent in squamous cell carcinoma (365).

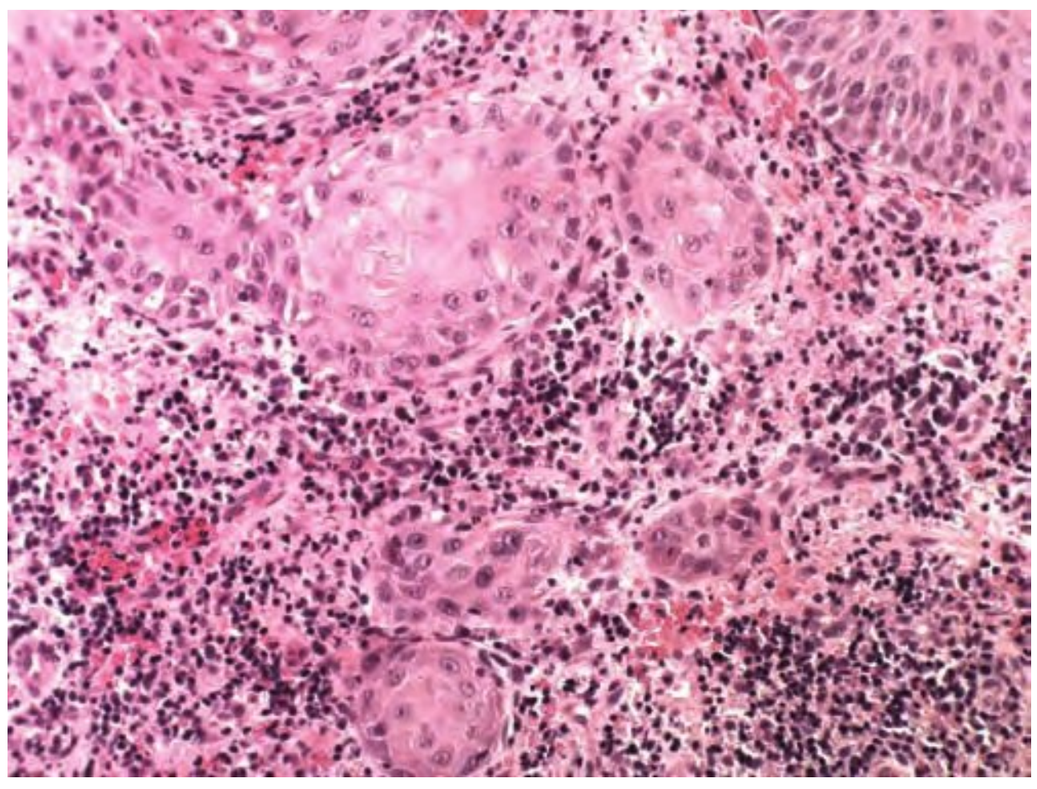


FIGURE 29-64. Pseudocarcinomatous hyperplasia. This curetting specimen shows a proliferative squamous lesion without substantial atypia and mimicking an invasive lesion.

Nevertheless, even when all of these criteria are taken into account, it may still be difficult to differentiate squamous cell carcinoma from pseudocarcinomatous hyperplasia by the study of just one histologic section (364). Multiple biopsies and detailed clinical data may be necessary for differentiation.

In every section in which a diagnosis of squamous cell carcinoma is contemplated, it is worthwhile to study the inflammatory infiltrate for the possible presence of granulomas, as seen in tuberculosis and the deep mycoses, or of intraepidermal abscesses, as seen in bromoderma. If such evidence is found, one may be dealing with pseudocarcinomatous hyperplasia instead of squamous cell carcinoma. In mucous membranes, and especially in the tongue, pseudoepitheliomatous hyperplasia of considerable degree and strongly simulating squamous cell carcinoma may be seen above a granular cell tumor.

Differential Diagnosis. Differentiation of pseudocarcinomatous hyperplasia from verrucous carcinoma rarely causes difficulties because in verrucous carcinoma there is verrucous upward proliferation and downward proliferation. In addition, verrucous carcinoma shows more pronounced keratinization in the downward extensions, which appear bulbous rather than sharply pointed.

BASAL CELL CARCINOMA

Basal cell carcinomas are seen almost exclusively on hair-bearing skin, especially on the face. Except in the nevoid basal cell carcinoma syndrome (see page 825), they rarely occur on the palms (369,370) or on the soles (371,372). Their occurrence on the mucous membrane is doubted; instances of basal cell carcinoma of the oral mucosa reported in the literature (373) probably are ameloblastomas (374).

Basal cell carcinomas usually occur as single lesions, although the occurrence of several lesions, either simultaneously or subsequently, is not infrequent. About 40% of patients who have had a basal cell carcinoma will have one or more basal cell carcinomas within 10 years (375). Basal cell carcinomas generally occur in adults, although they may be seen in children (376–378). However, there are three rare forms of basal cell carcinoma with early onset. In the linear, unilateral basal cell nevus, all lesions are present at birth. In the nevoid basal cell syndrome and the Bazex syndrome, some patients manifest lesions before puberty.

Predisposing Factors. Although basal cell carcinomas may arise without apparent reason, there are several predisposing factors. The most common is a light skin color in association with prolonged exposure to strong sunlight (379). The predisposing effect of sun exposure is particularly evident in patients with xeroderma pigmentosum, in whom both basal cell carcinoma and squamous cell carcinoma are common (see Chapter 6). That prolonged sun exposure alone does not suffice to produce basal cell carcinomas is suggested by their great rarity on the dorsa of hands and fingers (380). Additional factors that

predispose a person to develop both basal cell carcinoma and squamous cell carcinoma are large or numerous doses of roentgen rays (381,382) and, less commonly, burn scars (383,384) and other scars (385). In contrast, most carcinomas of the skin caused by the prolonged intake of inorganic arsenic are squamous cell carcinomas, which often, like Bowen's disease, are located *in situ* (261,310). Occasionally, however, basal cell carcinomas, particularly superficial basal cell carcinomas, can result (304,305) (see Arsenical Keratosis and Carcinoma).

Occurrence of Metastases. As a rule, basal cell carcinomas do not metastasize. However, there are exceptions. The incidence of metastasis ranges from 0.01% in pathologic specimens (386) to 0.028% in dermatologic patients (387) to 0.1% in patients from surgical centers (388). A review published in 1984 described 175 cases with histologically proven metastases (389).

The typical case history of a metastatic basal cell carcinoma is that of a large, ulcerated, locally invasive and destructive primary lesion that has recurred despite repeated surgical procedures or radiotherapy (390–392). However, massive size, ulceration, and history of multiple recurrences are not absolute prerequisites for metastasis (393). Most observers have found no specific histologic type of basal cell carcinoma that is more capable of metastasizing than others (394–396). In addition, as a rule no evidence exists that the hosts' immunologic defenses are severely compromised (389). However, some authors assert that the metatypical or basosquamous type of basal cell carcinoma is the most likely to metastasize (397).

In contrast to metastatic squamous cell carcinoma of the skin, which shows lymphogenic metastases to lymph nodes in 80% to 90% of cases, in metastatic basal cell carcinoma, hematogenic and lymphogenic spread show about an even distribution (389). Although about 50% of the patients with metastatic basal cell carcinoma have metastases to lymph nodes as their first site of spread, lungs and bones also are frequently the first sites of involvement. Metastases to the liver, other viscera, and the skin or subcutaneous tissues have occurred. However, these areas were usually involved only when at least one of the three major sites of metastasis was also affected (398). The average survival time after metastasis to the lungs, bones, or internal organs is about 10 months (399).

Clinical Appearance. Five clinical types of basal cell carcinoma occur: (a) superficial basal cell carcinoma, (b) nodular basal cell carcinoma, (c) micronodular basal cell carcinoma, (d) infiltrating basal cell carcinoma, and (e) fibroepithelioma. In addition, there are three clinical syndromes in which basal cell carcinomas play an important part. They are (a) the nevoid basal cell carcinoma syndrome, (b) the linear unilateral basal cell nevus, and (c) the Bazex syndrome, showing follicular atrophoderma with multiple basal cell carcinomas.

Superficial basal cell carcinoma consists of one or several erythematous, scaling, only slightly infiltrated patches that slowly increase in size by peripheral extension. The patches are often surrounded, at least in part, by a fine, threadlike, pearly border (Fig. 29-65). The patches usually show small areas of



FIGURE 29-65. Superficial basal cell carcinoma. This tumor shows a well-demarcated edge.

superficial ulceration and crusting. In addition, their center may show smooth, atrophic scarring. In contrast to the first three types of basal cell carcinoma, which are commonly situated on the face, superficial basal cell carcinoma occurs predominantly on the trunk.

Nodular basal cell carcinoma begins as a small, waxy nodule that often shows a few small telangiectatic vessels on its surface (Fig. 29-66). The nodule usually increases slowly in size and often undergoes central ulceration. A typical lesion then consists of a slowly enlarging ulcer surrounded by a pearly, rolled border. This represents the so-called rodent ulcer (Fig. 29-67).

Micronodular basal cell carcinoma is diagnosed histologically and may have a diffusely infiltrative growth pattern that extends for some distance beyond the clinically apparent margins of the tumor. This subtype has been associated with a higher rate of



FIGURE 29-66. Nodular basal cell carcinoma. The lesion is well defined.



FIGURE 29-67. Basal cell carcinoma. This example has been neglected, producing a "rodent ulcer."

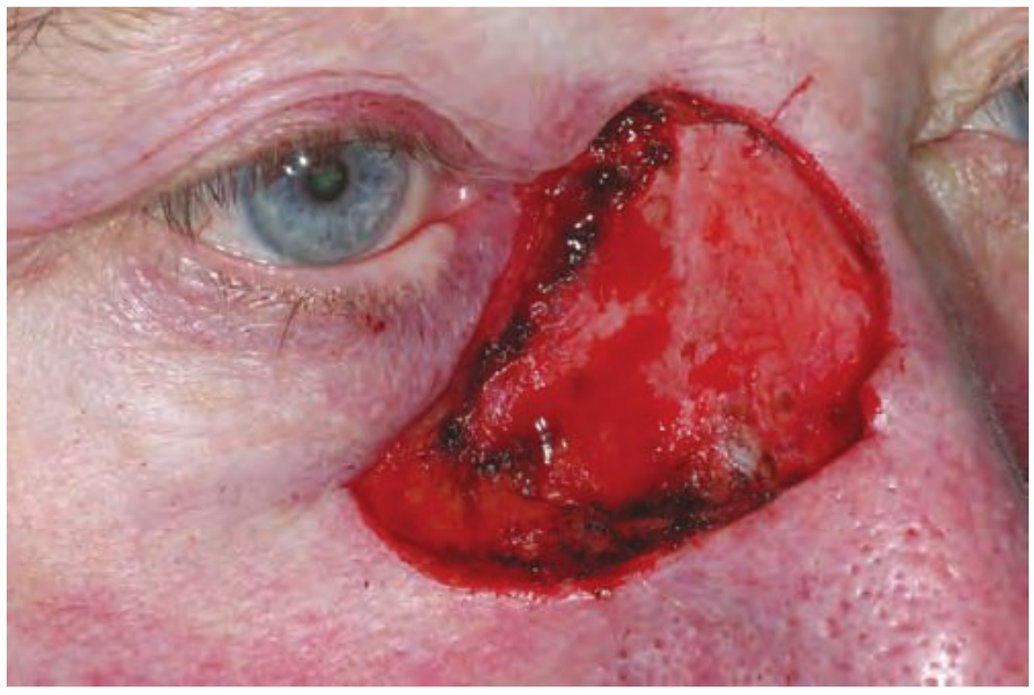


FIGURE 29-69. Micronodular basal cell carcinoma. An extensive resection was required, using Mohs' micrographic surgery, to achieve clear surgical margins.

local recurrence than other subtypes. The use of Mohs' micrographic surgery has been advocated to ensure complete excision of the infiltrating component (Figs. 29-68 and 29-69).

Most rodent ulcers possess a limited potential for growth; however, occasionally they can be infiltrative and aggressive and then can reach considerable size and invade deeply. On the face, they may destroy the eyes and nose (400), or they may penetrate the skull and invade the dura mater (401). Death may then ensue. (Such destructive basal cell carcinomas are seen occasionally also in the nevoid basal cell carcinoma syndrome; see text following.)

Pigmented basal cell carcinoma differs from the nodular type only by the brown pigmentation of the lesion.

Morphea-like or fibrosing basal cell carcinoma manifests as a solitary, flat or slightly depressed, indurated, yellowish plaque. The surface is smooth and shiny. The border is often ill defined (Fig. 29-70). The overlying skin remains intact for a long time before ulceration finally occurs. The term arises from a clinical resemblance to localized scleroderma or morphea. The tumors, despite being deeply infiltrative, may be mistaken clinically for a lesion of morphea or for a scar.

Fibroepithelioma consists of usually only one but occasionally of several raised, moderately firm, slightly pedunculated nodules covered by smooth, slightly reddened skin. Clinically, they resemble fibromas. The most common location is the back.

The *nevoid basal cell carcinoma syndrome* is an autosomal dominant disorder with low penetration. Small nodules appear between puberty and 35 years of age, and there may be hundreds or thousands of them (402). During the "nevoid" stage, the nodules slowly increase in number and size. They are haphazardly distributed over the face and body. During adulthood, many of the basal cell carcinomas undergo ulceration, and later in life, the disease sometimes enters a "neoplastic" stage in which some of the basal cell carcinomas, especially of the face, become invasive, destructive, and mutilating. Occasionally, even death occurs as



FIGURE 29-68. Micronodular basal cell carcinoma, with poorly defined clinical margins. An indication for Mohs' micrographic surgery.



FIGURE 29-70. Basal cell carcinoma, morpheic. The central part of the tumor is clearly seen, but the margins are not well defined.

the result of invasion of an orbit and of the brain (403–405). There also may be metastases to the lung (403).

Half of the adult patients with the nevoid basal cell carcinoma syndrome show numerous palmar and plantar pits 1 to 3 mm in diameter. These pits usually develop during the second decade of life and represent formes frustes of basal cell carcinoma (see Histopathology) (406). In addition, epidermal cysts are quite common (407).

Most patients show multiple skeletal and central nervous system anomalies (404), among which are odontogenic keratocysts of the jaws, anomalies of the ribs, scoliosis, mental retardation, and calcification of the falx cerebri. In several reported cases, there were also cerebellar medulloblastomas (408) or fibrosarcomas of a mandible or maxilla (409). In the jaw cysts, an ameloblastoma may arise (410).

The *linear unilateral basal cell nevus* is very rare. There is an extensive unilateral linear or zosteriform eruption, usually present since birth, consisting of closely set nodules of basal cell carcinoma (411). They may be interspersed with comedones (412,413) and striae-like areas of atrophy (414). The lesions do not increase in size with aging of the patient.

The *Bazex syndrome,* first described in 1966 (415), is dominantly inherited and shows as its main features (a) follicular atrophoderma characterized by widened follicular openings like "ice-pick marks" mainly on the extremities and (b) multiple, small basal cell carcinomas on the face, usually arising first in adolescence or early adulthood (416) but occasionally in late childhood (417). In addition, there may be localized anhidrosis or generalized hypohidrosis, as well as congenital hypotrichosis on the scalp and elsewhere (417).

Histopathology. Basal cell carcinomas tend to share the common features of a predominant basal cell type, peripheral palisading of lesional cell nuclei, a specialized stroma, and clefting artifact between the epithelium and the stroma. In addition, there are variable degrees of cytologic atypia and mitotic activity; some degree of these latter changes is virtually always present (Figs. 29-71 to 29-91). In nodular basal cell carcinoma, nodular masses of basaloid cells are formed that extend into the dermis in relation to a delicate, specialized tumor stroma (Figs. 29-75 to 29-77). Cystic spaces may form as a result of tumor necrosis or cellular dyshesion. The nuclei in basal cell carcinomas as a rule have a rather uniform appearance. They usually show no pronounced variation in size or intensity of staining and no abnormal mitoses, even in the rare instances of basal cell carcinoma with metastases. In the exceptional cases of basal cell carcinoma in which one finds, interspersed among the usual cells of basal cell carcinoma, cells with large hyperchromatic nuclei, multiple nuclei, and bizarre "starburst" mitoses, the clinical course is not different from that of the usual basal cell carcinoma (418,419).

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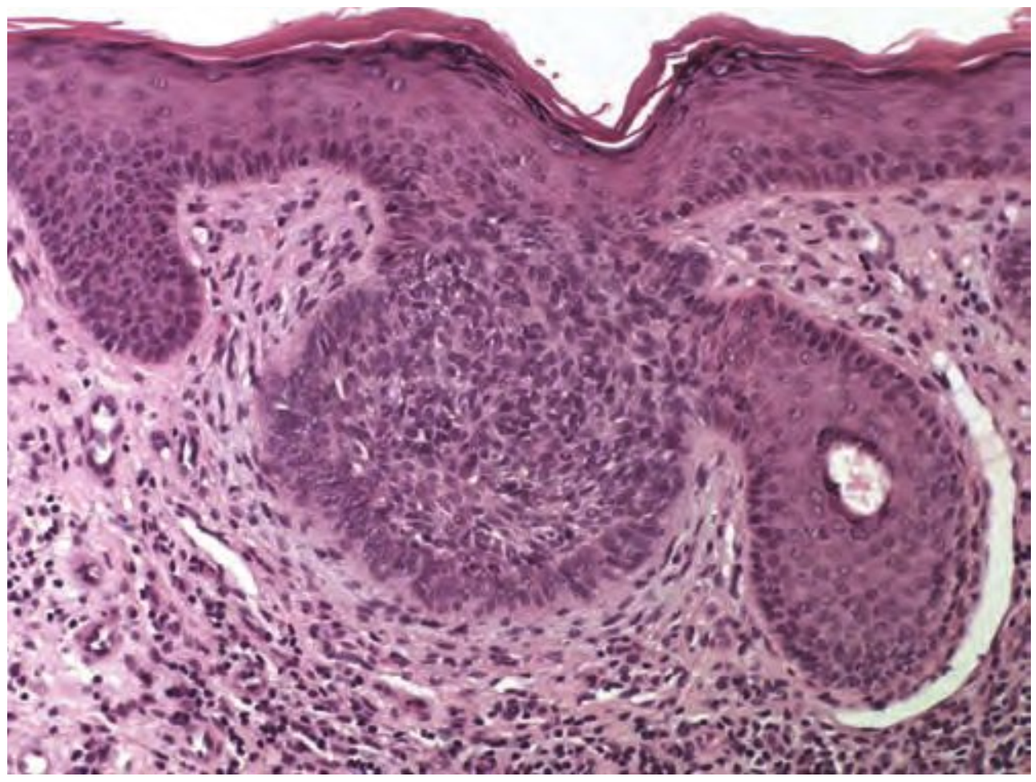


FIGURE 29-72. Superficial basal cell carcinoma. High magnification. The tumor shows a bud of cells in the bulge zone of a hair follicle similar to the primary epithelial germ buds in embryonal skin. A cleft is also present at the interface with the dermis.

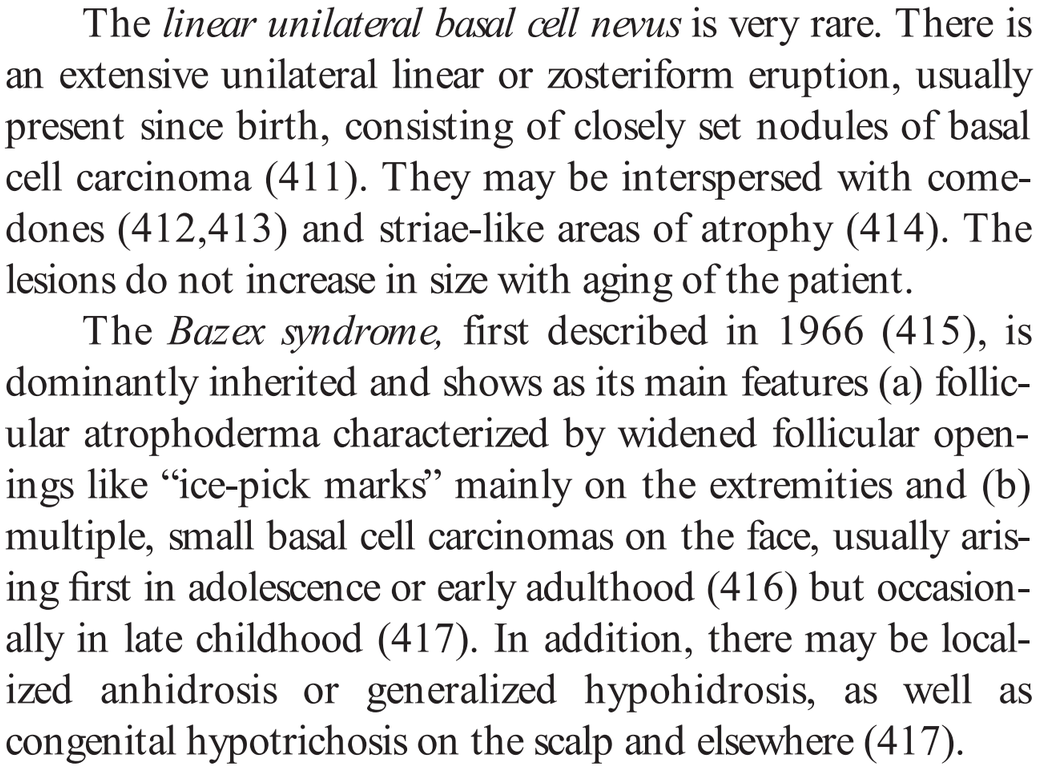


FIGURE 29-71. Superficial basal cell carcinoma. The tumor shows buds and irregular proliferations of tumor tissue attached to the undersurface of the epidermis.

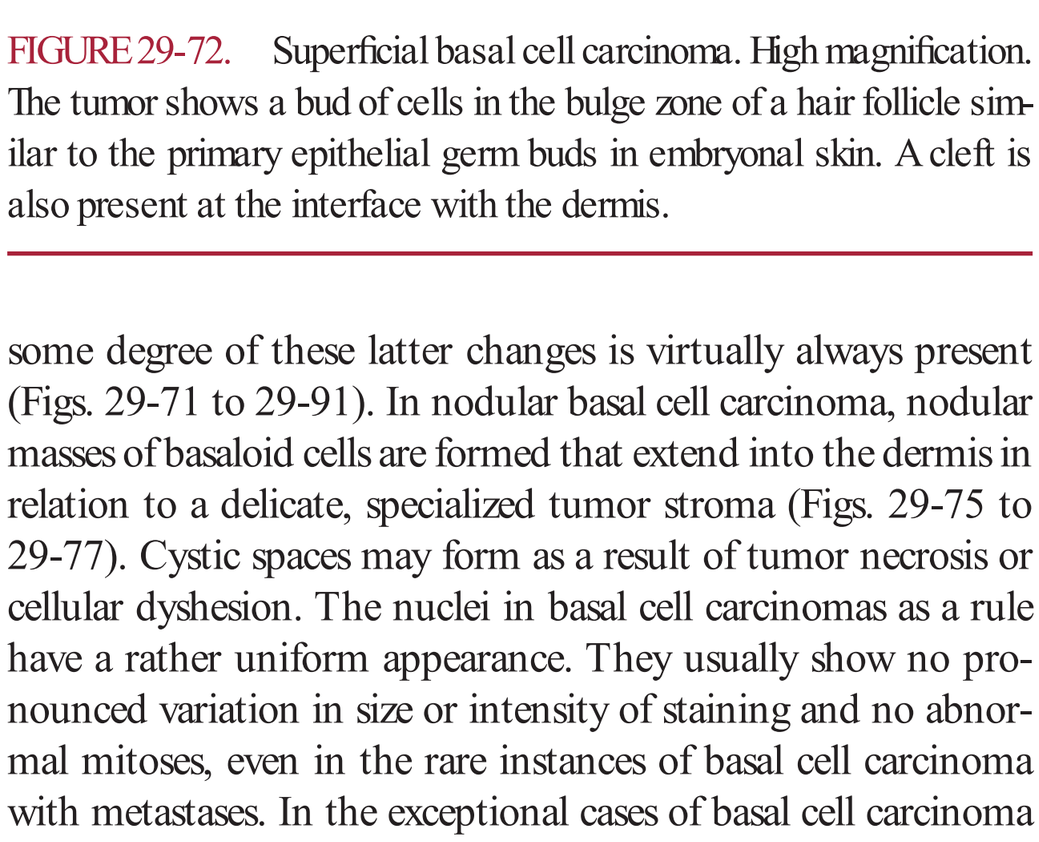


FIGURE 29-73. Superficial basal cell carcinoma. Ber EP4 staining highlights the tumor with normal epidermal structures unstained.

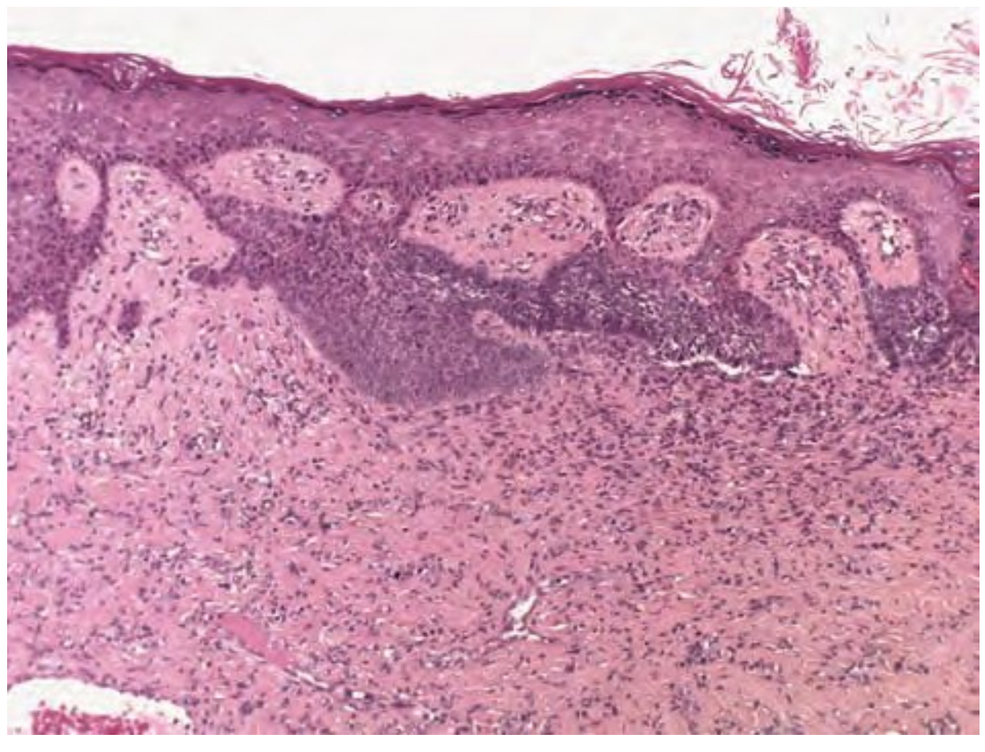


FIGURE 29-74. Dermatofibroma. There is a basal proliferation of basaloid cells mimicking the appearances of a superficial basal cell carcinoma.

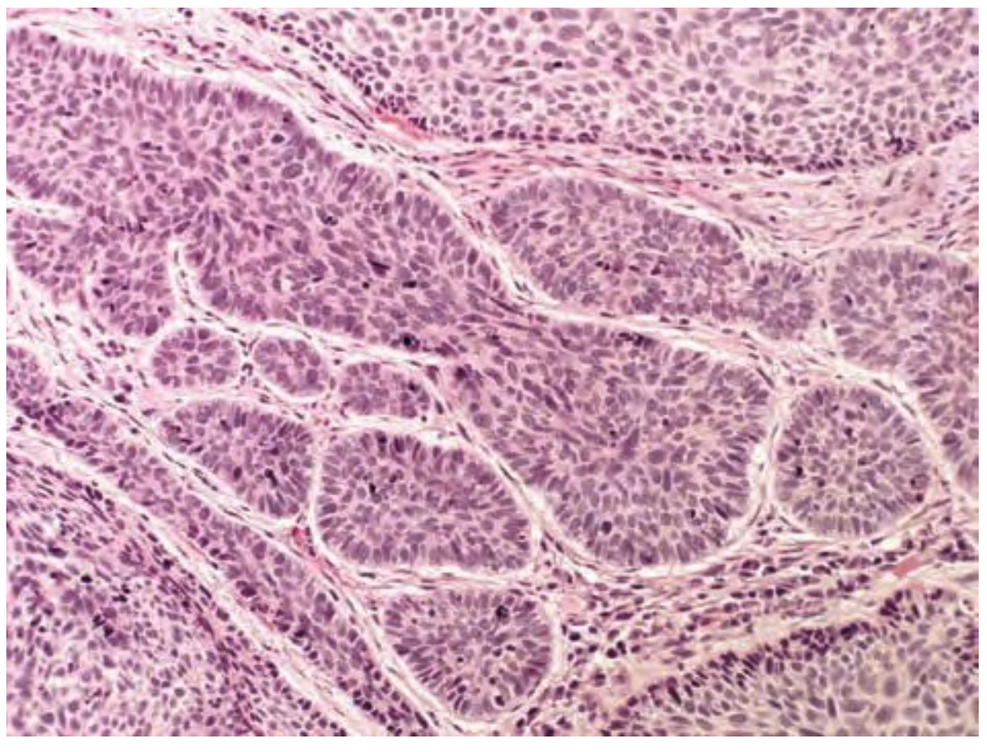


FIGURE 29-77. Nodular basal cell carcinoma. Medium magnification. The islands of tumor cells show peripheral palisading, as well as mitotic and apoptotic figures.

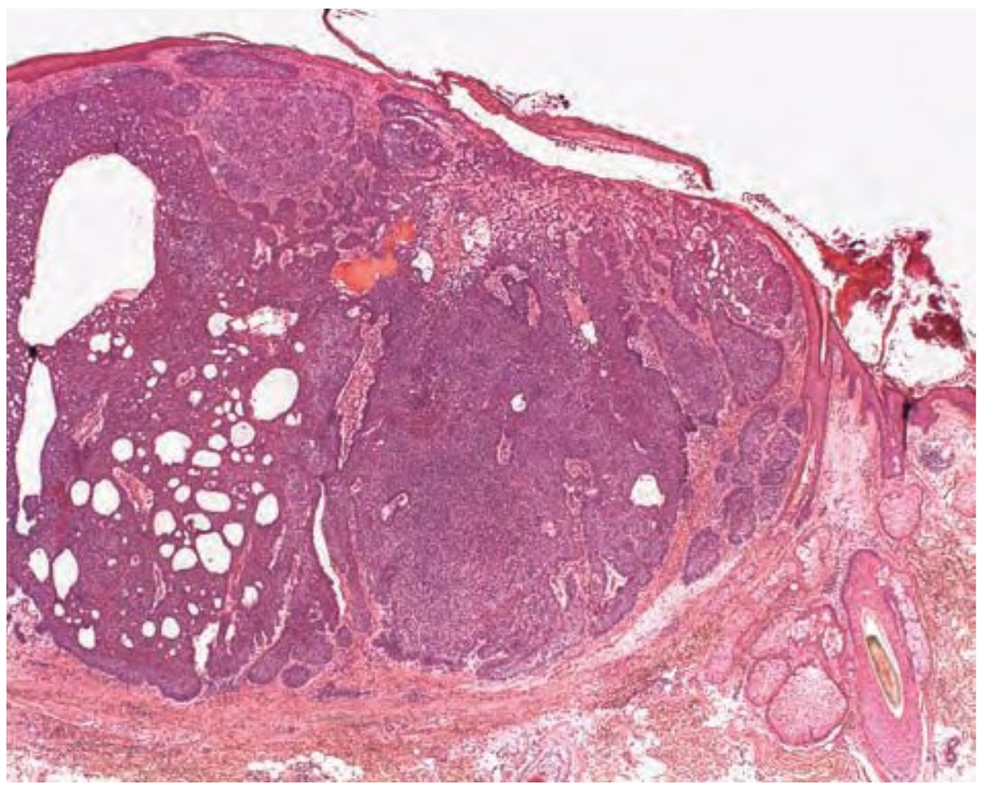


FIGURE 29-75. Basal cell carcinoma, nodular type. This excision specimen shows a nodular tumor with peripheral palisading.

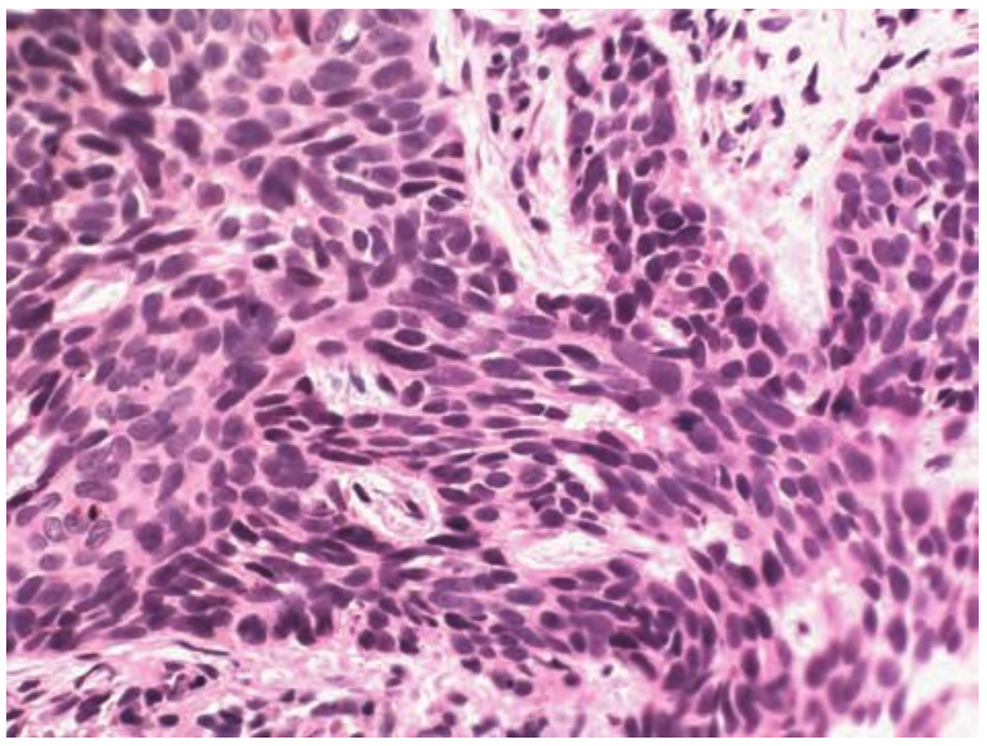


FIGURE 29-78. Basal cell carcinoma, solid type. High magnification. The basaloid tumor cells flow through the dermis with a variable degree of peripheral palisading.

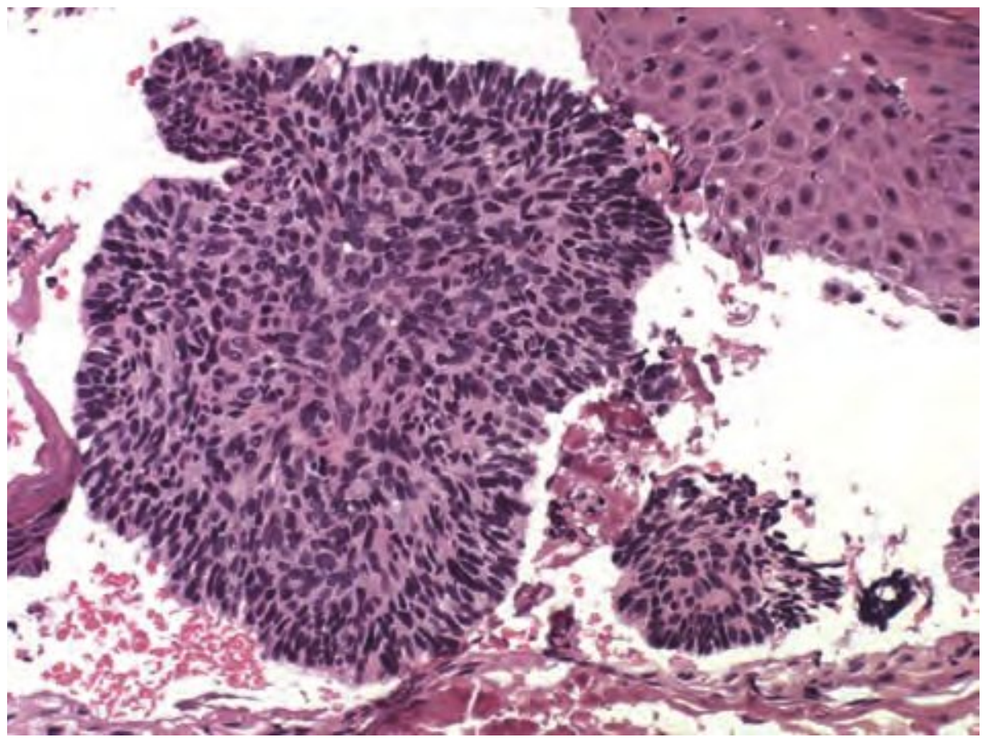


FIGURE 29-76. Basal cell carcinoma, nodular type. In this curetting specimen, nests of cells from a nodular basal cell carcinoma show peripheral palisading.

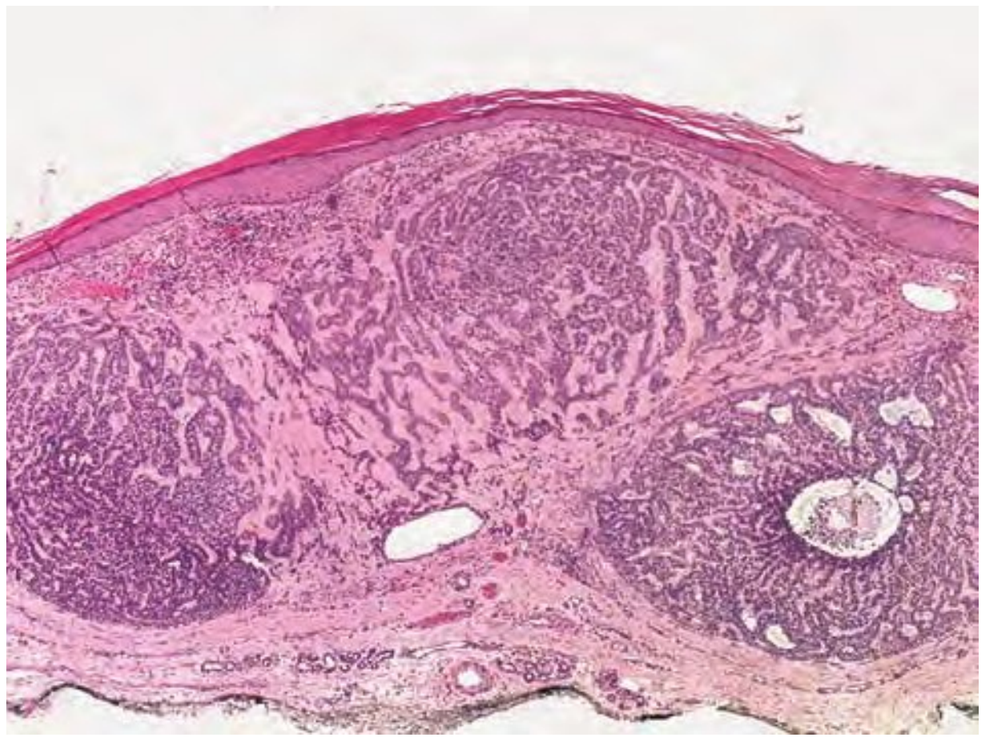


FIGURE 29-79. Adenoid basal cell carcinoma. Scanning magnification. The strands of epithelial cells form nodules, with a lacelike pattern of cells within the nodules.

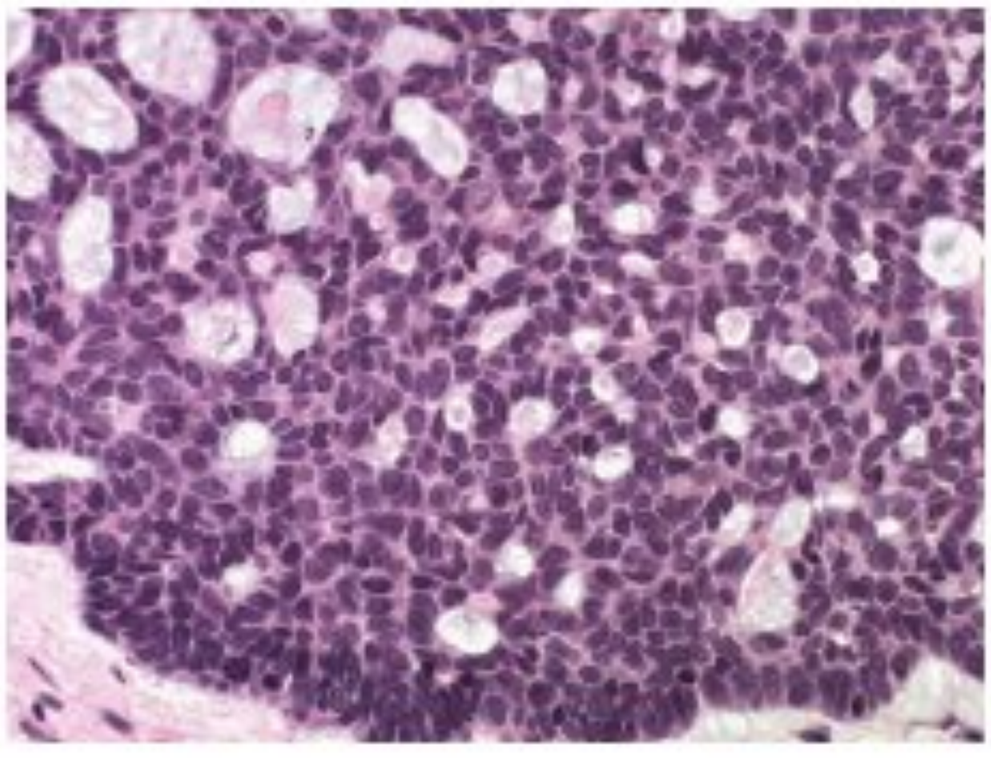


FIGURE 29-80. Adenoid basal cell carcinoma. High magnification. The strands of epithelial cells present a lacelike pattern. The stroma has a mucoid appearance.

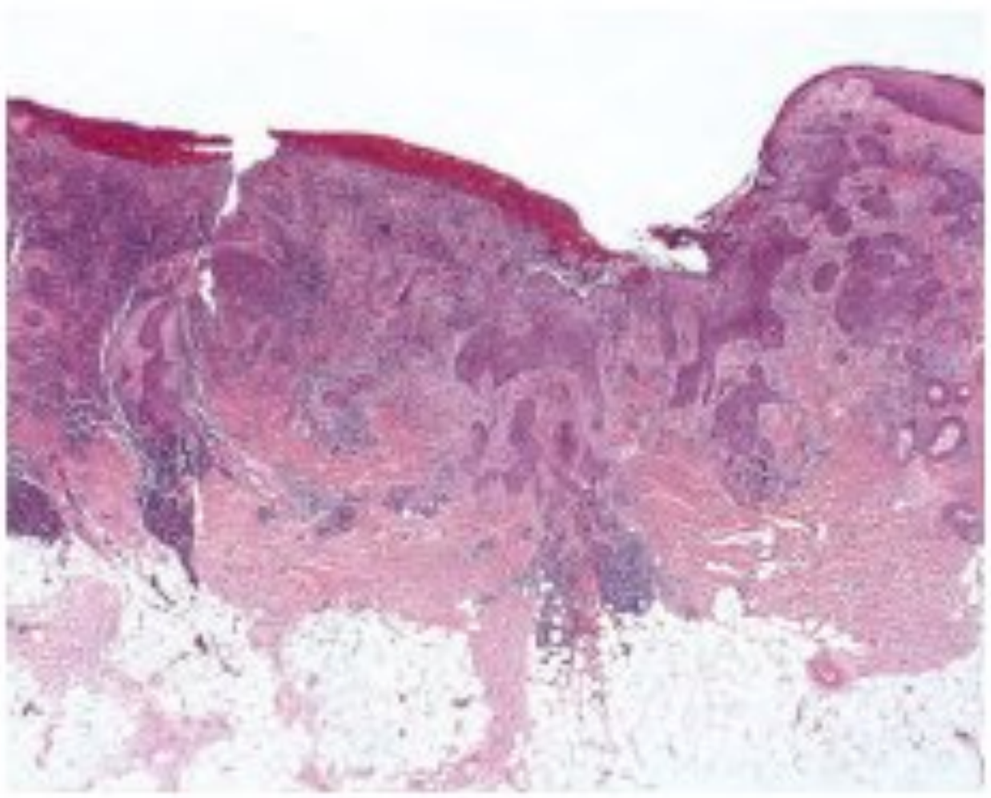


FIGURE 29-81. Micronodular basal cell carcinoma. The tumor is relatively symmetric and circumscribed, but with a more infiltrative element at its base.

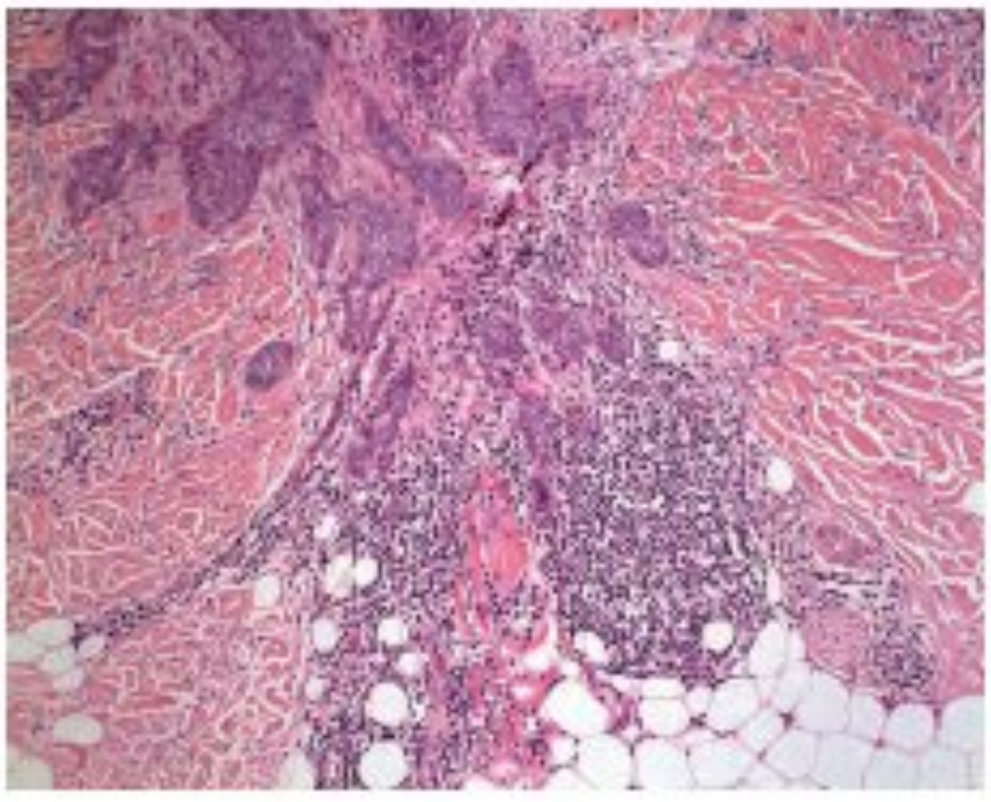


FIGURE 29-82. Micronodular basal cell carcinoma. Medium magnification. The infiltrative element at the base of the tumor extends through the full thickness of the dermis to the subcutis.

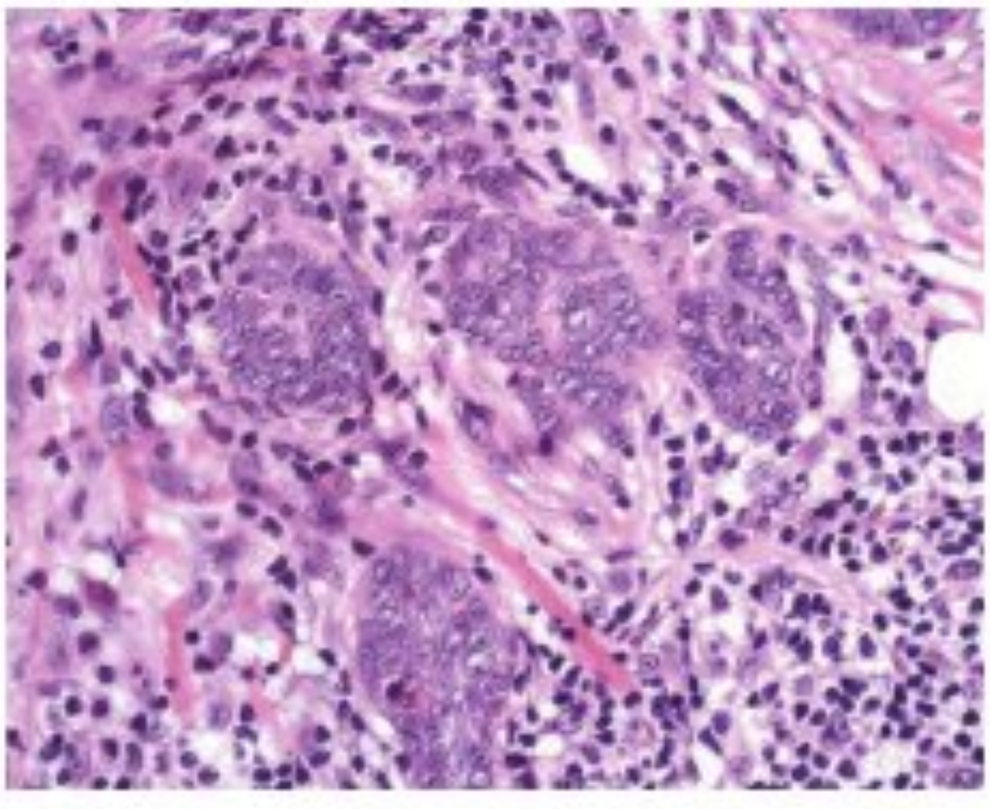


FIGURE 29-83. Micronodular basal cell carcinoma. High magnification. Micronodules of tumor infiltrate the deep dermis.

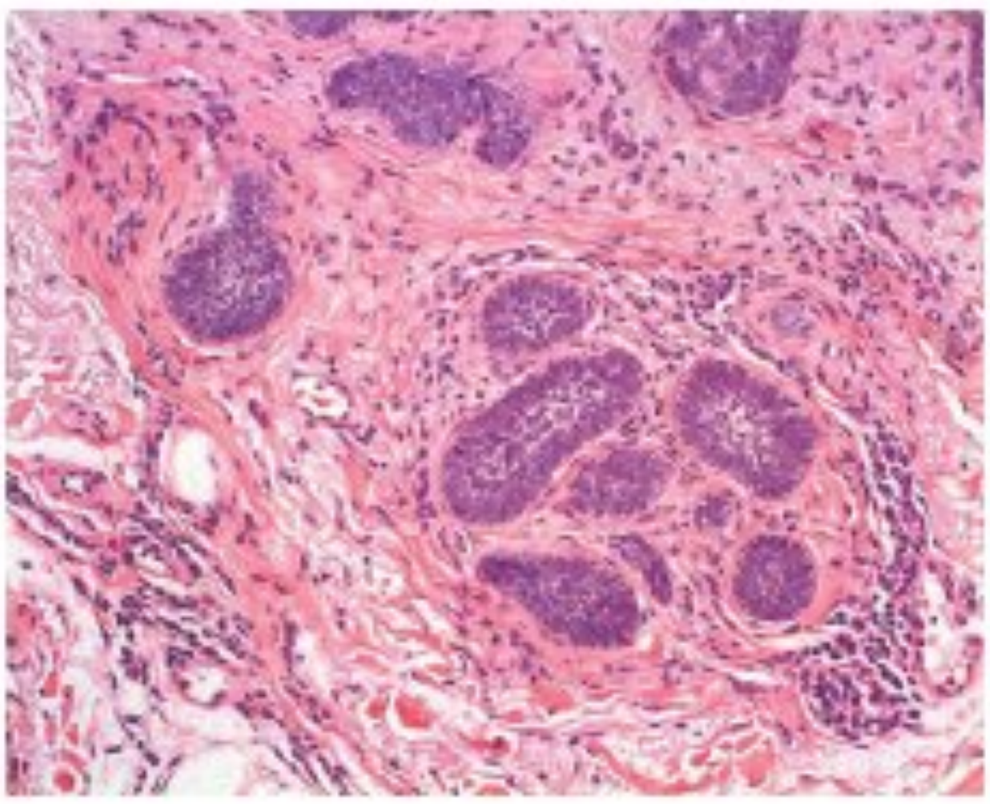


FIGURE 29-84. Micronodular basal cell carcinoma. High magnification. A less-inflamed example showing micronodules of invasive basal cell carcinoma.

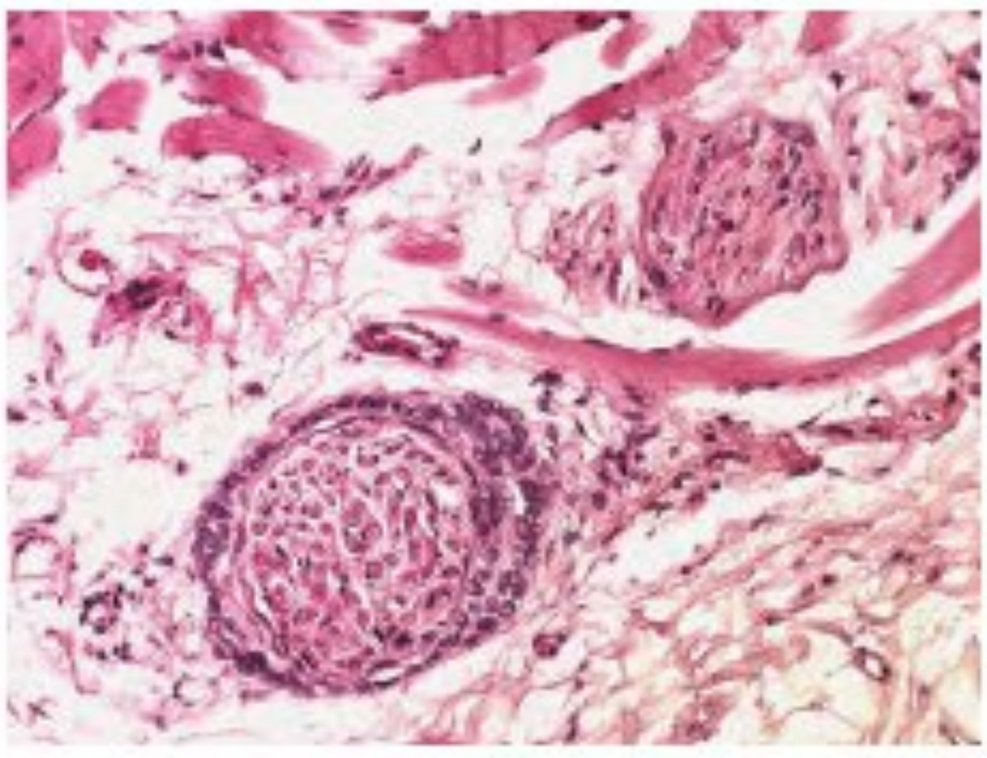


FIGURE 29-85. Micronodular basal cell carcinoma. High magnification. Tumor cells infiltrate around a dermal nerve close to the excision margin.

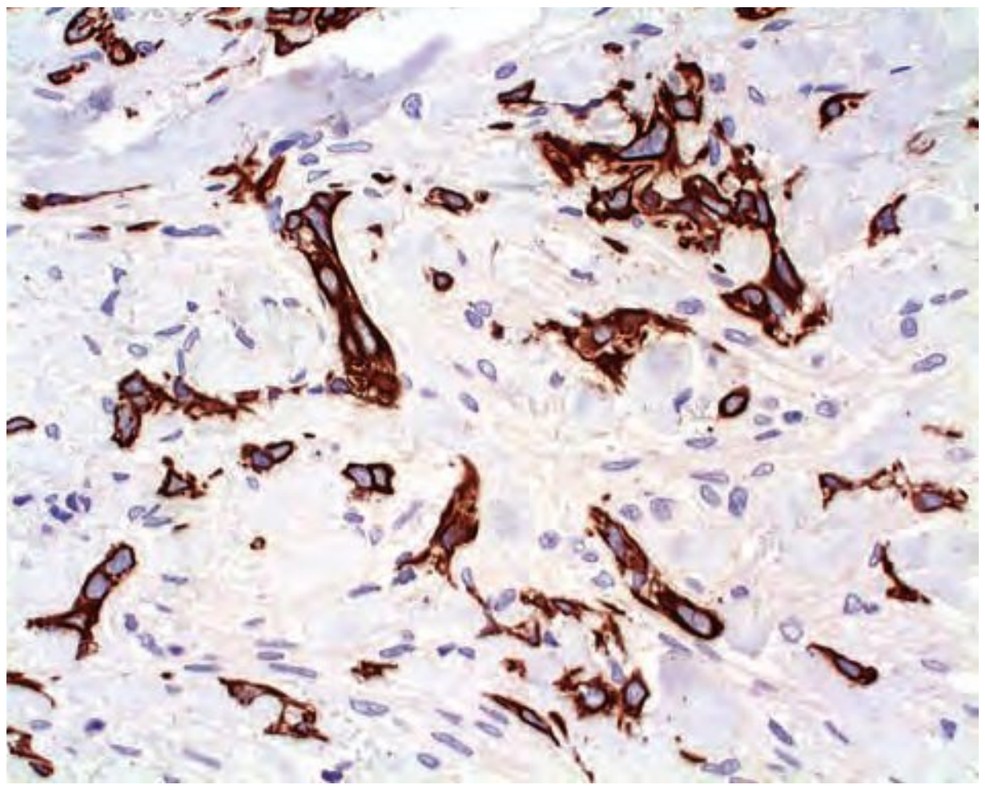


FIGURE 29-86. Basal cell carcinoma, morpheic. Basaloid cells, emphasized by cytokeratin staining, infiltrate the dermis within their specialized stroma.



FIGURE 29-89. Basal cell carcinoma showing follicular differentiation. Epithelium and stroma form structures reminiscent of follicular germs, and there is formation of a horn cyst resembling a follicular structure.

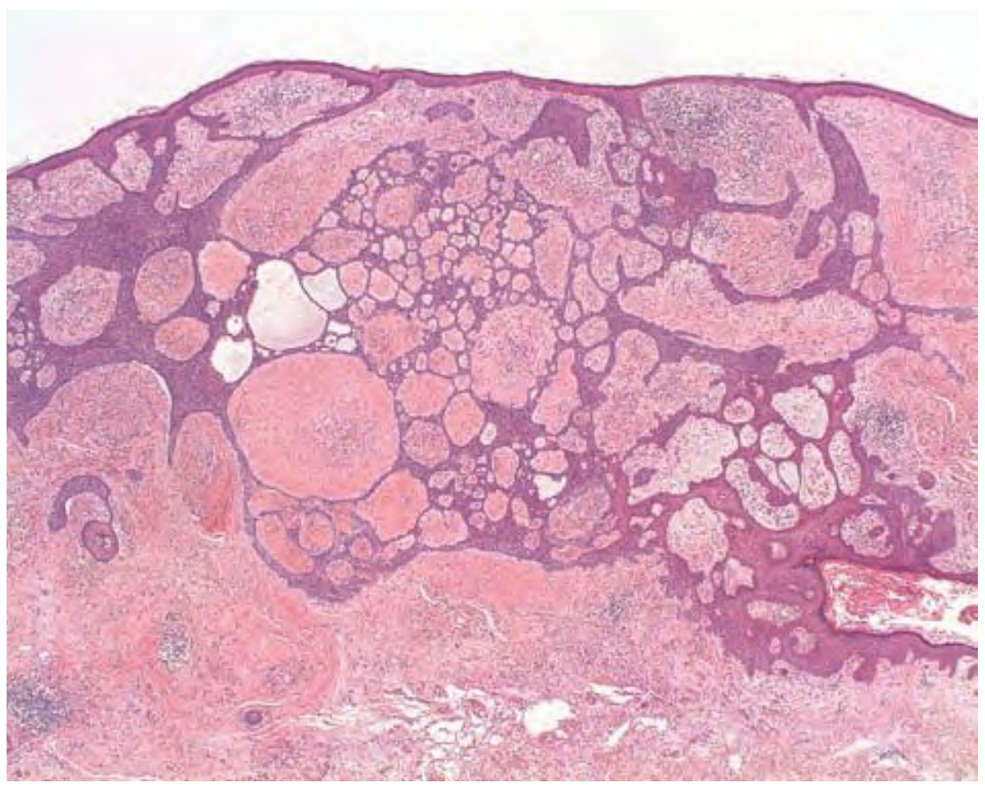


FIGURE 29-87. Fibroepithelioma of Pinkus (fibroepithelial basal cell carcinoma). The tumor has an elevated nodular appearance.

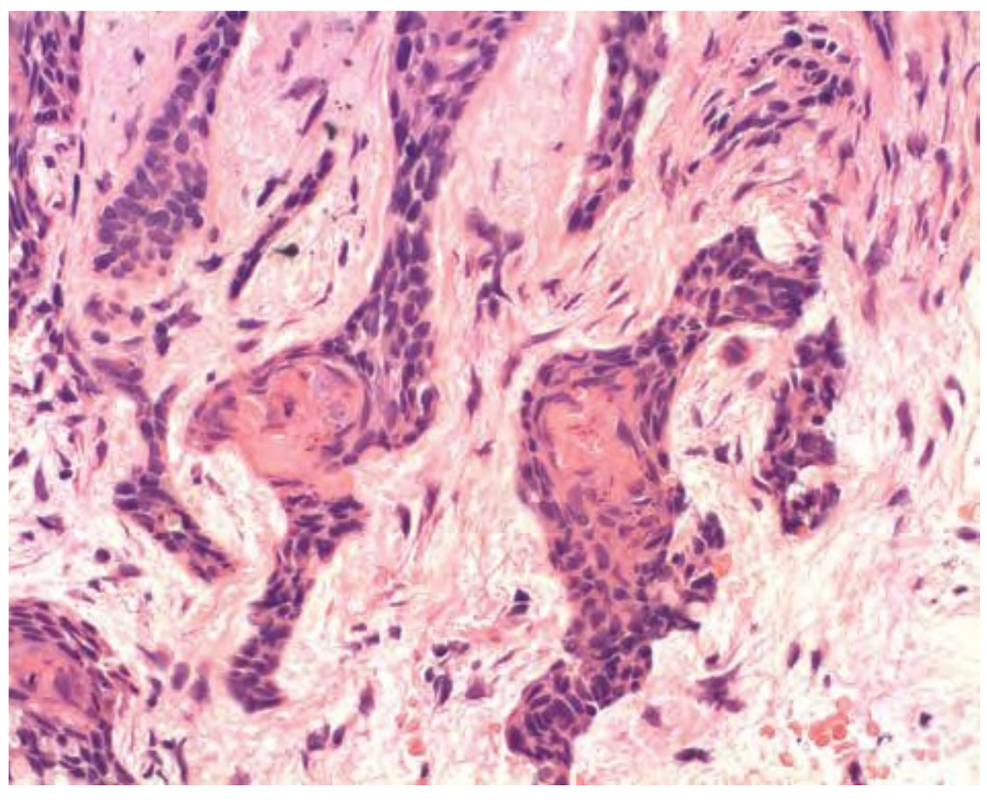


FIGURE 29-90. Basal cell carcinoma, infiltrative, metatypical. There is focal squamous differentiation within the infiltrating cords of basaloid cells.

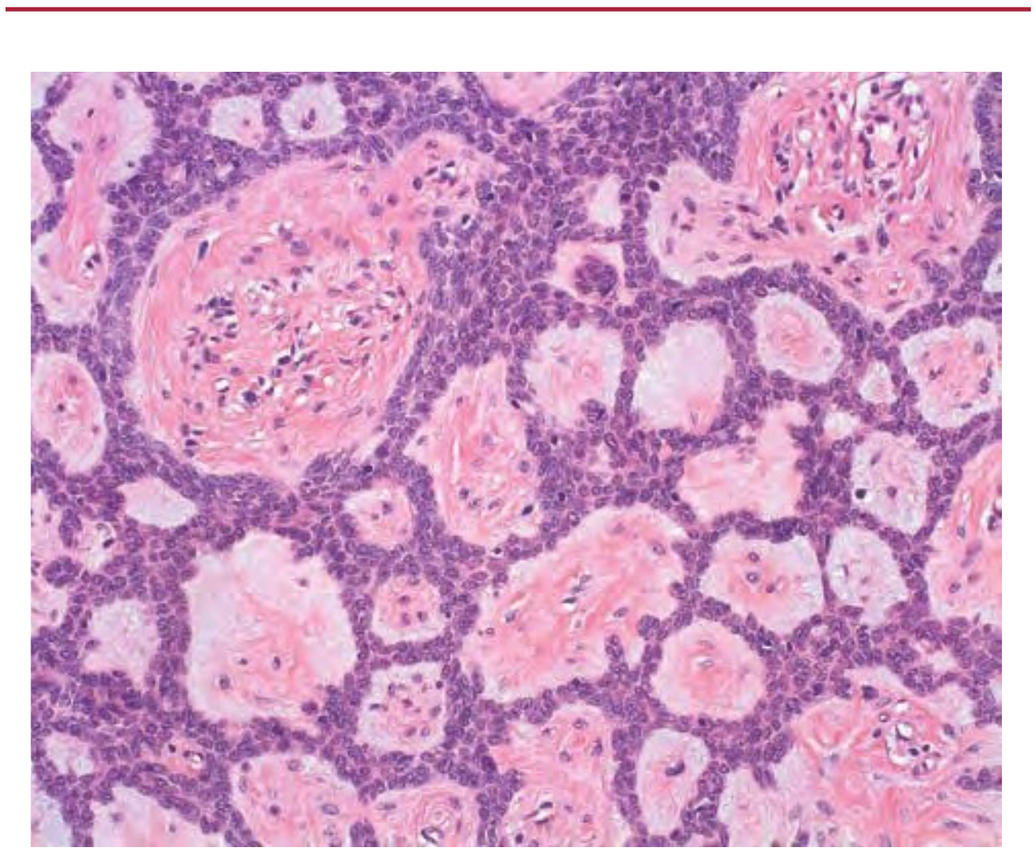


FIGURE 29-88. Fibroepithelioma of Pinkus (fibroepithelial basal cell carcinoma). Long, thin, branching, anastomosing strands of basal cell carcinoma are embedded in a fibrous stroma.

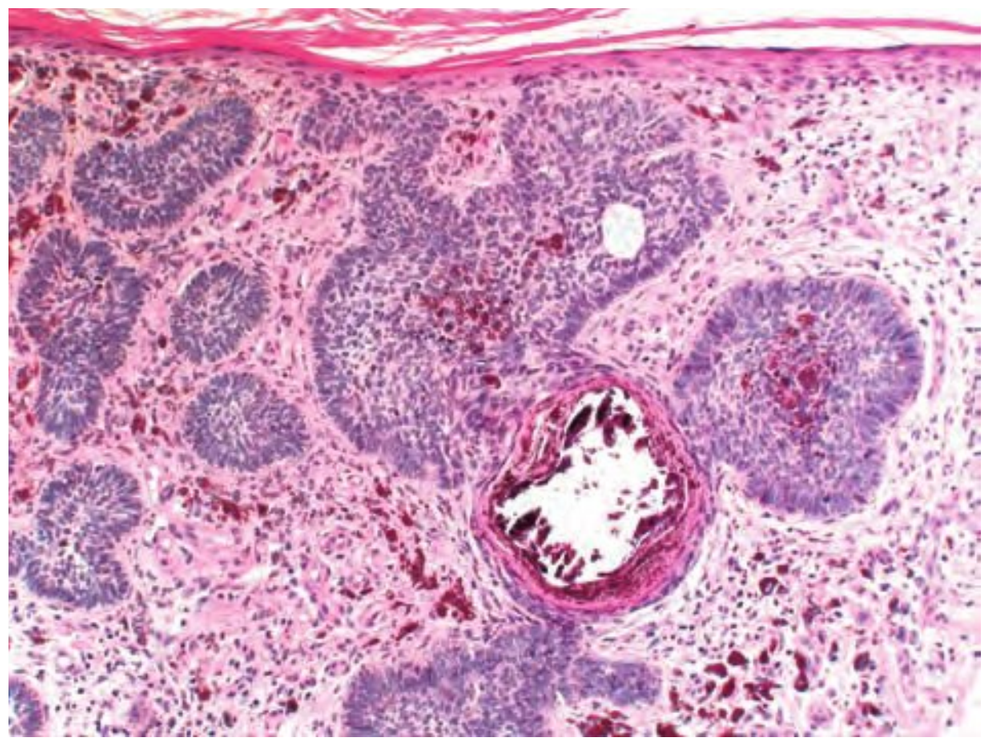


FIGURE 29-91. Pigmented basal cell carcinoma. Melanin pigment is present within solid islands of basal cell carcinoma and in macrophages between the islands of tumor cells.

The connective tissue stroma proliferates with the tumor and is arranged in parallel bundles around the tumor masses, so that a mutual relationship seems to exist between the parenchyma of the tumor and its stroma (420,431). The stroma adjacent to the tumor masses often shows numerous young fibroblasts; in addition, it may appear mucinous (432,433). Frequently there are areas of retraction of the stroma from tumor islands, resulting in peritumoral lacunae (Fig. 29-71). These lacunae once were regarded as a fixation artifact, but peritumoral lacunae can be observed also on cryostat sections. Immunostaining with antibodies to laminin, type IV collagen, and bullous pemphigoid has revealed the presence of laminin and type IV collagen on the stroma side of the lacunae, but bullous pemphigoid antigen is absent at the site of lacunae (434). Even though bullous pemphigoid antigen is diminished in other areas of basal cell carcinoma (435), it is likely that loss of this antigen contributes to the formation of peritumoral lacunae (434). Because these lacunae are quite typical for some basal cell carcinomas, their presence aids in the differentiation of basal cell carcinoma from other tumors, such as squamous cell carcinoma. In addition, stromal or intratumor deposits of amyloid are found quite frequently (see Pathogenesis) (436). A mild inflammatory infiltrate is often seen in the stroma of nonulcerated basal cell carcinomas but may be entirely lacking. If ulceration occurs, there usually is a rather pronounced inflammatory reaction.

From a histologic point of view, basal cell carcinomas can be divided into two groups: undifferentiated and differentiated. Those of the latter group show a slight degree of differentiation toward the cutaneous appendages of hair, sebaceous glands, apocrine glands, or eccrine glands. A sharp dividing line between the two groups cannot be drawn because many undifferentiated basal cell carcinomas show differentiation in some areas, and most differentiated basal cell carcinomas show areas lacking differentiation. By correlating the clinical classification with the histologic classification, it can be stated that nodular basal cell carcinoma, as well as the lesions of the nevoid basal cell carcinoma syndrome, the linear unilateral basal cell nevus, and the Bazex syndrome, may show differentiation or no differentiation, but the other four types of basal cell carcinoma—pigmented basal cell carcinoma, fibrosing basal cell carcinoma, superficial basal cell carcinoma, and fibroepithelioma—usually show little or no differentiation (Figs. 29-87 and 29-88).

From a clinical point of view it is probably more relevant to classify basal cell carcinomas into those with a low risk of recurrence (nodular, nodulocystic and fibroepithelioma of Pinkus) and those with a high risk of local recurrence (superficial, micronodular, infiltrative, morpheic, metatypical). Of these the *micronodular basal cell carcinoma* has received the least recognition but probably carries as high a risk of local recurrence as the others in the high-risk group (Figs. 29-81 to 29-85). They vary between symmetric, circumscribed examples and others that are asymmetric and infiltrate between collagen bundles. The risk of local recurrence may be related to the presence of perineural invasion (which may occur in other types of basal cell carcinoma as well; Fig. 29-85) and to the focal nature, in which the tumor may infiltrate deeply into the dermis to involve the excision margin (Fig. 29-82). Micronodular basal cell carcinoma is rarely seen without other forms of basal cell carcinoma differentiation. More typically, micronodular differentiation is seen toward the base of a tumor. When a basal cell carcinoma is infiltrating deeply into the dermis or reaches the subcutis, micronodular differentiation may frequently be present in the deeper compartment of the tumor. There is an overlap of appearances between morpheic and micronodular basal cell carcinomas. In deciding on the subtype with which one is dealing, the element representing more than 50% of the whole tumor should take precedence.

Basal cell carcinomas showing differentiation toward hair structures (Fig. 29-89) are called *keratotic*; toward sebaceous glands, *basal cell carcinomas with sebaceous differentiation*; and toward tubular glands, *adenoid* basal cell carcinomas (Figs. 29-79 and 29-80). A *signet ring cell* variant has also been described (437). In many differentiated basal cell carcinomas, differentiation is directed toward more than one of these cutaneous appendages. For example, areas of keratinization may be found in a tumor that also shows adenoid structures. No difference exists in the rate of growth between undifferentiated and differentiated basal cell carcinomas.

In more than 90% of basal cell carcinomas, a connection between tumor cell formations and the surface epidermis can be shown to exist (438). Occasionally, a tumor mass is found in contact with an outer root sheath. The peripheral cell layer of the tumor masses often shows a palisade arrangement, whereas the nuclei of the cells inside lie in a haphazard fashion. *Basal cell carcinomas* of the *infiltrative* type, also referred to as *aggressive* basal cell carcinomas, show the basaloid cells predominantly arranged as elongated strands only a few layers thick and with little or no palisading of the peripheral cells. Such strands can invade deeply. The demarcation of the tumor from the stroma is often poor (440). Immunohistochemical staining for cytokeratin may aid to highlight the infiltrating tumor cells (Fig. 29-86). There are cell aggregates that display an irregular, spiky configuration (441). The cells and their nuclei show great variations in size and shape (442). There may be foci of squamous differentiation (Fig. 29-90). The number of inflammatory cells depends to some degree on the extent of ulceration. There often is perineural infiltration (440), and, on the face, there may be invasion of bone (401).

Keratotic basal cell carcinoma shows parakeratotic cells and horn cysts in addition to undifferentiated cells. The parakeratotic cells possess elongated nuclei and a slightly eosinophilic cytoplasm, in contrast to the deeply basophilic cytoplasm of undifferentiated cells. The parakeratotic cells may lie in strands, in concentric whorls, or around the horn cysts. It is likely that they are cells with initial keratinization somewhat similar to the nucleated cells in the keratogenic zone of normal hair shafts. The horn cysts, which are composed of fully keratinized cells, represent attempts at hair shaft formation (443). Just as in the keratinization of the hair shaft, the horn cysts form without the interposition of granular cells. Some keratotic basal cell carcinomas possess horn cysts of considerable size.

Keratotic basal cell carcinoma shares with trichoepithelioma the presence of horn cysts, and it is sometimes difficult to decide whether a lesion represents a keratotic basal cell carcinoma or a trichoepithelioma (see Chapter 30). Clinical data may be necessary for a decision to be reached. The horn cysts must not be confused with the horn pearls that occur in squamous cell carcinoma (see Differential Diagnosis).

Basal cell carcinoma with sebaceous differentiation shows essentially a basal cell carcinoma in which there are interspersed aggregates of sebaceous cells. A clear-cut separation from sebaceoma (sebaceous epithelioma) is at times impossible because transitions exist. Most examples of lesions believed to represent basal cell carcinomas with sebaceous differentiation are probably actually sebaceomas (444).

Adenoid basal cell carcinoma shows formations suggesting tubular, glandlike structures. The cells are arranged in intertwining strands and radially around islands of connective tissue, resulting in a tumor with a lacelike pattern (Figs. 29-79 and 29-80). In rare instances, lumina may be surrounded by cells that have the appearance of secretory cells. The lumina may be filled with a colloidal substance or with an amorphous granular material, but definite evidence of secretory activity of the cells lining the lumina cannot be obtained, even with histochemical methods. Similarly, because of the low degree of differentiation of the cells, histochemical reactions that would indicate either apocrine or eccrine differentiation are negative (445). The tumor originally described as basal cell tumor with eccrine differentiation (446) is now regarded as an eccrine carcinoma and referred to as *syringoid eccrine carcinoma* (see Chapter 30).

Four uncommon histologic variants of basal cell carcinoma have been described: an adamantinoid type, a granular type, a clear cell type, and a type with matricial differentiation. *Adamantinoid basal cell carcinoma* shows a great histologic resemblance to dental ameloblastoma or adamantinoma (447). One observes solid masses of basaloid cells with palisading at the periphery. Inside this layer, the cells show elongated nuclei and stellate cytoplasm stretched as thin, connecting bridges across empty spaces, as seen in adamantinoma. In *granular basal cell carcinoma,* some of the tumor cells have the usual appearance of basaloid cells, whereas others show a gradual transition to granular cells. The granular cells show in their cytoplasm numerous eosinophilic granules with a tendency to coalesce (448,449). The eosinophilic lysosome-like granules greatly resemble those seen in granular cell tumor (see Chapter 35). In the *clear cell basal cell carcinoma,* the clear cell pattern may occupy all or part of the tumor islands. The clear cells contain vacuoles of different sizes filled with glycogen (450). The vacuoles often cause peripheral displacement of the nucleus, giving the cells a signet ring appearance (451). In *basal cell carcinoma with matricial differentiation,* islands of shadow cells, as seen in pilomatricoma, are located within a basal cell carcinoma (452).

Although about 75% of basal cell carcinomas are found on staining with dopa to contain melanocytes and melanin is present in about 25% of them (453), large amounts of melanin are encountered only rarely (Fig. 29-91). The melanin is produced by benign melanocytes that colonize the tumor. These tumors are called *pigmented basal cell carcinomas.*

Superficial basal cell carcinoma shows buds and irregular proliferations of tumor tissue attached to the undersurface of the epidermis (Figs. 29-71 and 29-72). The peripheral cell layer of the tumor formations often shows palisading. In most cases, there is little penetration into the dermis. The overlying epidermis usually shows atrophy. Fibroblasts, often in a fairly large number, are arranged around the tumor cell proliferations. In addition, a mild or moderate amount of a nonspecific chronic inflammatory infiltrate is present in the upper dermis.

In *fibroepithelioma,* first described by Pinkus in 1953 (420), long, thin, branching, anastomosing strands of basal cell carcinoma are embedded in a fibrous stroma (Figs. 29-87 and 29-88). Many of the strands show connections with the surface epidermis. Here and there, small groups of dark-staining cells showing a palisade arrangement of the peripheral cell layer may be seen along the epithelial strands, like buds on a branch. Usually, the tumor is quite superficial and is well demarcated at its lower border. Fibroepithelioma combines features of the intracanalicular fibroadenoma of the breast, the reticulated type of seborrheic keratosis, and superficial basal cell carcinoma (420). Fibroepithelioma can change into an invasive and ulcerating basal cell carcinoma (453).

The multiple basal cell carcinomas seen in the *nevoid basal cell carcinoma syndrome* present no features that distinguish them from ordinary basal cell carcinoma, even while they are still in the early nevoid stage and have not yet become invasive and destructive, as they may be later in the neoplastic stage (454). All of the diverse features of basal cell carcinoma, such as solid, adenoid, cystic, keratotic, superficial, and fibrosing formations, can be seen in the lesions of the nevoid basal cell carcinoma syndrome (455). Usually, a histologic distinction between the nevoid basal cell carcinoma syndrome and typical trichoepithelioma is easy because keratotic cysts are more prominent in the latter. However, some lesions of trichoepithelioma show relatively few horn cysts. A histologic distinction in such cases may be impossible (456), and clinical data will be necessary (see Chapter 30).

The palmar and plantar pits are a result of the premature desquamation of most of the horny layer (457). On histologic examination, the epidermal rete ridges beneath the pits are found to be crowded with cells resembling those of basal cell carcinoma. Overlying these rete ridges is a markedly thinned granular layer topped by a very thin layer of loose keratin (406). In some patients, the pits actually show the presence of small basal cell carcinomas at their base (458). In rare instances, one or several clinically visible basal cell carcinomas arise on the palms or soles in patients with palmar and plantar pits (457,459,460).

The jaw cysts represent odontogenic keratocysts. They are lined by a festooned epithelium consisting of two to five layers of squamous cells that form keratin without the presence of a granular cell layer (461). Each jaw cyst may consist of either one large cyst or multiple microcysts (455). Some of the

cutaneous cysts, instead of being epidermal cysts, have the appearance of the jaw cysts and are similar to those cysts seen in steatocystoma multiplex but without showing sebaceous lobules (461).

The basal cell carcinomas in *linear unilateral basal cell nevus* have a variable histologic appearance. The tumor formations may be solid, adenoid, keratotic, or cystic (412,462). In addition, there may be areas resembling trichoepithelioma (411) or eccrine spiradenoma (463). The walls of the comedones show numerous buds of basal cell carcinoma extending into the surrounding dermis (412,414).

The basal cell carcinomas encountered in the *Bazex syndrome* have a variable histologic appearance. Some of them are indistinguishable from trichoepithelioma (416,417). The areas of follicular atrophoderma show a dilated follicular ostium leading into a distorted and underdeveloped pilosebaceous unit (417).

The tumor described in 1926 by Jadassohn and regarded by him as an intraepidermal epithelioma analogous to one previously reported by Borst has been referred to as *Borst-Jadassohn epithelioma.* For a long time this tumor and similar tumors subsequently described were believed to be intraepidermal basal cell carcinomas because the cells composing the intraepidermal islands usually are small and have a deeply basophilic cytoplasm (464). However, on careful examination, it became evident that the cells composing the intraepidermal islands in the presumed intraepidermal basal cell carcinomas possess intercellular bridges and are seborrheic keratoses of the clonal type (77,465). The existence of an intraepidermal basal cell carcinoma is also unlikely because the close relationship that exists between tumor and stroma in basal cell carcinoma excludes the formation of intraepidermal nests, which would lack any contact with the stroma (466).

However, there are several types of tumors, some benign and some malignant, that on occasion show well-defined islands of cells within the epidermis that differ in their appearance from the surrounding epidermal cells (101). This is referred to as the *Jadassohn phenomenon.* Among the tumors that occasionally have an intraepidermal location are the following:

Clonal seborrheic keratosis. Some of these tumors show intraepidermal aggregates of basaloid cells suggestive of a basal cell carcinoma *in situ* (Figs. 29-10 and 29-11) (77), whereas others show intraepidermal islands of an irritated seborrheic keratosis simulating a squamous cell carcinoma *in situ*.

Bowen's disease. Occasionally, one observes clonal aggregates of Bowen's disease within the epidermis (467). At a later stage, there may be dermal invasion (468).

Intraepidermal poroma, also referred to as *hidroacanthoma simplex* (see Chapter 30) (469,470).

Intraepidermal malignant eccrine poroma (471). In cases of intraepidermal metastases of malignant eccrine poroma, the tumor masses extend through the superficial lymphatics from the dermis into the epidermis (see Chapter 31) (472).

The concept of intraepidermal tumors also includes Paget's disease of the breast, extramammary Paget's disease (see Chapter 30), intraepidermal junction nevus (see Chapter 28), and malignant melanoma *in situ* (see Chapter 28) (101).

Some authors still regard the intraepidermal epithelioma of Jadassohn as a distinct entity that may invade the dermis and occasionally cause metastases (473). It has been postulated that this tumor arises from acrosyringium keratinocytes or pluripotential adnexal cells and represents an adnexal carcinoma (473).

The existence of *basal cell carcinomas with features of squamous cell carcinoma* was first postulated in 1922 (474). Two types of basal squamous cell epitheliomas, referred to as *metatypical epitheliomas,* were recognized: a mixed and an intermediary type. The mixed type was described as showing focal keratinization consisting of pearls with a colloidal or parakeratotic center, and the intermediary type as showing two kinds of cells within a network of narrow strands, an outer row of dark-staining basal cells and an inner layer of cells appearing larger, lighter, and better defined than the basal cells and regarded as intermediate in character between basal and squamous cells.

Several authors have accepted the existence of basal squamous cell epitheliomas or metatypical epitheliomas (397, 475–477). They are considered by some to represent a transition from basal cell carcinoma to squamous cell carcinoma. It has been stated that a continuum extends from basal cell carcinoma at one extreme to squamous cell carcinoma at the other (477). The incidence of basal squamous cell carcinomas among basal cell carcinomas has been judged to be 3% (477), 8% (476), and even 12% (475). It has also been stated that basal squamous cell epitheliomas show a greater tendency to metastasize than basal cell carcinomas (397,475,477).

However, the existence of basal squamous cell epitheliomas is questioned by many (431,478–482). It would seem that the entirely different genesis of squamous cell carcinoma—a true anaplastic carcinoma of the epidermis—and basal cell carcinoma—a tumor composed of immature rather than anaplastic cells—makes the occurrence of transitional forms quite unlikely (see Pathogenesis). It can be assumed that the so-called mixed type of basal squamous cell epithelioma represents a keratotic basal cell carcinoma (Fig. 29-90) and that the intermediate type represents a basal cell carcinoma with differentiation into two types of cells (basal cell carcinoma with squamous differentiation). This form of differentiation is often seen deep to an area of ulceration. Other putative examples of basosquamous differentiation are better interpreted as *basal cell carcinoma with follicular differentiation* (Fig. 29-89).

Mixed carcinoma shows a squamous cell carcinoma contiguous to a basal cell carcinoma as a so-called collision tumor. It is likely that, in most instances, the squamous cell carcinoma develops secondary to the basal cell carcinoma. As other chronic ulcerative lesions, such as burns and stasis ulcers, basal cell carcinoma may stimulate the development of a squamous cell carcinoma. Before making a diagnosis of mixed carcinoma, however, one must rule out the possibility of pseudocarcinomatous hyperplasia occurring in a basal cell carcinoma.

Pathogenesis. Krompecher, the original describer of basal cell carcinoma, stated in 1903 that he regarded this tumor as a carcinoma of the basal cells of the epidermis and that those tumors that show a tendency toward gland formation are imitating the potential of the basal cells to form cutaneous glands (483). Krompecher's view is still supported by some (484–486). According to Geschickter and Koehler, only those basal cells with a potential to develop into glandular cells give rise to basal cell carcinoma. They suggested the designation *appendage cell carcinoma* (486a). Mallory held the opinion that basal cell carcinomas are carcinomas of hair matrix cells (486b). In 1947, Foot expressed the view that basal cell carcinomas are carcinomas that have developed from distorted primordia of dermal adnexa rather than from ordinary epidermal basal cells (443). He stated that the tumors imitate the embryonal development of one or all three types of adnexal primordia, that is, hair, sebaceous gland, and sweat gland.

The first author to express doubts that basal cell carcinomas are carcinomas was Adamson; in 1914, he stated that basal cell carcinomas are nevoid tumors originating "from latent embryonic foci aroused from their dormant state at a later period in life" (487). He believed that the latent embryonic foci usually are embryonic pilosebaceous follicles but occasionally are embryonic sweat ducts. Several other authors reached similar conclusions, among them Wallace and Halpert, who stated in 1950 that they regarded basal cell carcinomas as benign tumors arising from cells destined to form hair follicles (488). They proposed the term *trichoma* for them.

In 1948, Lever expressed his belief that basal cell carcinomas are not carcinomas and are not derived from basal cells, but rather are nevoid tumors, or hamartomas, derived from primary epithelial germ cells. In other words, basal cell carcinomas originate from incompletely differentiated, immature cells and not from anaplastic cells (488a). Although g-glutamyl transpeptidase activity is observed in the atypical cells in squamous cell carcinoma, Bowen's disease, and actinic keratoses, no g-glutamyl transpeptidase activity is expressed in the cells of basal cell carcinoma (489). In this view, basal cell carcinoma represents the least differentiated of the appendage tumors.

It was originally assumed, analogous to Adamson's view, that the primary epithelial germ cells giving rise to basal cell carcinoma are in all instances embryonic cells that lay dormant until the onset of neoplasia. Even though this view applies to the linear unilateral basal cell nevus, which is usually present from birth, it is likely that, as suggested by Pinkus, basal cell carcinomas occurring later in life arise not from dormant embryonic primary epithelial germ cells but from pluripotential cells that form continuously during life and, like embryonic primary epithelial germ cells, have the potential of forming hair, sebaceous glands, and apocrine glands (420). The fact that basal cell carcinomas may arise in sun-exposed areas and in areas of radiodermatitis supports this view. Their tendency to local invasion and tissue destruction, their capacity for local persistence and recurrence if not ablated, and their occasional capacity for metastasis support the concept that these lesions are carcinomas, albeit in most instances with little or no capacity for metastasis.

It is now widely accepted that disruption of the Hedgehog-Patched pathway is a key event in development of basal cell cancer. In addition to Patched gene alterations, p53 gene mutations are also frequently present (421–430). Lever's view that basal cell carcinomas are derived from primary epithelial germ cells has been developed in light of the recognition and characterization of epidermal stem cells.

Pilar Differentiation. Differentiation in basal cell carcinoma is predominantly toward pilar keratin. The presence of citrulline in keratinized structures indicates that the origin of the keratin is the hair matrix because epidermal keratin contains no citrulline (480). Studies with monoclonal cytokeratin antibodies support the assumption of pilar differentiation in basal cell carcinoma. Thus, a cytokeratin antibody binding to the follicular epithelium but not to the interfollicular epidermis stains all cells of basal cell carcinoma (490). Furthermore, a monoclonal antibody against basal cell carcinoma keratin stains, in addition to the cells of basal cell carcinoma, all follicular cells below the isthmus portion of normal anagen hair follicles (491). These findings contribute to the general view that basal cell carcinoma should be regarded as a hair follicle tumor rather than an epidermal tumor.

Stromal Factor. The importance of stroma in the development of basal cell carcinomas is borne out by the fact that autotransplants of basal cell carcinomas survive only when they include connective tissue stroma (492). In addition, the rarity of basal cell carcinomas on the palms and soles and the fact that the palmar and plantar pits of the nevoid basal cell carcinoma syndrome very rarely show a full-fledged basal cell carcinoma suggest that the palms and soles do not possess the stromal factor necessary for the formation of basal cell carcinomas (493).

Lack of Autonomy. Basal cell carcinomas, when transplanted to the anterior chamber of the rabbit's eye together with their connective tissue stroma, fail to grow, in contrast to squamous cell carcinoma (494). Furthermore, basal cell carcinomas, in contrast to many human tumors, do not grow when transplanted subcutaneously to athymic nude mice (495). These observations suggest a lack of autonomy of the cells of at least some basal cell carcinomas. Because autonomy of the tumor cell is a prerequisite for the formation of metastases and represents a characteristic feature of malignant tumors (496), the absence of autonomy in basal cell carcinoma is consistent with its inability to metastasize in most instances.

Site of Origin. The usual site of origin of basal cell carcinoma appears to be the surface epidermis. Alternatively, however, the tumor may originate from the outer root sheath of a hair follicle, and in the 2006 World Health Organization classification, basal cell carcinomas were classified with the skin adnexal tumors (1,497,498).

Of particular interest is the manner of growth of *superficial basal cell carcinoma.* Routine sectioning carried out perpendicular to the skin surface shows seemingly independent nests of basal cell carcinoma suggestive at times of the growth of primary epithelial germs in the embryonic skin. Thus it was at one time

widely assumed that the peripheral extension seen in superficial basal cell carcinoma was based on a "multicentric" growth characterized by the formation of new buds of tumor tissue at the periphery. However, on the basis of findings in serial sections and in wax reconstructions of superficial basal cell carcinomas, Madsen favored the theory of a "unicentric" origin (499,500). Madsen was able to show that the tumor strands are continuous but are attached to the undersurface of the epidermis only at intervals, like garlands. Madsen found not only in his wax reconstructions but also in sections cut parallel to the surface of the skin that individual tumor islands are interconnected. Oberste-Lehn (501), using a technique of separating the epidermis from the dermis by maceration, could not find such interconnections, but the possibility could not be excluded, as Madsen pointed out, that the interconnections had ruptured as a result of the maceration. It was subsequently shown, when trypsin was used for the separation of the epidermis from the dermis, that interconnections exist between tumor cell nests in superficial basal cell carcinoma. Similarly, three-dimensional reconstruction by means of serial horizontal microscopic sections and a special computer confirmed a unicentric origin (502).

Electron Microscopy. The predominant cell in undifferentiated basal cell carcinoma is characterized by a large nucleus, poorly developed desmosomes, and rather sparse tonofilaments. Thus the tumor cells differ from normal epidermal basal cells. They resemble the cells of the undifferentiated hair matrix (503) or the immature basal cells of the embryonic epidermis, particularly those of the primary epithelial germ (504,505). In addition to the prevalent large, light cells, a few cells that are smaller, darker, and more irregularly shaped can be found (438,504). The darkness of the latter cells is due to the abundance of ribonucleoprotein particles in their cytoplasm. A well-developed basement membrane separates the tumor from the dermis (503). Processes from the tumor cells do not usually penetrate the basement membrane in basal cell carcinoma, in contrast to squamous cell carcinoma, in which processes extend through a fragmented basement membrane into the stroma (506).

Keratinization is commonly observed by electron microscopy in basal cell carcinoma, especially in the keratotic type. In addition to well-developed desmosomes and many thick bundles of tonofilaments, dense clumps of homogeneous, dyskeratotic material are present in many keratinizing cells. A small number of keratohyaline granules are often seen. They probably represent trichohyaline granules, which occur in the process of keratinization of the inner root sheath and its cuticle (504).

Some basal cell carcinomas show areas of adenoid differentiation in which cells are grouped around glandlike lumina. Such cells may show pronounced infolding of the plasma membrane at their lateral borders as seen normally in eccrine ductal cells (439).

In pigmented basal cell carcinomas, most of the melanin is found within melanocytes of the tumor and in melanophages located in the connective tissue stroma. Although numerous melanosomes are present in the dendrites of the melanocytes, the tumor cells generally do not phagocytize the melanin-containing dendrites, resulting in a blockage of the transfer of melanin from melanocytes to the tumor cells (507,508). This is analogous to the blocked transfer from melanocytes to tumor cells in some pigmented seborrheic keratoses referred to as *melanoacanthoma*. Nevertheless, in occasional instances of pigmented basal cell carcinoma, some transfer of melanosomes to the tumor cells takes place. The tumor cells then contain melanosomes, which are located largely as melanosome complexes within lysosomes (504).

Presence of Amyloid. Cell proliferation in basal cell carcinoma is considerable. The experimentally determined cell-doubling time of 9 days, however, does not conform to the clinical observation that basal cell carcinoma, as a rule, is a very slowly growing tumor (509). This suggests that there must be cell death. In addition to phagocytosis by neighboring tumor cells and macrophages, apoptosis of tumor cells also often takes place, with transformation of the cells into colloid bodies and subsequently into amyloid (439,510). This conversion of epithelial cells into amyloid is analogous to that occurring in lichenoid and macular amyloidosis. Colloid bodies, demonstrable by direct immunofluorescence for immunoglobulin M, have been found in 89% of basal cell carcinomas (439). Amyloid has been observed in the stroma and inside the tumor islands both by histochemistry and by electron microscopy in as many as 65% of basal cell carcinomas (439,511). This amyloid shows positive staining with antikeratin antiserum, indicating that it is derived from tonofilaments (512). The fact that the amyloid is permanganate resistant indicates that it is not secondary amyloid (512). The presence of amyloid may contribute to an apparent lack of sensitivity to radiotherapy (514).

Differential Diagnosis. Differentiation of basal cell carcinoma from squamous cell carcinoma can sometimes be difficult—so difficult that some authors believe that intermediate forms (basal squamous cell epitheliomas) occur. However, as a rule, differentiation is fairly easy. One of the best points of differentiation is that most cells of basal cell carcinoma stain deeply basophilic, whereas most cells of squamous cell carcinoma, at least in low-grade lesions, have an eosinophilic tint due to partial keratinization. The cells in high-grade squamous cell carcinoma may appear basophilic because of the absence of keratinization. However, they differ from basal cell carcinoma by showing much greater atypicality of their nuclei and their mitotic figures. It is important to remember that keratinization is not a prerogative of squamous cell carcinoma; it occurs also in basal cell carcinoma with differentiation toward hair structures (see Keratotic Basal Cell Carcinoma). Keratinization in basal cell carcinomas may be partial and then result in parakeratotic bands and whorls, or it may be complete and result in horn cysts. The keratinization seen in the horn cysts differs from that seen in the horn pearls of squamous cell carcinomas by being abrupt and complete rather than gradual and incomplete. The fairly common presence in basal cell carcinoma of areas of retraction of the tumor cell masses from the surrounding connective tissue also aids in the differentiation of this tumor from squamous cell carcinoma, in which such areas of retraction are rarely found.

The differential diagnosis of basal cell carcinoma from trichoepithelioma is discussed in Chapter 31. Of particular

importance is the differentiation of fibrosing basal cell carcinoma from the relatively recently described desmoplastic trichoepithelioma. Both tumors have in common thin strands of small basaloid cells embedded in a dense, fibrous stroma, but desmoplastic trichoepithelioma also shows a considerable number of horn cysts. Many tumors originally diagnosed as basal cell carcinomas in children and teenagers could be reclassified as desmoplastic trichoepithelioma (515).

In making a biopsy diagnosis it is important to have sections that adequately represent the lesion. It is curious that in punch biopsies the initial sections may not show the tumor. Further sections should always be examined if the clinical diagnosis is one of basal cell carcinoma (517). There is also a limited evidence base to recommend the most effective and economical excision margins. It seems likely that a margin of 3 mm may be adequate in most cases, but in high-risk basal cell carcinoma this may be insufficient (518–521).

EPIDERMAL TUMORS IN IMMUNOSUPPRESSED HOSTS

The widespread use of immunosuppressive therapy as part of organ transplantation and in the treatment of some immunologically mediated diseases has led to a new phenomenon of rapidly developing warts and epidermal tumors (516). There is a spectrum of squamous atypia ranging from typical viral warts through dysplastic or atypical warts to squamous cell carcinomas, which are often very poorly differentiated (Fig. 29-92).



FIGURE 29-92. Squamous cell carcinoma in a renal transplant recipient. The patient has a carcinoma on the chest and multiple keratoses on the back of the hand and arm.

The squamous cell carcinomas have been shown to have similar proliferative potential to similar lesions in hosts with normal immune function (522), although they lack the host immune response that would normally be present (523). They also share the same early expression of keratin 17 seen in a number of epidermal hyperproliferative states (524). Mutations of p53 may play a part in the development of the tumors (525). Rapidly progressing multiple squamous cell carcinomas have also been reported in association with chronic myeloid leukemia (526). Basal cell carcinomas tend to show an infiltrative rather than a nodular growth pattern more frequently in immunosuppressed patients (527). Kaposi's sarcoma can also present as a fulminant process after liver or kidney transplantation (528,529) and may recur with the introduction of cyclosporin A therapy (530). It has also been suggested that HIV-positive hosts have an increased risk of developing malignant melanoma (531).

KERATOACANTHOMA

Two types of keratoacanthoma exist: solitary and multiple.

Solitary Keratoacanthoma

Solitary keratoacanthoma was first described in 1889 by Hutchinson as a "crateriform ulcer of the face," and since 1950 it has been recognized as an entity and differentiated from squamous cell carcinoma, which it often resembles clinically and histologically (532–534). Solitary keratoacanthoma occurs in elderly persons usually as a single lesion; however, occasionally there are several lesions, or new lesions develop. The lesion consists of a firm, dome-shaped nodule 1.0 to 2.5 cm in diameter with a horn-filled crater in its center (Fig. 29-93). The sites of predilection are exposed areas, where about 95% of solitary keratoacanthomas occur, but they may occur on any hairy cutaneous site (535). They have not been reported on the palms, soles, or mucous surfaces, although, in rare instances,



FIGURE 29-93. Keratoacanthoma. The lesion is symmetric, with keratin protruding from its center.

they occur subungually (see text following). Keratoacanthomas located on the vermilion border of the lip probably arise from hair follicles in the adjacent skin (536). Keratoacanthomas usually reach their full size within 6 to 8 weeks and involute spontaneously, generally in less than 6 months. Healing takes place with a slightly depressed scar. In some instances, a keratoacanthoma increases in size for more than 2 months and takes up to 1 year to involute (535).

An increased incidence of keratoacanthoma is observed in immunosuppressed patients (537). In addition, keratoacanthomas commonly occur in the Muir-Torre syndrome of sebaceous neoplasms and keratoacanthomas associated with visceral carcinomas (see Chapter 30). Keratoacanthomas may be the only type of cutaneous tumor present in this syndrome (538,539).

There are three rare clinical variants of solitary keratoacanthoma. In two forms—giant keratoacanthoma and keratoacanthoma centrifugum marginatum—the keratoacanthoma attains a large size. In *giant keratoacanthoma,* the growth rapidly reaches a size of 5 cm or more and may cause destruction of underlying tissues. Nevertheless, spontaneous involution takes place after several months, often accompanied by detachment of a large keratotic plaque. The most common sites are the nose (540,541) and the eyelids (537,542,543). In *keratoacanthoma centrifugum marginatum,* the lesion may reach a size of 20 cm in diameter. There is no tendency toward spontaneous involution; instead, there is peripheral extension with a raised, rolled border and atrophy in the center of the lesion. The most common locations are the dorsa of the hands (544,545) and the legs (546,547). The third rare variant is *subungual keratoacanthoma,* which shows a destructive crateriform lesion with keratotic excrescences under the distal portion of a fingernail. It fails to regress spontaneously, is tender, and by roentgenogram shows damage to the terminal phalanx by pressure erosion (548–550).

Claims have been made that keratoacanthoma can undergo transformation into a squamous cell carcinoma either spontaneously (544,551) or as a result of immunosuppression (537,552). It appears more likely, however, that the squamous cell carcinoma existed from the beginning in such instances (see Differential Diagnosis) (535,553).

Histopathology. The architecture of the lesion in a keratoacanthoma is as important to the diagnosis as the cellular characteristics. Therefore, if the lesion cannot be excised in its entirety, it is advisable that a fusiform specimen be excised for biopsy from the center of the lesion and that this specimen include the edge at least of one side and preferably of both sides of the lesion (554). A shave biopsy is inadvisable because the histologic changes at the base of the lesion are often of great importance in the differentiation from squamous cell carcinoma. Frequently a curettage specimen will be submitted, in which case clear distinction between keratoacanthoma and squamous cell carcinoma may be impossible to achieve with confidence.

In the early proliferative stage, one observes a horn-filled invagination of the epidermis from which strands of epidermis protrude into the dermis. These strands are poorly demarcated from the surrounding stroma in many areas and may contain cells showing nuclear atypia (555), as well as many mitotic figures (556). Even atypical mitoses may be seen occasionally (557). Dyskeratotic cells, that is, cells showing individual cell keratinization, may also be seen in areas that otherwise do not show advanced keratinization. However, even at this early stage, some of the tumor areas show a fairly pronounced degree of keratinization, giving them an eosinophilic, glassy appearance. In the dermis, a rather pronounced inflammatory infiltrate is present (556). Perineural invasion is occasionally seen in the proliferative phase of keratoacanthoma and should not be overinterpreted as conclusive evidence of malignancy (558,559).

A fully developed lesion shows in its center a large, irregularly shaped crater filled with keratin (Fig. 29-94). The epidermis extends like a lip or a buttress over the sides of the crater. At the base of the crater, irregular epidermal proliferations extend both upward into the crater and downward from the base of the crater. These proliferations may still appear somewhat atypical, but less so than in the initial stage; the keratinization is extensive and fairly advanced, with only a thin shell of one or two layers of basophilic, nonkeratinized cells at the periphery of the proliferations, whereas the cells within this shell appear eosinophilic and glassy as a result of keratinization (Fig. 29-95). There are many horn pearls, most of which show complete keratinization in their center. The base of a fully developed keratoacanthoma appears regular and well demarcated

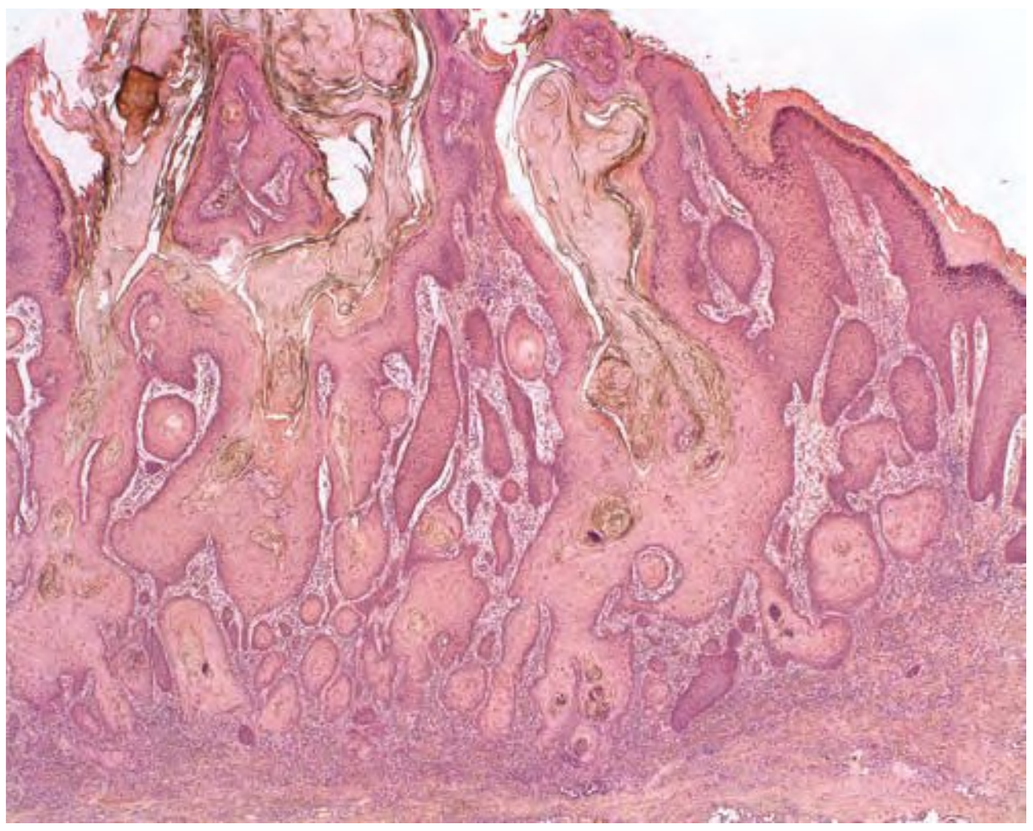


FIGURE 29-94. Keratoacanthoma. Low magnification. There is a central, keratin-filled crater. On the right, the epidermis extends like a buttress over the side of the crater. Irregular epidermal proliferations extend downward from the base of the crater into the dermis. This tumor is quite large and relatively deeply infiltrative, and the term "keratoacanthoma-like squamous cell carcinoma" might reasonably be applied to it.

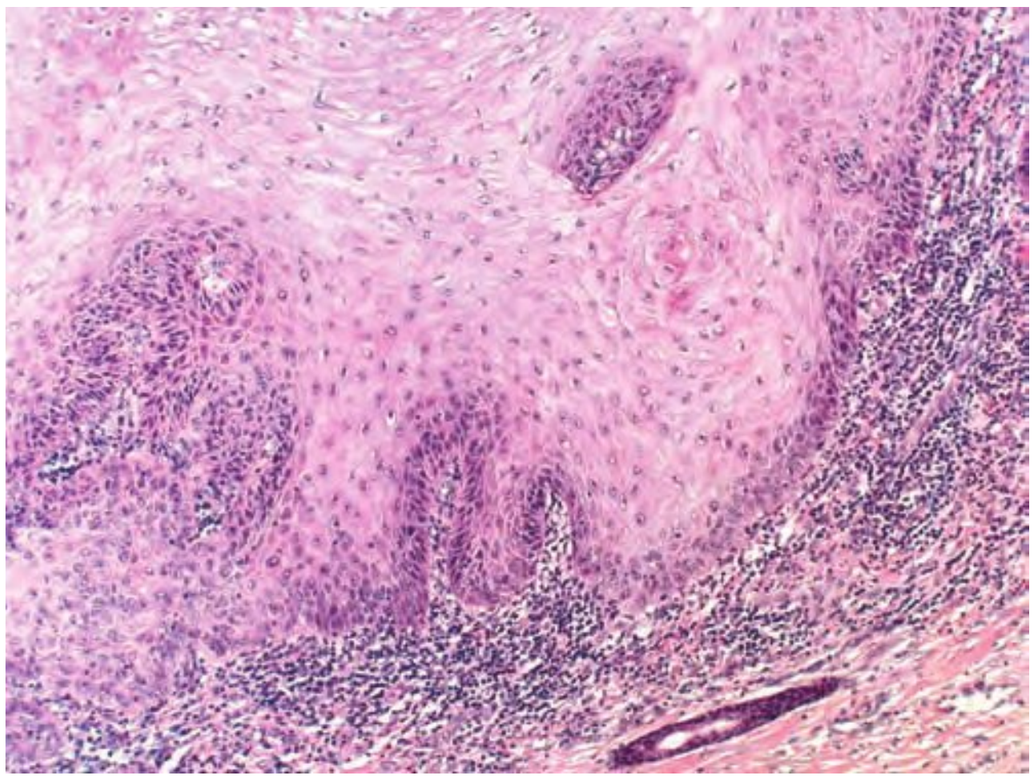


FIGURE 29-95. Keratoacanthoma. Medium magnification. The proliferation at the base to some extent resembles squamous cell carcinoma. However, there is more keratinization than is usual in squamous cell carcinoma, giving the tumor islands a glassy appearance. The lesion lies above the level of the sweat gland coils in the dermis.

and usually does not extend below the level of the sweat glands, in contrast to squamous cell carcinoma, which frequently does. A rather dense inflammatory infiltrate is often present at the base of the lesion (535,560).

In the involuting stage, proliferation has ceased, and most cells at the base of the crater have undergone keratinization. There may be shrunken, eosinophilic cells analogous to colloid or Civatte bodies among the tumor cells located nearest to the stroma as well as in the stroma, suggesting that cell degeneration followed by apoptosis contributes to the involution of the keratoacanthoma (547). Gradually, the crater flattens and finally disappears during healing.

Pathogenesis. It is generally agreed that the lesion starts with hyperplasia of the infundibulum of one or several adjoining hair follicles and with squamous metaplasia of the attached sebaceous glands (561). The application of cutaneous carcinogens to the skin of animals frequently produces, among other tumors, lesions with the histologic appearance of keratoacanthomas, and these tumors also have their origin in the infundibulum of one or several hair follicles (562).

The cause of keratoacanthoma is not known. The theory of a viral genesis has not been confirmed. The electron microscopic findings are largely nonspecific. However, keratoacanthomas, like squamous cell carcinomas and lesions of Bowen's disease, often show the presence of fairly numerous intracytoplasmic desmosomes (563,564).

Differential Diagnosis. Differentiation of typical, mature lesions of keratoacanthoma from squamous cell carcinoma generally is not difficult. In favor of a diagnosis of keratoacanthoma are the architecture of a crater surrounded by buttresses and the high degree of keratinization, which is manifested by the eosinophilic, glassy appearance of many of the cells. Clinical data are also of great value: Rapid development of an exophytic lesion showing a central, horn-filled crater speaks for keratoacanthoma rather than for squamous cell carcinoma.

The greatest difficulties in the differentiation of a keratoacanthoma from a squamous cell carcinoma are encountered in very early lesions because a horn-filled invagination may be seen in squamous cell carcinoma, and cells with an atypical appearance may occur in a keratoacanthoma. Occasionally, an early keratoacanthoma shows a greater degree of nuclear atypia than do some squamous cell carcinomas (565). In addition individual cell keratinization can occur in keratoacanthoma. On rare occasions, even adenoid formations caused by dyskeratosis and acantholysis can occur in keratoacanthoma (566). Thus it was found on reclassification in one study that in only 81% of the cases of keratoacanthoma could a diagnosis of squamous cell carcinoma be fully excluded, and that in only 86% of the cases of squamous cell carcinoma could keratoacanthoma be ruled out with certainty. These findings explain why, on rare occasions, lesions classified as keratoacanthoma cause metastases (553). Great caution is indicated in the diagnosis of giant keratoacanthomas. Several cases diagnosed as such turned out to be squamous cell carcinomas either by metastasizing (567) or by deep invasion into muscle (568).

Because it is widely agreed that squamous cell carcinomas can masquerade as keratoacanthomas clinically and histologically (535,569), it is best to err on the safe side in a case of doubt and to proceed on the assumption that the lesion is a squamous cell carcinoma. Where the tumor is well differentiated and has architectural features of keratoacanthoma, the term "keratoacanthoma-like squamous cell carcinoma" can be used.

Attempts at differentiating between keratoacanthoma and squamous cell carcinoma by histochemical or immunohistochemical methods have shown distinct differences in typical cases but not necessarily in borderline cases.

There are two variants of *multiple keratoacanthoma*: the multiple self-healing epitheliomas of the skin, or Ferguson Smith type, and the eruptive keratoacanthomas, or Grzybowski type. Both variants are rare in comparison with solitary keratoacanthoma.

In *multiple self-healing epitheliomas* of the skin, lesions begin to appear in childhood or adolescence on any part of the skin, including the palms and soles, but especially on the face and the extremities. Subungual lesions have also been described (549). Generally, there are no more than a dozen lesions at any one time (570). The lesions may reach the same size as solitary keratoacanthomas and after a few months heal with a depressed scar (571,572). In some cases, however, the lesions do not heal (534). In some patients, the condition is inherited (573,574).

In *eruptive keratoacanthoma,* lesions do not appear until adult life. Many hundreds of follicular papules are present, measuring from 2 to 3 mm in diameter (575,576). The oral mucosa and larynx may be involved (577,578).

Histopathology. The histologic appearance of the lesions of multiple self-healing epitheliomas of the skin is similar to that of solitary keratoacanthoma (570,572). More frequently than in solitary keratoacanthoma, the cutaneous proliferations in multiple self-healing epitheliomas of the skin are seen to be continuous with the follicular epithelium (579). The cutaneous lesions in eruptive keratoacanthoma show less crater formation than those in solitary keratoacanthoma. The mucosal lesions lack a crater and can easily be misinterpreted as squamous cell carcinoma (578,579).

Pathogenesis. It appears likely that multiple keratoacanthoma basically represents the same condition as solitary keratoacanthoma and that predisposition or genetic factors are responsible for the greater number of lesions (580). In multiple as in solitary keratoacanthoma, lesions arising in hair-bearing parts of the skin have their onset in the upper portion of a hair follicle, whereas the site of origin of lesions arising on the palms, the soles, and the mucous membranes is not apparent (577).

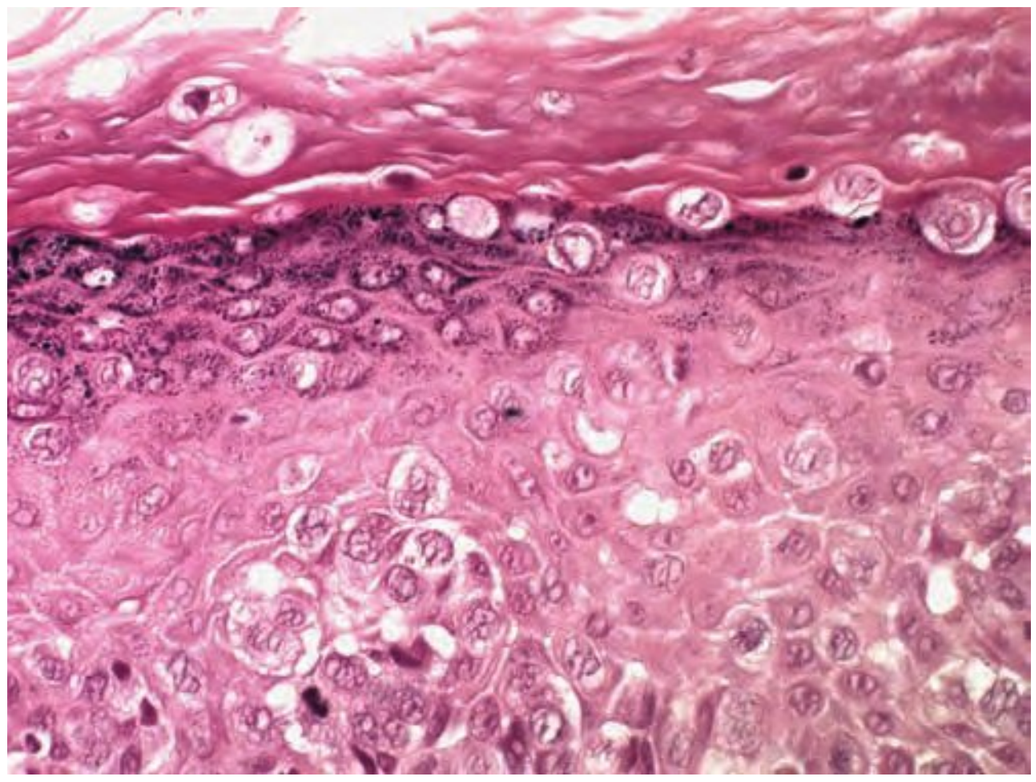


FIGURE 29-96. Paget's disease. High magnification. Large, rounded Paget cells with ample pale-staining cytoplasm, devoid of intercellular bridges, are scattered through the epidermis.

PAGET'S DISEASE

Paget's disease of the breast occurs almost exclusively in women. Only a few instances of its occurrence in the male breast have been described (581). Of interest is its occurrence in the male breast after treatment of a carcinoma of the prostate with estrogen (582). The cutaneous lesion in Paget's disease of the breast begins either on the nipple or the areola of the breast and extends slowly to the surrounding skin. It is always unilateral and consists of a sharply defined, slightly infiltrated area of erythema showing scaling, oozing, and crusting. There may or may not be ulceration or retraction of the nipple.

The cutaneous lesion is nearly always associated with carcinoma of the breast, and in more than half of the patients, a mass can be felt on palpation of the breast. Metastases in the axillary lymph nodes were found by one group of investigators in about 67% of their patients with a palpable mass of the breast and in 33% of those without a palpable mass (583). This contrasts with the experience of others, who encountered no axillary metastases in the absence of a palpable mass of the breast (584).

A clinical picture indistinguishable from that of early Paget's disease of the nipple may be seen in erosive adenomatosis of the nipple, a benign neoplasm of the major nipple ducts (see Chapter 30) (585).

Histopathology. In early lesions of Paget's disease of the breast, the epidermis usually shows only a few scattered Paget cells. They are large, rounded cells that are devoid of intercellular bridges and contain a large nucleus and ample cytoplasm. The cytoplasm of these cells stains much lighter than that of the adjacent squamous cells (Fig. 29-96). As the number of Paget cells increases, they compress the squamous cells to such an extent that the latter may merely form a network, the meshes of which are filled with Paget cells lying singly and in groups. In particular, one often observes flattened basal cells lying between Paget cells and the underlying dermis.

The dermis in Paget's disease shows a moderately severe chronic inflammatory reaction. Although Paget cells do not invade the dermis from the epidermis, they may be seen extending from the epidermis into the epithelium of hair follicles (586).

Histologic examination of the mammary ducts and glands nearly always shows malignant changes in some of them. At first, the carcinoma is confined within the walls of the ducts and glands, but the tumor cells ultimately invade the connective tissue. From then on, lymphatic spread and metastases occur, just as in other types of mammary carcinoma. In mammary Paget's disease, the malignant changes have their onset in the lactiferous ducts and from there extend into the epidermis, but there are rare instances in which the malignant cells are confined to the epidermis of the nipple or involve only the most distal portion of one lactiferous duct (587).

Pathogenesis. As long as *electron microscopic examination* constituted the major factor in analyzing the derivation or the direction of differentiation of the cells in Paget's disease of the nipple, no clear decision could be reached on whether the constituting cells were keratinocytes or glandular cells. The presence of desmosomes between neighboring Paget cells and between Paget cells and keratinocytes seemed to support a derivation from keratinocytes (588). On the other hand, scattered desmosomes are normally found connecting the cells of the lactiferous ducts (589), and wherever cytoplasmic processes of Paget cells lie in contact with the basal lamina, no hemidesmosomes are present, as they would be in the case of keratinocytes. In addition, Paget cells can be found bordering small lumina in areas in which groups of Paget cells lie together (589,590).

Immunohistochemical studies in recent years have proved beyond any doubt the glandular derivation of the Paget cells of both mammary and extramammary Paget's disease. Thus, carcinoembryonic antigen is regularly found in Paget cells. Whereas intervening keratinocytes and melanocytes do not

stain, carcinoembryogenic antigen is present in the cells of normal eccrine and apocrine glands (591). Furthermore, Paget cells express cytokeratins typical of glandular epithelia but do not react with antibodies to epidermal keratin (592). CAM 5.2 is a low–molecular-weight cytokeratin marker that stains Paget's cells in 70% to 90% of cases. The adjacent epidermis, which is rich in high–molecular-weight cytokeratins, does not stain. Cytokeratin 7 is a more sensitive, but not specific, marker for Paget's disease. In addition to staining Paget's cells, it may also stain intraepidermal Merkel cells and Toker cells, and so positive staining needs to be correlated with morphology when interpreting the appearances in a section (616).

Enzyme histochemistry in Paget's disease of the breast has shown the presence of an apocrine enzymatic pattern in the intraepidermal Paget cells consisting of a strong reactivity for acid phosphatase and esterase and only a weakly positive reaction for aminopeptidase and succinic dehydrogenase (593). This finding suggests that the intraepidermal Paget cells in Paget's disease of the breast are derived from mammary gland cells, because the mammary gland represents a modified apocrine gland.

Differential Diagnosis. Paget's disease of the breast must be differentiated from Bowen's disease and the superficial spreading or "pagetoid" type of malignant melanoma *in situ*. Although vacuolated cells may occur in both Paget's disease and Bowen's disease, one observes clear-cut transitions between the vacuolated cells and epidermal cells only in Bowen's disease. Furthermore, one may observe in Bowen's disease, but not in Paget's disease, clumping of nuclei within multinucleated epidermal cells and individual cell keratinization. In addition, the cells in Bowen's disease do not contain carcinoembryonic antigen but react with prekeratin contained in rabbit antihuman prekeratin antiserum (594).

In the superficial spreading or pagetoid type of malignant melanoma *in situ*, as in the epidermis of Paget's disease of the breast, there are large, vacuolated cells scattered through the epidermis. The difficulty in distinguishing between the two types of cells may be increased by the fact that Paget cells occasionally also contain melanin. The most important points to remember in differentiating the two types of cells are as follows: (a) Paget cells are separated in many areas from the dermis by flattened basal cells, whereas melanoma cells border directly on the dermis; (b) Paget cells do not invade the dermis, whereas melanoma cells often do; (c) the tumor cells of malignant melanoma contain abundant cytoplasmic S100 protein, but in tissues from Paget's disease, S100 protein is usually absent in the tumor cells, although it may be seen in myoepithelial cells, Langerhans cells, and Schwann cells of cutaneous nerves (595); and (d) melanoma cells, unlike Paget cells, may be positive for the HMB-45 antigen, Melan-A, and other melanocytic markers.

EXTRAMAMMARY PAGET'S DISEASE

Extramammary Paget's disease most commonly affects the vulva (300), less commonly the male genital area (596) or the perianal area (551), and, in exceptional cases, the axillae, the region of the ceruminal glands (597), or that of Moll's glands (598). In cases with involvement of the axillae, the genital area may also be affected (599). Thus extramammary Paget's disease involves areas in which apocrine glands are normally encountered. Only very few cases of an association between mammary and vulvar Paget's disease have been described (600). In rare instances, extramammary Paget's disease is a secondary event caused by extension of an adenocarcinoma either of the rectum to the perianal region, of the cervix to the vulvar region (601), or of the urinary bladder to the urethra and glans penis (602) or to the groin (603). On the other hand, longstanding genital Paget's disease can extend inward to the cervix and urinary tract (604).

In extramammary Paget's disease, the clinical picture shows a slowly enlarging reddish patch with oozing and crusting. The patch resembles an eczematous lesion but has a sharp, irregular border. In extramammary Paget's disease, in contrast to the mammary type, itching is common.

Histopathology. Extramammary Paget's disease shares with Paget's disease the presence of varying numbers of Paget cells within the epidermis. In some instances, the Paget cells are found to be limited to the epidermis. Frequently, Paget cells can also be identified within the epithelium of some hair follicles or eccrine sweat ducts (605). Such *in situ* malignancy associated with extramammary Paget's disease has the same favorable prognosis as extramammary Paget's disease limited to the epidermis. However, the prognosis is much more serious in cases in which the Paget cells have invaded the dermis from the epidermis (605,606) or from an underlying sweat gland carcinoma (607). In this respect, extramammary Paget's disease differs from mammary Paget's disease, in which invasion of the dermis from the overlying epidermis does not occur (586). Glandular clusters with a central lumen, absent in mammary Paget's disease, may be seen in the lower epidermis in extramammary Paget's disease (605,608).

Immunohistochemical staining typically shows that in primary Paget's disease the Paget cells stain positively for cytokeratin 7, whereas in secondary cases the cells may be cytokeratin 20 positive (616).

In cases of "secondary" extramammary Paget's disease, the process extends either from a mucous-secreting adenocarcinoma of the rectum to the perianal skin (609,610), from a mucous-secreting endocervical carcinoma to the vulva (601), or from a transitional cell carcinoma of the urinary bladder with urethral extension (602,603). The prognosis in secondary extramammary Paget's disease is poor.

The prognosis of "primary" extramammary Paget's disease generally is better than that of mammary Paget's disease. In two large combined series of 123 patients with vulvar Paget's disease, only 26 patients (21%) showed an underlying invasive carcinoma in the dermis at the time of operation (605,606). In the other 79%, the Paget cells were present only within the epidermis and the epithelium of the cutaneous appendages, so that the process was still *in situ*. Thus one author observed only

2 examples of invasive sweat gland carcinoma among more than 100 cases of extramammary Paget's disease (607), and another author reported none among 12 cases (592). However, the rate of local recurrence is high even after seemingly adequate excision. The reasons for this are that (a) the extent of histologically demonstrable disease is often far greater than that of the clinically visible lesion and (b) extramammary Paget's disease, in contrast to mammary Paget's disease, can arise multifocally even in clinically normal-appearing areas of the skin (611).

Pathogenesis. At one time, the view was widely accepted that in primary extramammary Paget's disease the Paget cells in the epidermis are there as a result of an *in situ* upward extension of an *in situ* adenocarcinoma of sweat glands along eccrine or apocrine ducts (608,612). This view is analogous to the generally accepted views that secondary extramammary Paget's disease represents an extension of a rectal, cervical, or urinary bladder adenocarcinoma and that the development of mammary Paget's disease is an extension of an epidermotropic lactiferous duct carcinoma. The fact that an underlying *in situ* adenocarcinoma often could not be demonstrated was explained by the anatomic differences between the breast, which has only 20 large, conspicuous lactiferous ducts, and the genital skin, which has thousands of small apocrine and eccrine glands, making location of the particular small gland involved by carcinoma technically difficult (608). Staining with antikeratin monoclonal antibodies indicated that upward extension of an *in situ* adenocarcinoma derived from malignant secretory cells present within sweat ducts can occur (613).

Even though in some cases extramammary Paget's disease is the result of extension of an underlying apocrine or eccrine sweat gland carcinoma to the overlying epidermis, in most instances it has its origin within the epidermis (606). Careful subserial total sectioning of excised lesions of vulvar Paget's disease showed that the lesions within the epidermis and its appendages have a multifocal origin (611). Another pertinent argument in favor of the independence of the epidermal foci from any appendageal foci is the observation that in cases with extensive epidermal lesions, involvement of eccrine ducts and glands is often sparse and involvement of apocrine ducts and glands almost invariably absent, even though some Paget cells form apocrine glandular structures in the epidermis (605). Even if there is continuity between the epidermal and the ductal foci, there is no certain way of determining whether the extension is in an upward or downward direction. However, the clinching argument in favor of the autonomy of the epidermal foci in primary extramammary Paget's disease is the fact that, in contrast to mammary Paget's disease, dermal invasion generally originates from the epidermis and not ductal or glandular structures (605,606).

In cases in which the extramammary Paget's disease arises within the epidermis and extends from there at a later date into the adnexa and still later from the epidermis into the dermis, the question is, Which cell gives rise to the Paget cell? Two possibilities have been suggested, although proof for either is lacking. The first is that the Paget cell arises within the poral portion of an apocrine duct (614). The second is that, because the disease tends to occur in areas rich in apocrine glands and because there is in some cases unequivocal evidence of apocrine differentiation in the epidermis, intraepidermal Paget cells may be formed by pluripotential germinative cells within the epidermis that go awry trying to form apocrine structures (596,605,605a,605b).

Immunohistochemical studies indicate an apocrine genesis of extramammary Paget's disease. It is true that carcinoembryonic antigen merely indicates that the extramammary Paget cells are glandular rather than epidermal cells and does not decide whether they are apocrine or eccrine (591,592). However, two immunoreactants for apocrine glands—gross cystic disease fluid protein (615) and apocrine epithelial antigen (592)—have been shown to react with the Paget cells of extramammary Paget's disease, providing evidence for an apocrine pattern of differentiation.

The majority of cases of mammary and extramammary Paget's disease are cytokeratin 7 positive. Those few cases that are negative have been reported to be more commonly associated with the presence of an underlying malignancy. In contrast, cytokeratin 20 is found more frequently in cases of extramammary Paget's disease with an underlying malignancy. The pattern of cytokeratin expression can therefore be used to predict the likelihood of the presence or absence of an associated internal malignancy (616).

Differential Diagnosis. Extramammary Paget's disease, like Paget's disease of the breast, must be differentiated from Bowen's disease and especially from superficial spreading or pagetoid malignant melanoma *in situ* (see Paget's Disease, Differential Diagnosis).

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CHAPTER 30

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Tumors of the Epidermal Appendages

CLASSIFICATION OF THE APPENDAGEAL TUMORS

Historically, tumors of the epidermal appendages have been classified into four groups, which exhibit histologic features analogous to those of hair follicles, sebaceous glands, apocrine glands, and eccrine glands. In general, this type of diagnostic nosology based on the microscopic attributes of appendageal structures has been practical for the classification of adnexal lesions.

However, in some cases, the diagnosis of adnexal neoplasms presents unique difficulties, in part related to the wide variety of tumors, the substantial frequency of one lesion exhibiting histologic features of two or more adnexal lines, and the complicated nomenclature (1–5). Histogenesis is a concept that implies that the histologic appearance of a tumor is similar to the histology of the organ/structure from which the tumor arose ("cell of origin"). These concepts of appendageal tumorigenesis are being modified by new experimental data describing mechanisms governing the proliferation and differentiation of pluripotent stem cells that may be situated within various niches in the epidermis and associated adnexa.

In general, tumors are not derived directly from mature (differentiated, postmitotic) cells; rather, tumors originate from multipotential stem cells present within the epidermis or its appendageal structures (6). Such cells, when undergoing neoplastic transformation, may aberrantly express one or more lines of appendageal differentiation to varying degrees, given that these cells are not restricted to one line of differentiation. Taken together, these concepts predict that the histologic features of a tumor are related to the activation of molecular pathways responsible for forming the mature adnexal structure. The degree to which the eccrine, apocrine, sebaceous, and follicular differentiation programs are activated and recapitulated gives a tumor its histologic features. These concepts predict that tumors, including adnexal tumors, may imprecisely resemble their mature counterparts and that multiple lines of differentiation may be seen simultaneously in the same tumor (6). Given that tumor cell physiology is somewhat abnormal, it is remarkable that a significant percentage of adnexal neoplasms manifest predominantly one adnexal differentiation program (Table 30-1).

Benign adnexal tumors in which there is an admixture of follicular, eccrine, sebaceous, and/or apocrine differentiation, such as sebaceous units in combination with either eccrine and/or apocrine elements, are occasionally a source of diagnostic confusion. Differentiation is probably influenced not only by genetic potential, but also by field effects such as regional vascularity and molecular microenvironmental attributes of the epidermis, dermis, or subcutis (6). In human skin, keratinocytes with markers of stem cells appear to reside in the "bulge," and cells with the capability of proliferating and differentiating along appendageal lines (progenitor cells) appear to traffic from this site to the basilar epidermis, the sebaceous gland, and the hair follicle (7–9).

In addition to benign tumors, there are carcinomas of the epidermal appendages, which have the potential to metastasize. Three types of glandular carcinoma are recognized: carcinomas of sebaceous glands, eccrine glands, and apocrine glands. Other epithelial carcinomas exhibiting various types of follicular differentiation have been reported, such as pilomatrical carcinoma, malignant proliferating trichilemmal cyst, trichilemmal carcinoma, and trichoblastic carcinoma (Table 30-1).

As noted, the histopathology of a tumor often can be interpreted by comparing it to the histology of skin appendages. For example, clear or pale cell change due to cytoplasmic glycogen may recapitulate the embryonic acrosyringium in a nodular hidradenoma or the glycogenated follicular outer root sheath in a trichilemmoma. Cytoplasmic fat vacuoles that indent the nucleus are typical of sebaceous differentiation, which is seen in sebaceous glands, sebaceous adenomas, and sebaceous carcinomas. Many adnexal tumors contain a distinctive, fibrotic, eosinophilic hyaline stroma that envelops the epithelial elements. This stroma assists in differentiating many basaloid adnexal neoplasms from basal cell carcinoma. Eccrine tumors commonly exhibit a nearly acellular hyalinized eosinophilic stroma with dilated thin-walled vessels (e.g., nodular hidradenoma, eccrine poroma). Tubule formation and focal keratinization occurring in eccrine tumors tend to differentiate them from renal cell or other metastatic clear cell carcinomas. Historically, immunohistochemistry has been of little value in definitively distinguishing among the phenotypic patterns of adnexal neoplasms (10); however, with the identification of specific mutations in genes associated with appendageal neoplasms—for example, CYLD1 in cylindromas (11)—further research on these tumors using current technologies, especially cDNA

TABLE 30-1 Classification of Tumors of Epidermal Appendages

Lesion type	Follicular differentiation	Sebaceous differentiation	Apocrine differentiation	Eccrine differentiation
Hyperplasias, hamartomas	Hair follicle nevus Dilated pore Generalized hair follicle hamartoma Basaloid follicular hamartoma	Nevus sebaceous Sebaceous hyperplasia	Apocrine nevus	Eccrine nevus
Benign neoplasms	Trichofolliculoma Pilar sheath acanthoma Fibrofolliculoma Trichodiscoma Trichoepithelioma Trichoblastoma Trichoadenoma Pilomatricoma Trichilemmoma Tumor of follicular infundibulum Trichilemmal horn Proliferating trichilemmal cyst	Sebaceous adenoma Sebaceoma	Aprocrine hidrocystoma Hidroadenoma papilliferum Syringocystadenoma papilliferum Tubular apocrine adenoma Erosive adenomatosis of the nipple Apocrine cylindroma	Eccrine hidrocystoma Syringoma Eccrine cylindroma Eccrine poroma Eccrine syringofibroadenoma Mucinous syringometaplasia Eccrine spiroadenoma Papillary eccrine adenoma Nodular hidradenoma Chondroid syringoma
Malignant neoplasms	Pilomatrix carcinoma Malignant proliferating trichilemmal tumor Trichilemmal carcinoma Trichoblastic carcinoma	Sebaceous carcinoma	Malignant apocrine cylindroma	Porocarcinoma Malignant eccrine spiroadenoma Malignant nodular hidradenoma Malignant chrondroid syringoma Eccrine adenocarcinoma Microcystic adnexal carcinoma Aggressive digital papillary adenocarcinoma Adenoid cystic carcinoma Mucinous eccrine carcinoma Syringoid eccrine carcinoma Malignant eccrine cylindroma

microarrays, microRNA microarrays, and proteomic studies, may yield additional molecular markers useful for classifying these lesions.

Lesional histology evolves with time and in response to local effects. A trichilemmal cyst, possibly stimulated by inflammatory mediators, may, as it ages, transform into a proliferating trichilemmal cyst and ultimately into the solid pilar tumor of the scalp. It is almost certain that tumor progression, the "process whereby tumors go from bad to worse," also operates in adnexal tumors, as it does in most tumor types. From a clinical point of view, adnexal neoplasms should not always be regarded as precursors of malignancy.

Classification of the Benign Appendageal Tumors

The four groups of benign appendageal tumors with differentiation toward hair, sebaceous glands, apocrine glands, and eccrine glands can be divided, according to a gradient of decreasing differentiation, into three major subgroups: (a) hyperplasias, hamartomas, and cysts; (b) benign tumors; and

(c) malignant tumors (Table 30-1). This classification is similar to the approach of the recent World Health Organization International Histological Classification of Tumours monograph (12).

Of the three subgroups of benign appendageal lesions, the hyperplasias, hamartomas, and cysts are composed of mature or nearly mature structures. The benign neoplasms, in general, show less complete differentiation than the hyperplasias; nonetheless, well-developed, differentiated or partially differentiated structures are present. The malignant neoplasms exhibit a lower degree of differentiation, and these lesions may not form differentiated cells or structures.

Although most of the benign appendage tumors fit well into one of the entities listed in Table 30-1, tumors in an intermediate stage of differentiation are occasionally encountered (13).

Ontogeny of the Benign Appendageal Tumors

Three possibilities exist for the development of benign appendageal tumors: development from primary epithelial germs, from pluripotential stem cells, or from cells of preexisting structures. In 1948, the thesis was advanced that cutaneous tumors differentiating toward hair, sebaceous glands, or apocrine glands developed from primary epithelial germ cells and were primary epithelial germ tumors, and, furthermore, that the hyperplasias, adenomas, and benign epitheliomas arose from primary epithelial germ cells that had attained a certain degree of differentiation before the onset of neoplasia (14).

Given that pluripotent stem cells give rise to cutaneous appendageal structures and that stem cells are continually present in the skin, it is likely that the benign appendageal tumors arise from stem cells that possess the potential of differentiating into tumors with hair, sebaceous gland, or apocrine structures (6). Appendageal tumors associated with genetic syndromes, such as multiple cylindromas, multiple trichoepitheliomas, and the nevoid basal cell carcinoma syndrome, are probably derived from abnormally regulated pluripotent cells that are directed to form abnormal appendageal structures rather than mature appendages. This scenario is likely to be true in sporadic occurrences of these same adnexal tumors. In some instances, pluripotent cells differentiate in more than one direction, as is seen most commonly on the scalp, where a syringocystadenoma may exhibit three different lines of appendageal differentiation.

Terminology

The terms *nevus*, *hamartoma*, and *carcinoma* used in the classification of the benign appendage tumors require definition.

The term *nevus* is used in the literature in two different ways, referring (a) to a tumor composed of nevus cells derived from melanocytes (nevocellular nevus, melanocytic nevus, pigmented nevus) or (b) to a lesion that is usually present at birth and is composed of mature or nearly mature structures, such as nevus sebaceous, eccrine nevus, nevus verrucosus, and nevus flammeus. To avoid confusion, it is advisable to use the term *nevus* with a qualifying adjective and to assume that *nevus* without a qualifying adjective designates a tumor composed of melanocytic nevus cells.

The term *hamartoma* is appropriate for those nevi that have no melanocytic nevus cells and, like congenital hyperplasias, are composed of mature or nearly mature structures. *Hamartoma,* derived from the Greek word *hamartanein* (to fail, to err), was chosen as the designation for "tumor-like malformations showing a faulty mixture of the normal components of the organ in which they occur" (15).

The term *epithelioma* has been used by many authors as a synonym for *carcinoma.* However, because the literal meaning of the word is "tumor of the epithelium," the term may be employed as a designation of benign as well as of malignant tumors of the epithelium, provided that a qualifying adjective is added (16). Because the term has been used for both benign and malignant neoplasms, it seems best to avoid its use except in a clearly defined historical context. The term *carcinoma* is used for malignant epithelial tumors, including those that are characterized by a tendency to inexorable growth with local invasion and tissue destruction as well as those that may in addition have capacity for distant metastasis. As in previous editions, we have selected terms that are widely understood and used, not necessarily those that are above all semantic dissection (17).

TUMORS WITH DIFFERENTIATION TOWARD HAIR FOLLICLE COMPONENTS

Hair Follicle Nevus

This rare, small tumor presents as a small nodule on the face, often at birth. It has also been referred to as congenital vellus hamartoma (18–20). A few reported cases have raised the possibility of a novel neurocutaneous syndrome (21,22).

Histopathology. There are focally increased vellus hair follicles, occasionally accompanied by a few small sebaceous glands (Fig. 30-1) (23).



FIGURE 30-1. Hair follicle nevus. Increased numbers of small hair follicles are present in the dermis.

Differential Diagnosis. The small vellus hair follicles present in the central face resemble the hair follicles in a hair follicle nevus. Other entities to consider in the differential diagnosis include accessory tragus and hair follicle hamartoma (21,24).

Trichofolliculoma

Trichofolliculoma occurs in adults as a solitary lesion, usually on the face but occasionally on the scalp or neck. It consists of a small, skin-colored, dome-shaped nodule. Frequently, there is a central pore. If such a central pore is present, a wool-like tuft of immature, usually white hairs may be seen emerging from it, a highly diagnostic clinical feature (25).

Histopathology. On histologic examination, the dermis contains a cystic cavity lined by squamous epithelium; this cyst contains keratinized material and frequently fragments of hair shafts that are birefringent on polaroscopic examination (Fig. 30-2) (26). In cases with a visible central pore, the cystic space is continuous with the surface epidermis, an indication that the lesion is analogous to an enlarged, distorted hair follicle. In some cases, multiple cystic spaces are present in the dermis. Radiating from the wall of these cysts are many small, yet well-differentiated hair follicles (Fig. 30-3). Well-developed secondary hair follicles often show a hair papilla (Fig. 30-3). Furthermore, these follicles usually have an outer and an inner root sheath, the latter of which may contain eosinophilic trichohyaline granules and, located in the center, a small hair shaft (Fig. 30-3). These fine hairs are visualized best where the secondary hair follicles appear in cross sections. Small groups of sebaceous gland cells may be embedded in the walls of the secondary hair follicles (27). In some of the more rudimentary secondary follicles, one observes a central horn cyst in place of a hair, as seen also in trichoepithelioma (28). The lesional stroma is rich in fibroblastic cells; these cells are oriented in parallel bundles that encapsulate the epithelial proliferations in a manner resembling that of the normal fibrous root sheath (29). Glycogen can be demonstrated in the outer root sheath of the secondary hair follicles, just as it is seen in mature hair follicles (26).

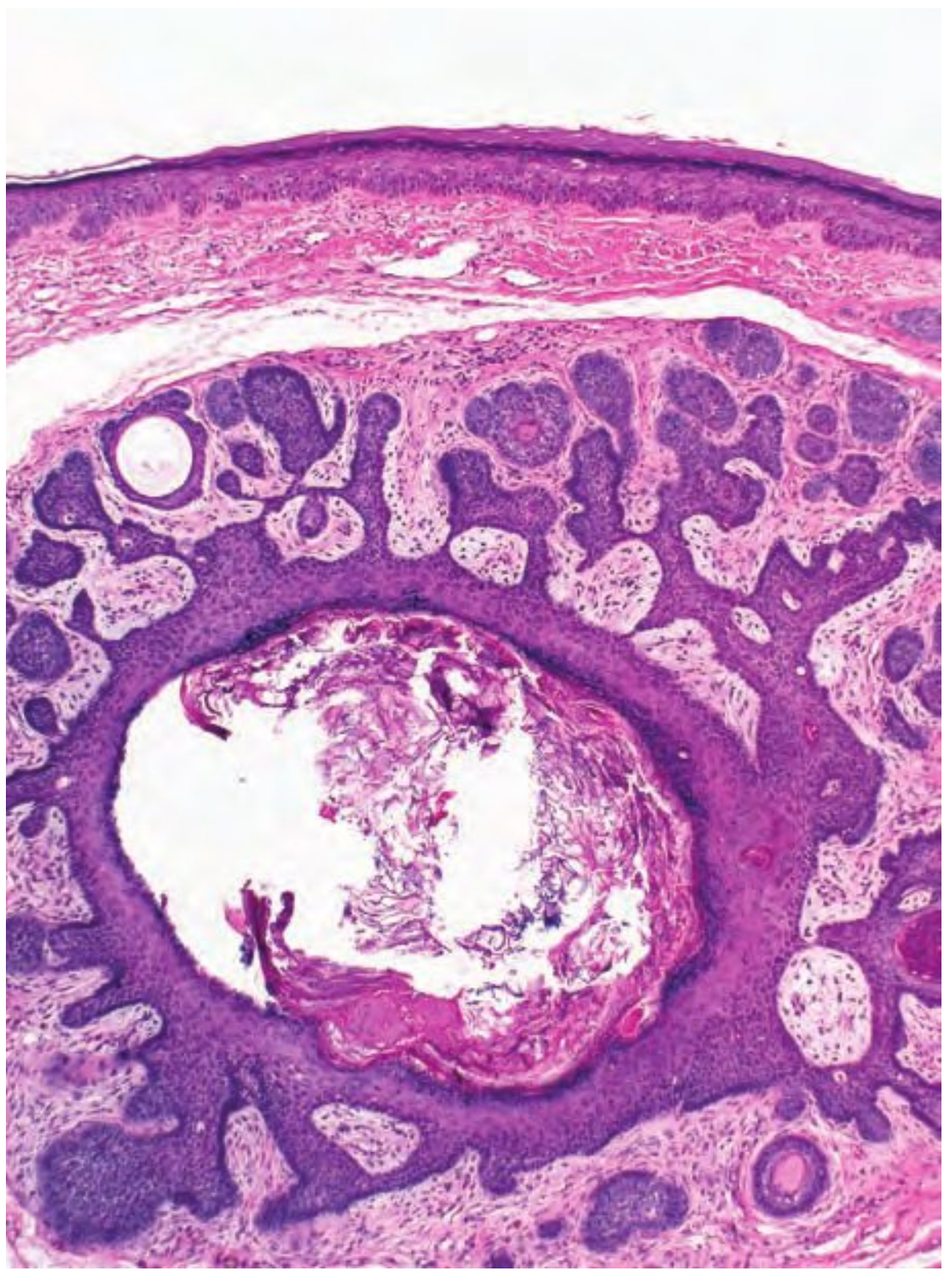


FIGURE 30-2. Trichofolliculoma. In the dermis, there is a keratin-filled cyst lined by squamous epithelium with associated follicular structures.

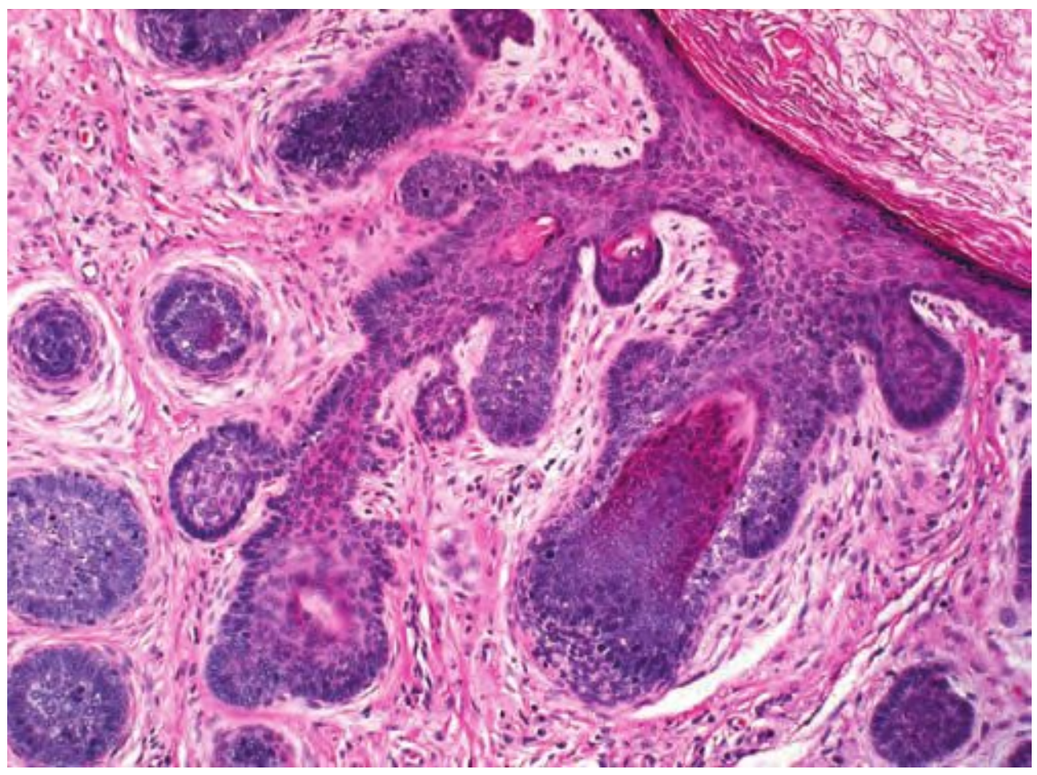


FIGURE 30-3. Trichofolliculoma. Emanating from the cyst wall are numerous small "secondary" hair follicles, some of which show, in addition to a hair and an outer root sheath, an inner root sheath with trichohyaline granules.

In all trichofolliculomas, epithelial strands interconnect the secondary hair follicles. Because these epithelial strands differentiate in the direction of the outer root sheath, the peripheral cell row is palisaded, and because of their glycogen content, the cells within the strands appear large and vacuolated (29).

Additional Studies. Experimental evidence suggests that trichofolliculomas undergo morphologic changes corresponding to the normal hair follicle cycle (30). The folliculosebaceous cystic hamartoma consists of a folliculosebaceous proliferation with a cystlike infundibular dilation and a mesenchymal stroma with variable fibroplasia. Folliculosebaceous cystic hamartoma exhibits many features of a trichofolliculoma, but it typically manifests more prominent sebaceous differentiation and a more prominent surrounding stroma, although some consider it an evolutionary stage of trichofolliculoma (31,32). Transgenic mice that overexpress a stabilized form of the β-catenin protein develop trichofolliculomas (33); therefore, increased signaling through the β-catenin pathway may play a role in the development of trichofolliculomas in humans. Recent work

with transgenic mice expressing increased epidermal expression of the *Noggin* gene, an inhibitor of bone-morphogenetic protein protein signaling, exhibit appendageal tumors resembling trichofolliculomas (34).

Sebaceous Trichofolliculoma

Sebaceous trichofolliculoma, a variant of trichofolliculoma, occurs in anatomic regions rich in sebaceous follicles, such as the nose. This tumor exhibits a centrally depressed, fistula-like opening from which terminal hairs and vellus hairs protrude (35).

Histopathology. There is a rather large, irregularly shaped, centrally located cavity lined by squamous epithelium. Many radially arranged, pilosebaceous follicles connect to the cavity. These follicles contain sebaceous ducts and numerous well-differentiated, large sebaceous lobules, as well as hair follicles containing partially terminal and partially vellus hairs (35).

Differential Diagnosis. Unlike folliculosebaceous cystic hamartoma, which presents as a solitary papule or nodule, sebaceous trichofolliculoma clinically presents with a central porelike opening that exhibits protruding hairs. Histopathologically, folliculosebaceous cystic hamartoma is additionally characterized by stromal mesenchymal prominence, a finding not seen in the previously reported cases of sebaceous trichofolliculoma (36).

Dilated Pore and Pilar Sheath Acanthomas

Dilated pore and pilar sheath acanthomas clinically share with trichofolliculoma and sebaceous trichofolliculoma the presence of a central pore and, histologically, the presence of a large cystic space that is continuous with the surface epidermis, lined by squamous epithelium, and filled with keratinous material.

The dilated pore, described in 1954 by Winer, occurs on the face, usually as a solitary lesion and predominantly in adult males. It has the appearance of a giant comedone and typically does not possess palpable induration (37).

The pilar sheath acanthoma, described in 1978, is usually found on the skin of the upper lip of adults. It is seen elsewhere on the face only rarely. It occurs as a solitary skin-colored nodule with a central porelike opening (38).

Histopathology. The dilated pore differentiates toward the infundibulum both architecturally and cytologically (39). It shows a markedly dilated pilar infundibulum lined by an epidermis that is atrophic near the ostium but hypertrophic deeper in the cystic cavity, where it shows many rete ridges and irregular thin proliferations into the surrounding stroma (Figs. 30-4 and 30-5). The keratin-filled cystic cavity may extend into the subcutaneous fat. In the lower portion, small sebaceous gland lobules and vellus hair follicles may be attached to the lining epithelium (40).

The *pilar sheath acanthoma* differs from the dilated pore by showing a larger, irregularly branching cystic cavity. In place of thin proliferations, as seen in the dilated pore, numerous lobulated masses of cells radiate from the wall of the cystic cavity into the dermis and the subcutaneous tissue (Fig. 30-6) (38). The pilar sheath acanthoma can exhibit some features of the outer root sheath, in that portions of the lesion may show peripheral palisading and contain varying amounts of glycogen (Fig. 30-7) (41). It has been suggested that pilar sheath acanthomas can manifest differentiation of all components of the pilosebaceous unit (39,42).



FIGURE 30-4. Dilated pore of Winer. An irregular cystic cavity containing keratin is present in the dermis.

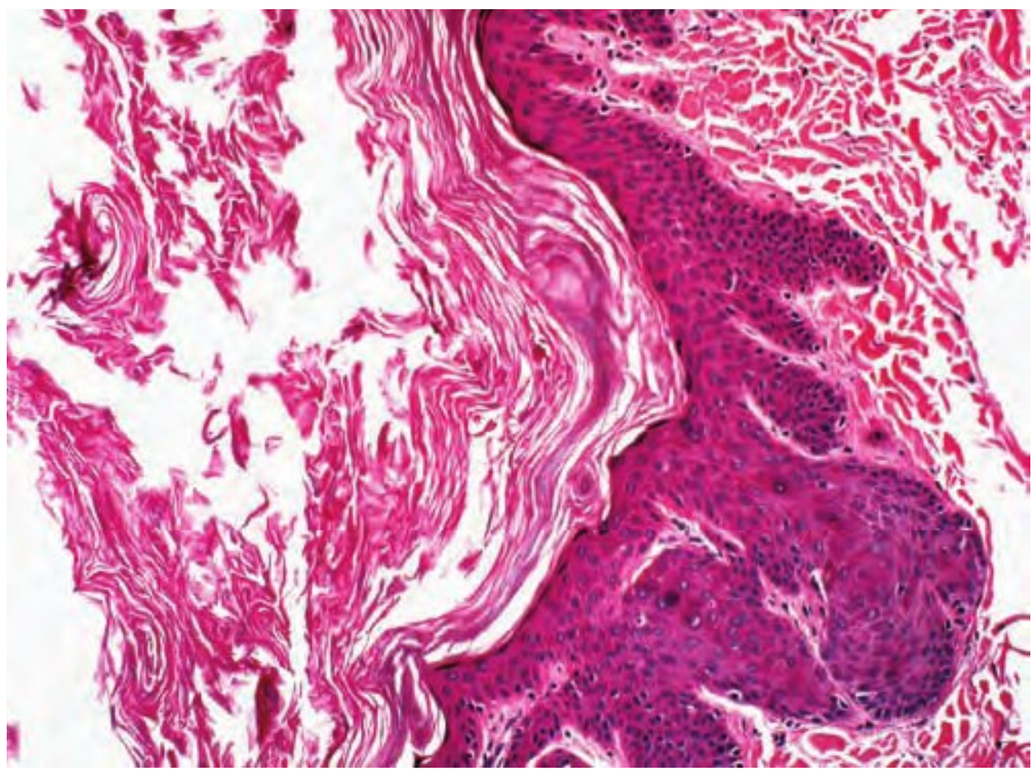


FIGURE 30-5. Dilated pore of Winer. Small projections of epithelial cells extend from the wall of the cyst into the surrounding dermis.



FIGURE 30-6. Pilar sheath acanthoma. Lobulated masses of cells extend from the cystic cavity into the surrounding dermis.

Fibrofolliculoma and Trichodiscoma

Fibrofolliculomas and trichodiscomas consist of 2- to 4-mm, yellow-white, smooth, dome-shaped lesions often on the face. The lesions can be solitary or multiple. Multiple fibrofolliculomas have been described in association with trichodiscomas and acrochordons (43,44). This triad is now referred to as the Birt-Hogg-Dubé syndrome and is inherited in an autosomal dominant fashion (43).

In patients with the Birt-Hogg-Dubé syndrome the lesions are present in considerable number mainly on the face and neck. In such cases, the trichodiscomas are clinically indistinguishable from the fibrofolliculomas (45). In this syndrome, there is an increased risk for the development of renal tumors and colonic polyps (46,47). In a patient reported with a large connective tissue nevus, fibrofolliculomas were present in large numbers within as well as around the connective tissue nevus (45).

Besides occurring in association with multiple fibrofolliculomas, multiple trichodiscomas also occur without them, as small papules either widely disseminated or localized to one area (48,49).

Histopathology. *Fibrofolliculomas* exhibit a central distorted hair follicle that is surrounded by a mantle of basophilic, fibrous stroma (Fig. 30-8). Numerous thin, anastomosing bands of follicular epithelium extend into this stroma (Fig. 30-9) (43,45).

Trichodiscomas are seen in the dermis as an area of fine fibrillary connective tissue containing ectatic blood vessels (Figs. 30-10 and 30-11). Epithelial hyperplasia resembling follicular structures, including those seen in fibrofolliculomas, is often seen. A hair follicle is usually found at the margin of the lesion (43,45). Trichodiscomas have been regarded as hamartomas of the mesodermal component of hair disks (48).

The pedunculated acrochordons seen in association with multiple fibrofolliculomas may contain only dermal connective

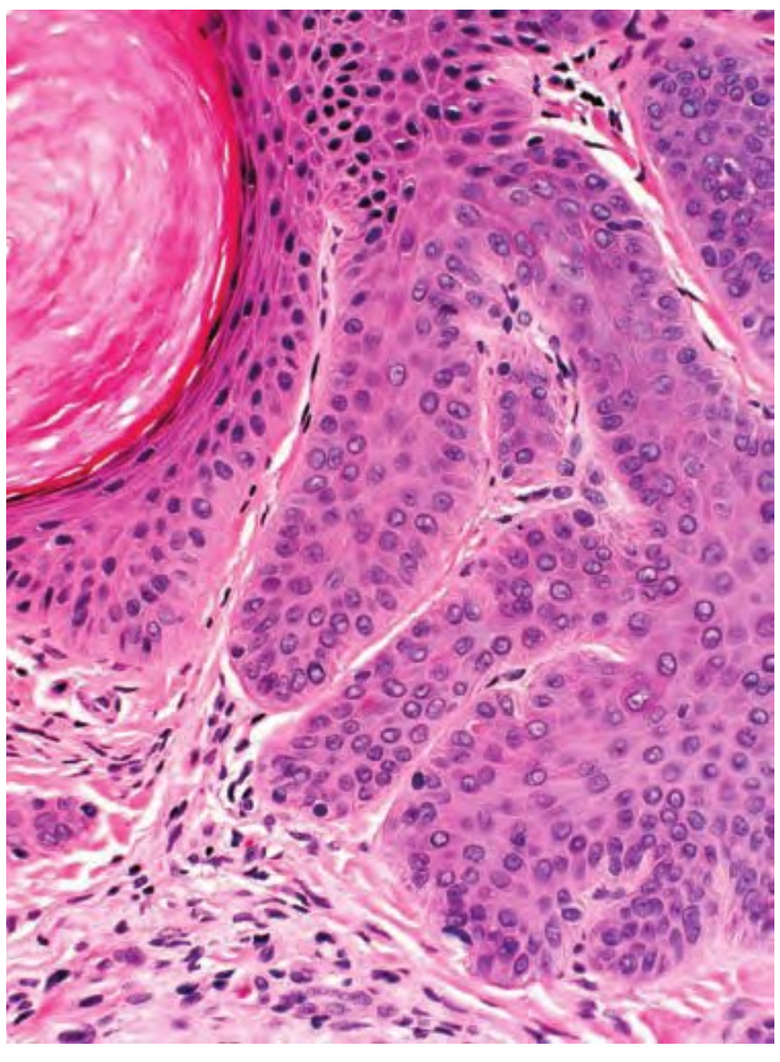


FIGURE 30-7. Pilar sheath acanthoma. The lobulated masses are comprised of bland cells resembling infundibular keratinocytes.

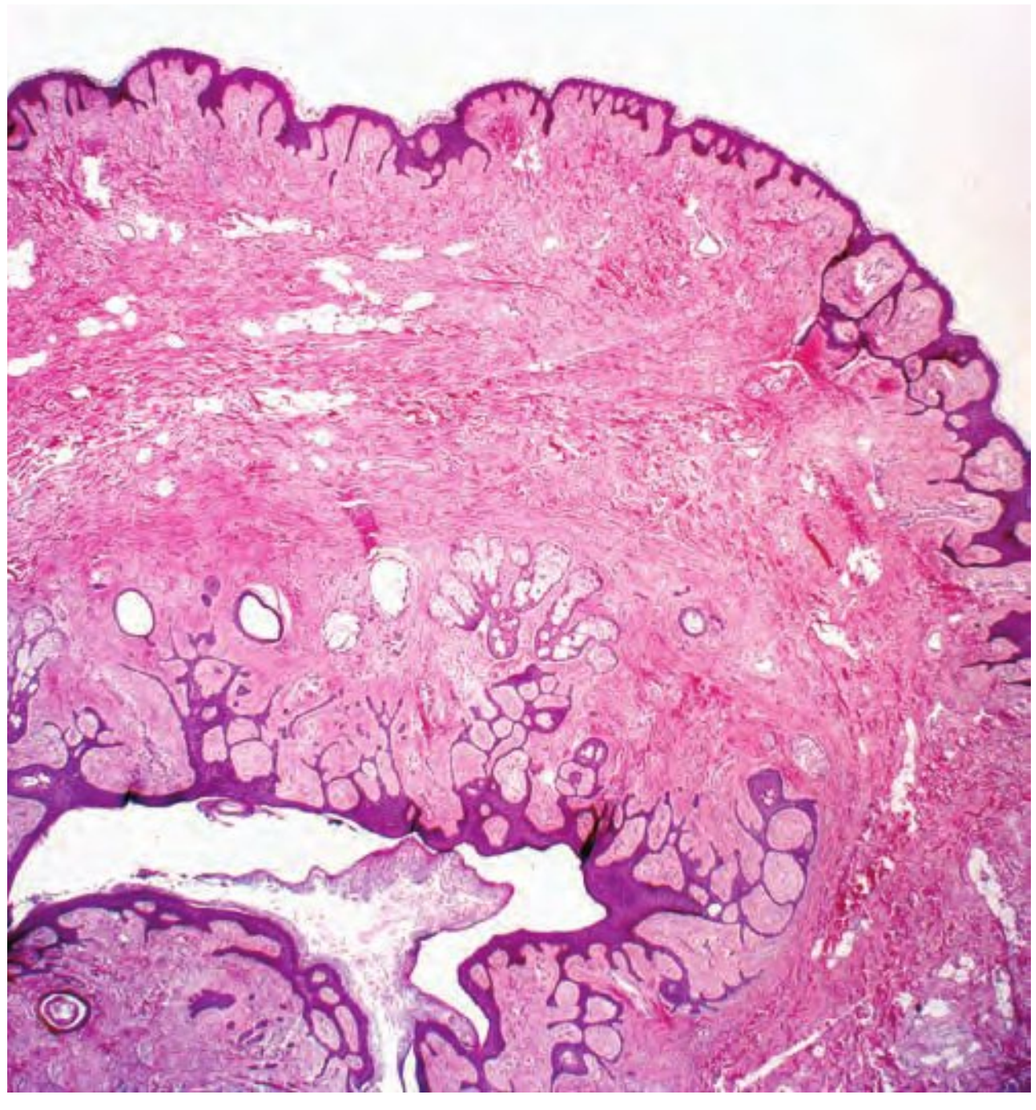


FIGURE 30-8. Fibrofolliculoma. In the dermis, there is a distorted cystic structure associated with epithelial cords and a fibrous stroma.

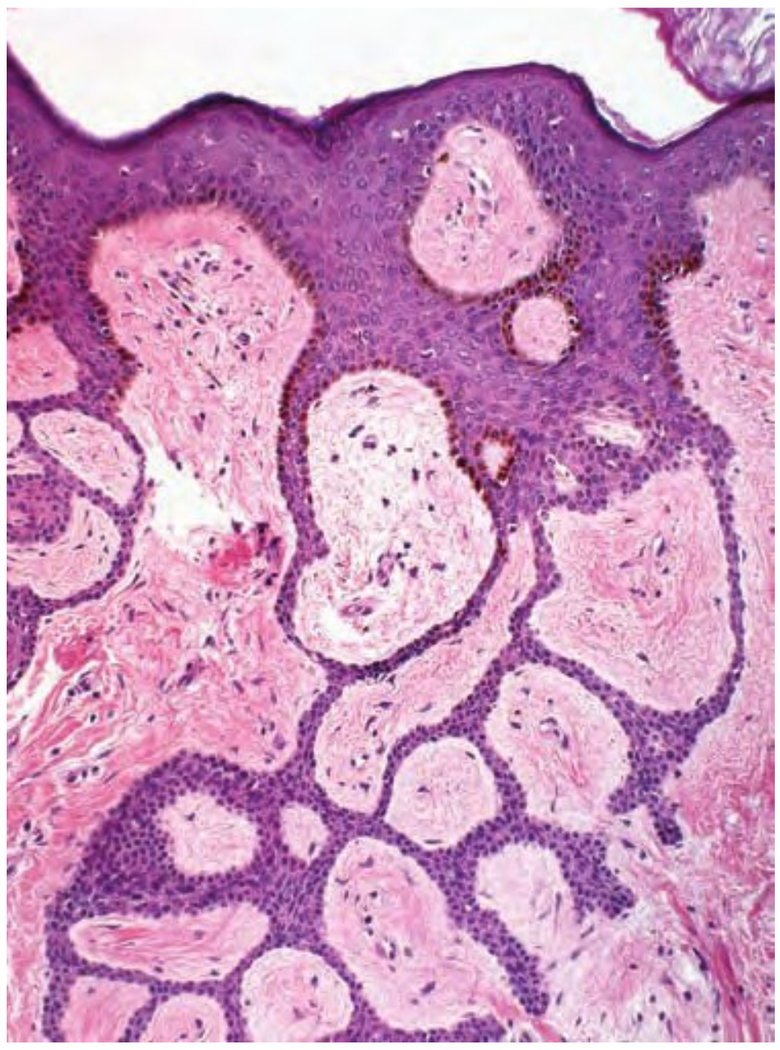


FIGURE 30-9. Fibrofolliculoma. Numerous thin, anastomosing bands of follicular epithelium extend into the bland fibrocellular stroma.

tissue. However, in some instances, they contain thin, anastomosing strands of epithelium; they are regarded as fibrofolliculomas displaying the configuration of an acrochordon (48).

Additional Studies. Birt-Hogg-Dubé syndrome is associated with mutations in the folliculin gene on chromosome 17p; the gene is believed to function as a tumor suppressor, but the function of this molecule is unclear (50). Steffen and Ackerman considered that histopathologically, fibrofolliculoma and trichodiscoma are hamartomas of follicular epithelium, follicular mantles, and perifollicular connective tissue (51). The immunophenotypic characteristics of syndromic-associated and sporadic types are identical and consist of perifollicular

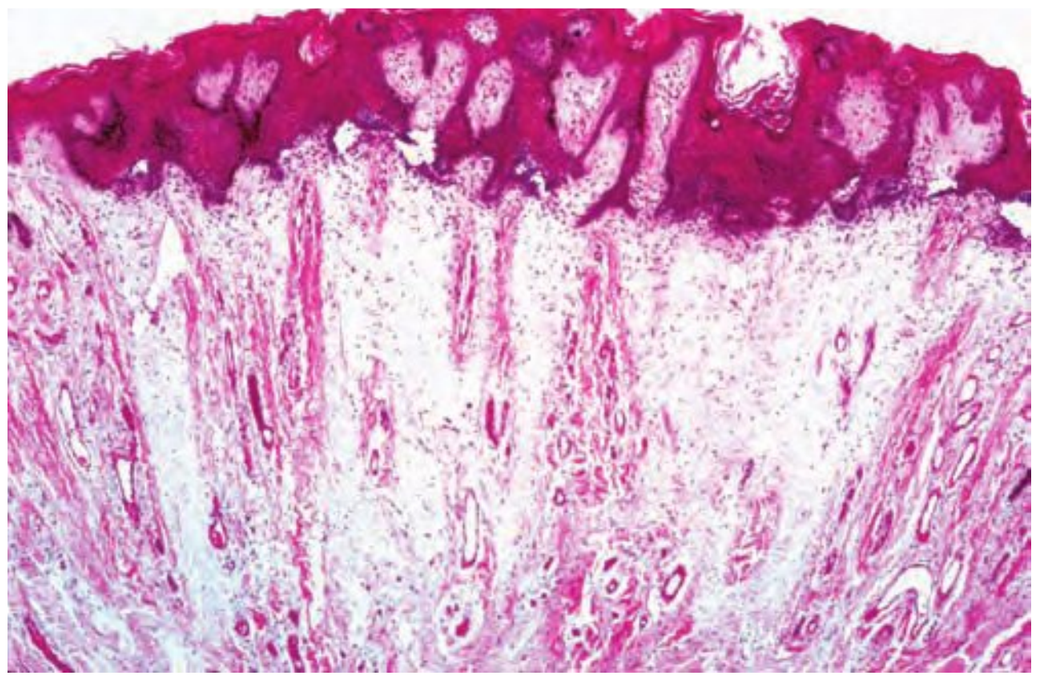


FIGURE 30-10. Trichodiscoma. Present in the dermis are areas of fine, fibrillar connective tissue.

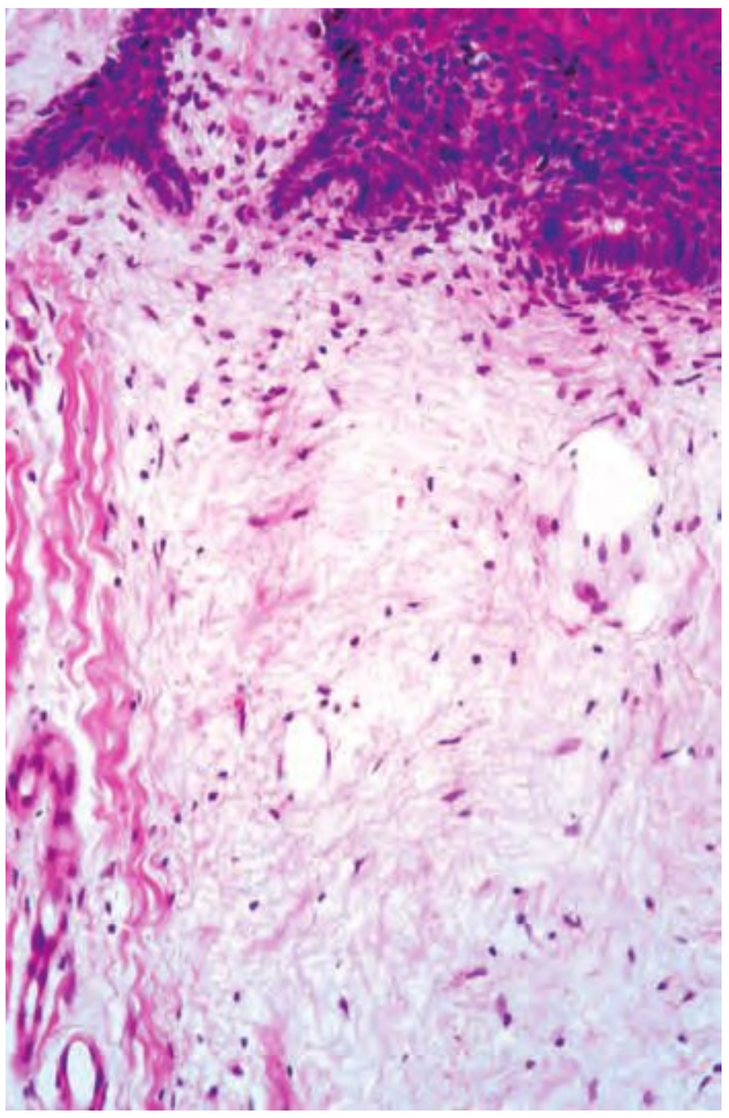


FIGURE 30-11. Trichodiscoma. The altered connective tissue exhibits ectatic vessels, a myxomatous appearance, increased numbers of mature fibrocytic cells, and basaloid follicular epidermal hyperplasia.

spindle cells that are positive for vimentin and CD34 and negative for factor XIII. These findings suggest that these lesions originate from the hair follicle mantle (52).

Trichoepithelioma

Trichoepithelioma occurs either in multiple lesions or as a solitary lesion. The name *trichoepithelioma* is preferable to other designations, such as *epithelioma adenoides cysticum* and *multiple benign cystic epithelioma*, because it is more indicative that the differentiation of this tumor is toward hair structures.

Multiple trichoepitheliomas are transmitted as an autosomal dominant trait (53). In most instances, the first lesions appear in childhood and gradually increase in number (54). Numerous rounded, skin-colored, firm papules and nodules usually between 2 and 8 mm in diameter are seen located mainly in the nasolabial folds, but also the nose, forehead, and upper lip. Occasionally, lesions are seen also on the scalp, neck, and upper trunk. Ulceration of the lesions occurs rarely. Transformation of one or several lesions into basal cell carcinomas is a very rare event. Most of the cases reported as such in the past are now regarded as instances of nevoid basal cell carcinoma syndrome (19,55). Nevertheless, there have been a few cases of basal cell carcinoma arising in the setting of multiple trichoepitheliomas (56–58). The simultaneous presence of trichoepithelioma and cylindroma, the latter of which is also dominantly inherited, has been observed repeatedly (see Cylindroma).

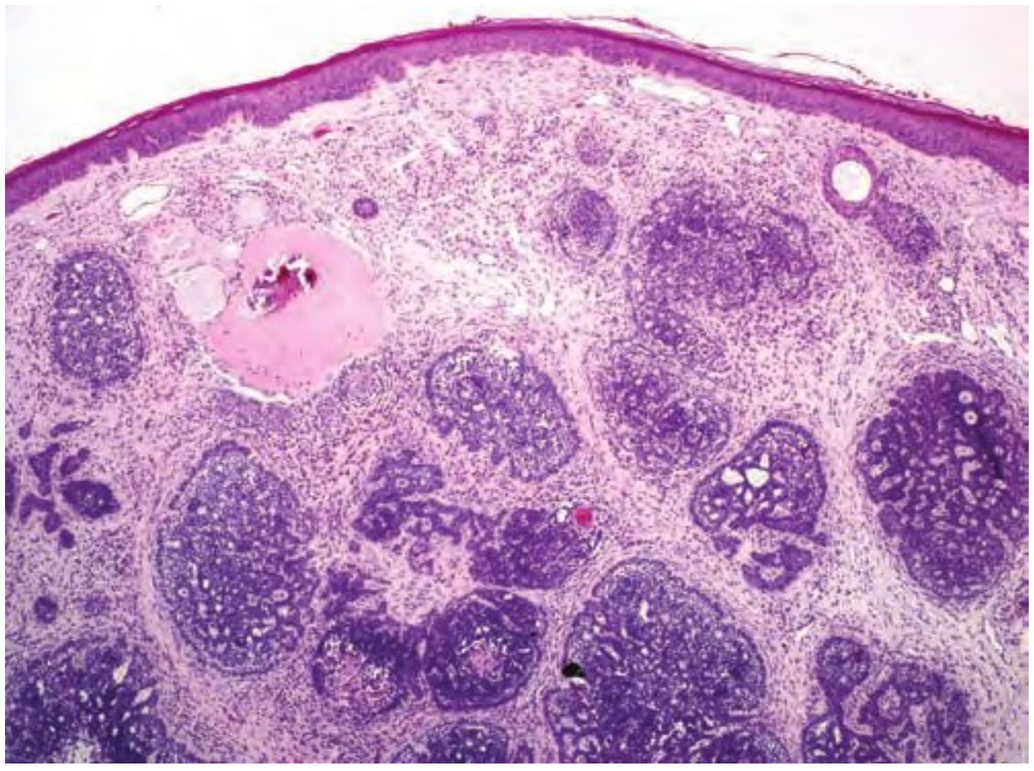


FIGURE 30-12. Trichoepithelioma. A dermal tumor with a prominent stroma, horn cysts of varying sizes, and basaloid epithelial formations.

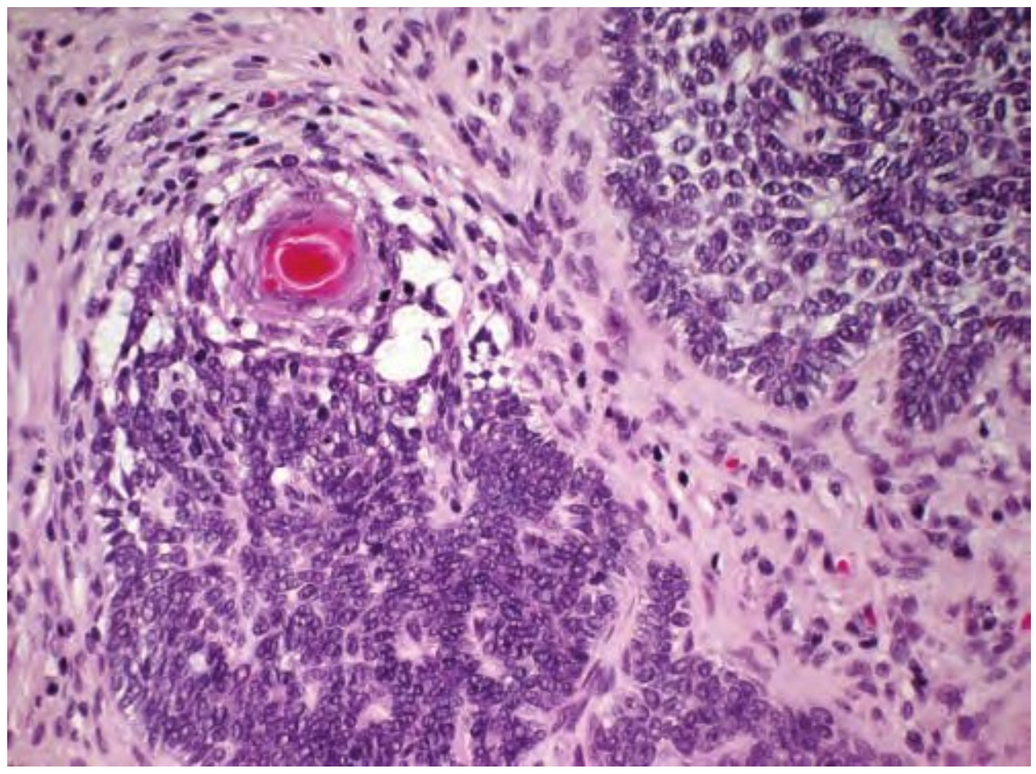


FIGURE 30-13. Trichoepithelioma. Fibroblasts encircle and are tightly associated with the basaloid epithelial islands, lacking the retraction artifact typical of basal cell carcinoma.

Solitary trichoepithelioma occurs more commonly than multiple trichoepitheliomas (54). It is not inherited and consists of a firm, elevated, flesh-colored nodule usually less than 2 cm in diameter. Its onset usually is in childhood or early adult life (59). Most commonly, the lesion is seen on the face, but it may occur elsewhere. The presence within the same tumor of a solitary trichoepithelioma and an apocrine adenoma has been described (60).

Giant solitary trichoepithelioma, measuring several centimeters in diameter, is a distinct variant of trichoepithelioma (61). It arises in later life and occurs most commonly on the thigh and in the perianal region (61,62).

Histopathology. As a rule, multiple trichoepitheliomas are superficial dermal lesions. They appear well circumscribed, small, and symmetric on histologic examination. Horn cysts are the most characteristic histologic feature, although they may be absent in some lesions. They consist of a fully keratinized center surrounded by basophilic cells that have the same appearance as the cells in the basal cell carcinoma, except that they tend to lack high-grade atypia and mitoses, which may be prominent in some but not all carcinomas (Figs. 30-12 and 30-13). The keratinization is abrupt and complete, in the manner of so-called "trichilemmal" keratinization, as opposed to the horn pearls of squamous cell carcinoma. Quite frequently, one observes one or a few layers of cells with eosinophilic cytoplasm and large, oval, pale, vesicular nuclei situated between the basophilic cells and the horn cysts (54).

A second major component of multiple trichoepitheliomas are tumor islands composed of basophilic cells of the same appearance as epidermal or skin appendage basal cells, which usually are arranged in a lacelike or adenoid network but occasionally also as solid aggregates (Fig. 30-13). These tumor islands show peripheral palisading of their cells and are surrounded by a stroma with increased numbers of fibroblasts. The fibroblasts encircle and are tightly associated with the basaloid islands, lacking the retraction artifact typical of basal cell carcinoma (Fig. 30-13). Both the adenoid and the solid aggregates show invaginations, which contain numerous fibroblasts and resemble follicular papillae, also known as papillary mesenchymal bodies (Fig. 30-14) (63).

Additional findings, observed in some but not all trichoepitheliomas, are the presence of a foreign-body giant-cell reaction in the vicinity of ruptured horn cysts, calcium deposits either within the foci of the foreign-body reaction or within intact horn cysts, and amyloid (54,64).

Occasionally, some lesions in patients with multiple trichoepitheliomas show relatively little differentiation toward hair structures. They contain only a few horn cysts, with many areas resembling basal cell carcinoma (54). Such lesions can be difficult to distinguish from those of a keratotic basal cell

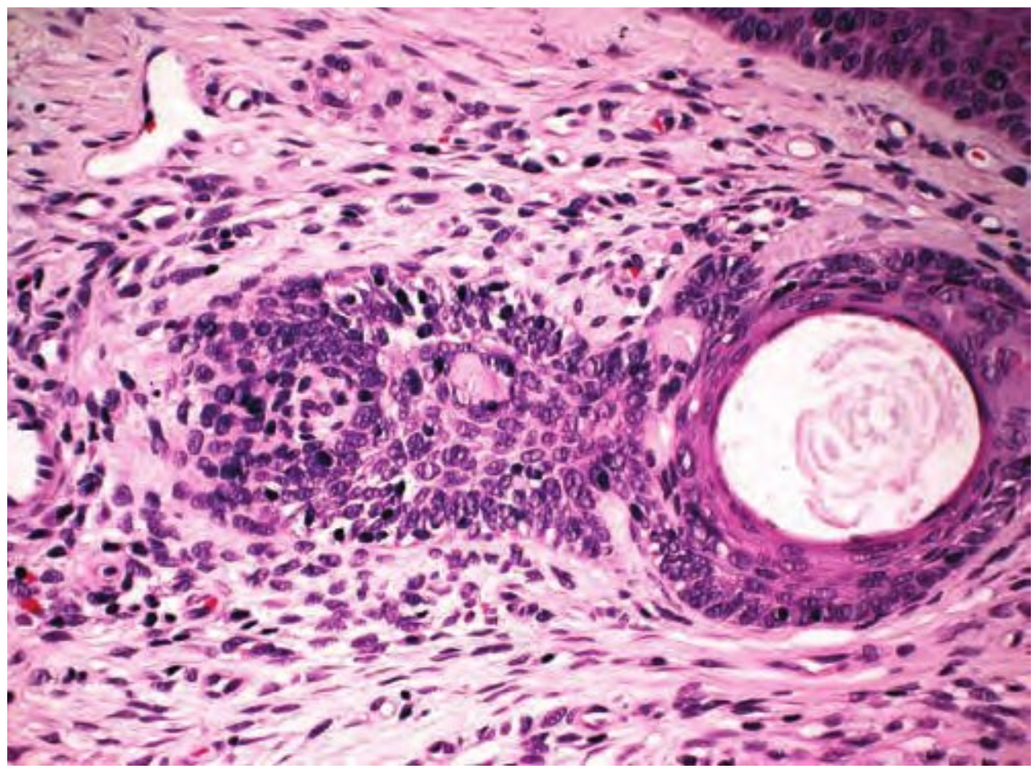


FIGURE 30-14. Trichoepithelioma. Some of the basophilic islands form papillary mesenchymal bodies resembling follicular papillae.

carcinoma, which may also show horn cysts. Thus, on a histologic basis, it may be difficult definitively to distinguish between multiple trichoepitheliomas and basal cell carcinoma (see Differential Diagnosis).

Solitary trichoepithelioma often has a high degree of differentiation toward hair structures. Solitary lesions with relatively little differentiation toward hair structures could be classified as keratotic basal cell carcinoma. If a lesion is to qualify for the diagnosis of solitary trichoepithelioma, it should contain numerous horn cysts and abortive hair papillae and show only few areas with the appearance of basal cell carcinoma (59). Mitotic figures should be rare or absent, and the lesion should not be unduly large, asymmetric, or infiltrative.

Additional Studies. It is assumed that the basophilic cells surrounding horn cysts are similar to hair matrix cells and that the horn cysts represent attempts at hair shaft formation. The eosinophilic cells seen occasionally around horn cysts probably represent cells with initial keratinization and are similar to the nucleated cells seen in normal hair shafts at the keratogenous zone.

Histochemical staining with the Gomori stain for alkaline phosphatase has shown positive staining in many invaginations at the periphery of tumor islands and strands, indicative of a differentiation toward hair papillae (65). An immunohistochemical analysis using a panel of monoclonal antikeratin antibodies suggests that trichoepitheliomas differentiate toward the outer root sheath (66). The expression of cytokeratin 15 in a subset of trichoepitheliomas suggests that these tumors contain cells that are related to hair follicle stem cells in the follicular bulge (67). Electron microscopic study has confirmed that the horn cysts of trichoepithelioma represent immature hair structures, with abrupt development of the horn cells from hair matrix cells (68).

The putative gene for multiple familial trichoepitheliomas has been localized to chromosome 9p21 (69). Several known tumor suppressor genes, including *p15*, *p16*, and *p19*, have been assigned to this region (70). However, loss of heterozygosity on chromosome 9p21 has not been found in sporadic trichoepitheliomas (71). Conversely, in sporadic trichoepitheliomas loss of heterozygosity has been found on chromosome 9q23 (71). In addition, deletions causing overexpression of the human homologue of the *Drosophila* patched gene (*Ptch*) have been found in trichoepitheliomas as in basal cell carcinoma (72). A large body of recent work has demonstrated that mutations in the CYLD2 gene, which appears to function as an ubiquitin-specific protease, are present in some cases of multiple familial trichoepitheliomas (73–79).

The close relationship between trichoepithelioma and basal cell carcinoma has been explained on the basis of the assumption that they have a common genesis from pluripotential cells, which, like primary epithelial germ cells, may develop toward hair structures (14). This hypothesis is supported by the fact that *patched* gene mutations are seen in both tumors (80). Because cells of various degrees of maturity may occur in the same lesion, trichoepithelioma may have areas consistent with the histologic picture of basal cell carcinoma and vice versa.

Differential Diagnosis. The difficulty of differentiating multiple trichoepitheliomas from keratotic basal cell carcinoma on histologic grounds has been pointed out, and the need for clinical data has been stressed. Diagnosis may be assisted, in a given case, by clinical data, such as the number and distribution of the lesions and the presence of hereditary transmission. In addition, certain histologic features, as well as immunohistochemical stains, can assist in differentiating between the two. The presence of well-formed horn cysts, papillary-mesenchymal bodies, and lack of high-grade atypia and mitoses favor the diagnosis of trichoepithelioma (81). Histologic features that favor basal cell carcinoma include the presence of myxoid stroma and stromal retraction or clefting around the basaloid islands (64). Focal positive CD34 staining of the fibroblastic stroma has been shown in trichoepitheliomas, whereas in basal cell carcinoma, this staining pattern was not seen (82). However, in a separate study similar CD34 staining was found in trichoepitheliomas but also in many metatypical basal cell carcinomas (83). Staining of the outermost epithelial layer for bcl-2 has been seen in several trichoepitheliomas. In contrast, basal cell carcinomas frequently stain diffusely (83,84). Immunohistochemistry for CD10 may be helpful in differentiating trichoepitheliomas from basal cell carcinomas. CD10 stains the stromal cells but not the epithelial cells in trichoepitheliomas, whereas in basal cell carcinomas, CD10 is present in the epithelial cells and rarely in the stromal cells (85).

The differentiation of multiple trichoepitheliomas from the nevoid basal cell carcinoma syndrome on histologic grounds can be just as difficult. This, too, often requires clinical information. Although both diseases are dominantly inherited and have multiple lesions, the lesions in multiple trichoepitheliomas present mainly in the nasolabial fold, remain small, and hardly ever ulcerate, whereas the lesions in the nevoid basal cell carcinoma syndrome are haphazardly distributed and, especially in the late, "neoplastic" phase, can grow to considerable size, ulcerate deeply, and show severely destructive growth. In addition, patients with the nevoid basal cell carcinoma syndrome almost invariably show multiple skeletal and central nervous system anomalies and frequently show multiple palmar and plantar pits.

Desmoplastic Trichoepithelioma

Desmoplastic trichoepithelioma, typically a sporadic lesion, was formerly considered a solitary trichoepithelioma (54,59). However, it has sufficient clinical and histologic characteristics to be regarded as a distinct variant of trichoepithelioma. The term *desmoplastic trichoepithelioma* appears preferable to the designation *sclerosing epithelial hamartoma* because it stresses the relationship of the lesion to solitary trichoepithelioma (86,87).

Clinically, the tumor almost always is located on the face, measures from 3 to 8 mm in diameter, and is markedly indurated. In many instances, there is a raised, annular border

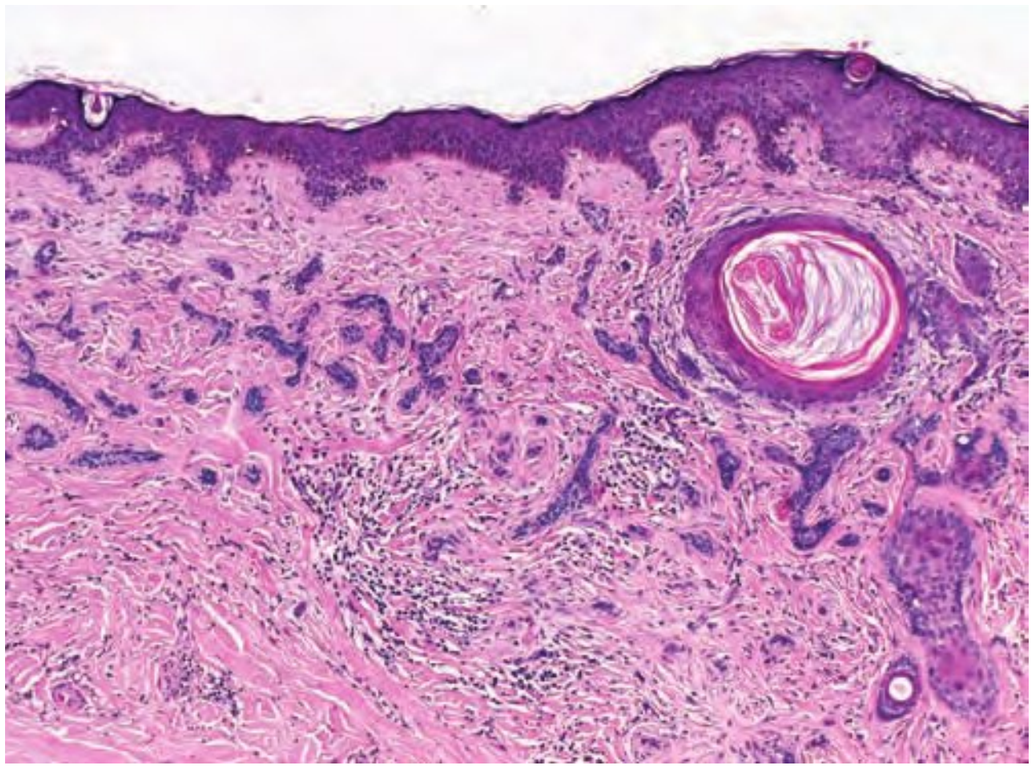


FIGURE 30-15. Desmoplastic trichoepithelioma. Horn cysts and narrow strands of epithelial cells are embedded in a fibrous stroma.

and a depressed nonulcerated center, causing the lesion to resemble granuloma annulare (86). Most commonly, the lesion appears in early adulthood, but it quite frequently appears in the second decade of life (87). It is much more common in females than in males (86). Familial desmoplastic trichoepitheliomas have been reported infrequently (88,89).

Histopathology. The three characteristic histologic features are narrow strands of tumor cells, horn cysts, and a desmoplastic stroma (Figs. 30-15 and 30-16) (86). The tumor strands usually are from one to three cells thick and are composed of small basaloid cells with prominent oval nuclei and scant cytoplasm. Usually there are numerous horn cysts, which in some cases are large (90). Considerable amounts of densely collagenous and hypocellular stroma are present. Large aggregates of tumor cells are not seen. Foreign-body granulomas at the site of ruptured horn cysts and areas of calcification within some of the horn cysts are seen in many tumors.

Differential Diagnosis. The resemblance to microcystic adnexal (eccrine) carcinoma and syringoma may be considerable, especially if a superficial specimen is taken for biopsy. Like desmoplastic trichoepithelioma, microcystic adnexal carcinoma has horn cysts, strands of basaloid cells, and a dense desmoplastic stroma. It differs, however, by showing ductal structures, a deeply infiltrating growth, and often perineural invasion (91). The diagnosis of microcystic adnexal carcinoma should be considered in any tumor resembling a trichoepithelioma or a syringoma in which the lesional cells extend to the base of the specimen. Syringomas, which usually are periorbital, rarely have horn cysts, foreign-body granulomas, or calcification (86).

Desmoplastic trichoepithelioma may also resemble morphea-like (fibrosing) basal cell carcinoma. However, in morphea-like basal cell carcinoma, horn cysts are absent. Of value in ruling out basal cell carcinoma, especially the morphea-like form, are the absence of mitoses, individual cell necrosis, and mucinous stroma and the lack of foci of separation artifact of lesional epithelium and stroma (86). The immunostains for CD34 and bcl-2, discussed previously, also may assist in discriminating between the two lesions (83,84,92). In addition, matrix metalloproteinase stromelysin-3 (ST-3) expression has been demonstrated in morphea-like basal carcinomas but not desmoplastic trichoepitheliomas (93). The presence of Merkel cells has been shown in desmoplastic trichoepitheliomas and not morphea-like basal cell carcinomas (94).

Occasional lesions of solitary or desmoplastic trichoepithelioma cannot reliably be distinguished from keratotic or morphea-like basal cell carcinomas, respectively. A descriptive report and a recommendation for complete excision are appropriate in such cases.

Trichoblastoma

Trichoblastomas are benign skin lesions that recapitulate in some form the developing hair follicle. They differ from trichoepitheliomas in size, location, and lack of keratinizing cysts (95). Trichoblastomas are usually about 1.0 cm in size and most commonly occur on the scalp (Fig. 30-17) (96). Multiple lesions have been described (97). As mentioned, these lesions are benign, and aggressive forms may represent a type of basal cell carcinoma (98,99).

Histopathology. Trichoblastomas consist of a proliferation of follicular germ cells manifested by a combination of various proportions of mesenchymal and epithelial cells. A spectrum of lesions is seen, depending on the proportions of mesenchymal and epithelial components. At one end of the spectrum is the predominantly mesenchymal variant, termed the trichogenic fibroma, and at the other end is the classic trichoblastoma composed predominantly of basaloid epithelial islands (96). The classic large lesion is comprised of islands of basaloid cells occupying the dermis with occasional extension into the subcutaneous fat (Fig. 30-18). These basaloid islands demon-

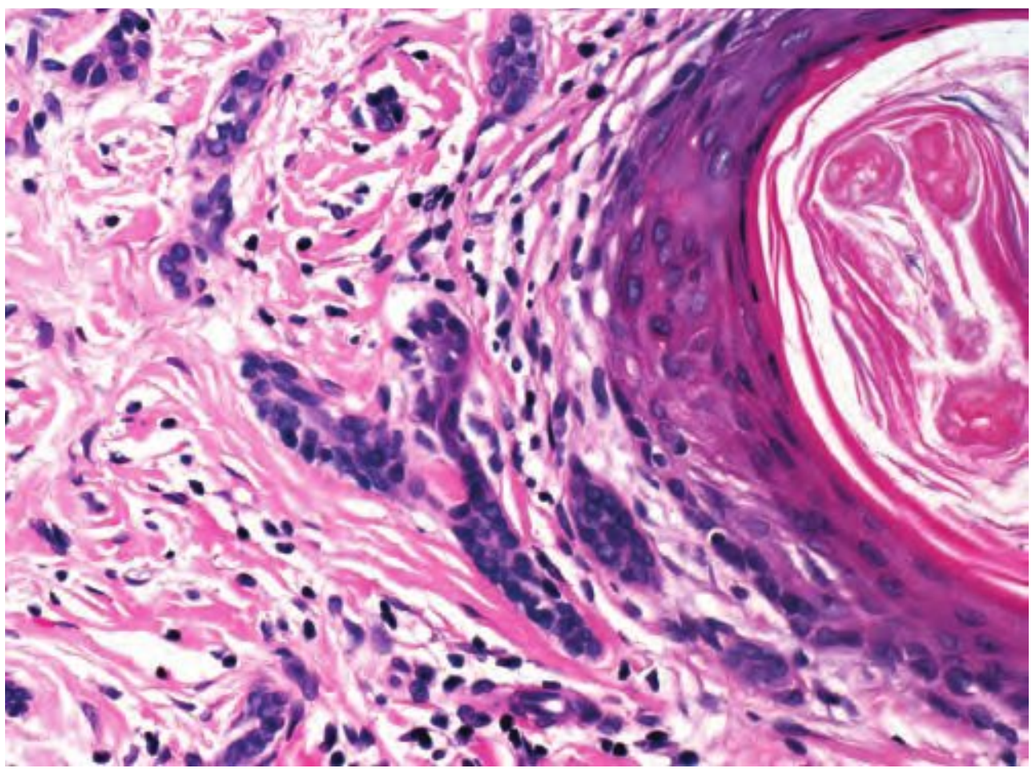


FIGURE 30-16. Desmoplastic trichoepithelioma. The strands of tumor cells are comprised of small basaloid cells and are usually one to three cells thick.



FIGURE 30-17. Trichoblastoma. A circumscribed, pigmented nodule is noted on the scalp.

strate peripheral palisading and a fibrocellular stroma similar to that surrounding follicles; mitotic activity can be seen (Fig. 30-19). There is no overlying epidermal connection. The trichogenic fibroma variant displays small basaloid epithelial islands, exhibiting follicular differentiation, dispersed in a fibrotic stroma (Figs. 30-20 and 30-21). Less common variants have been described, including giant, clear cell, pigmented, rippled-pattern trichoblastomas, and cutaneous lymphadenoma (100–104).

FIGURE 30-18. Trichoblastoma. Large islands of basaloid tumor cells are present in the dermis exhibiting peripheral palisading associated with a fibrous stroma.

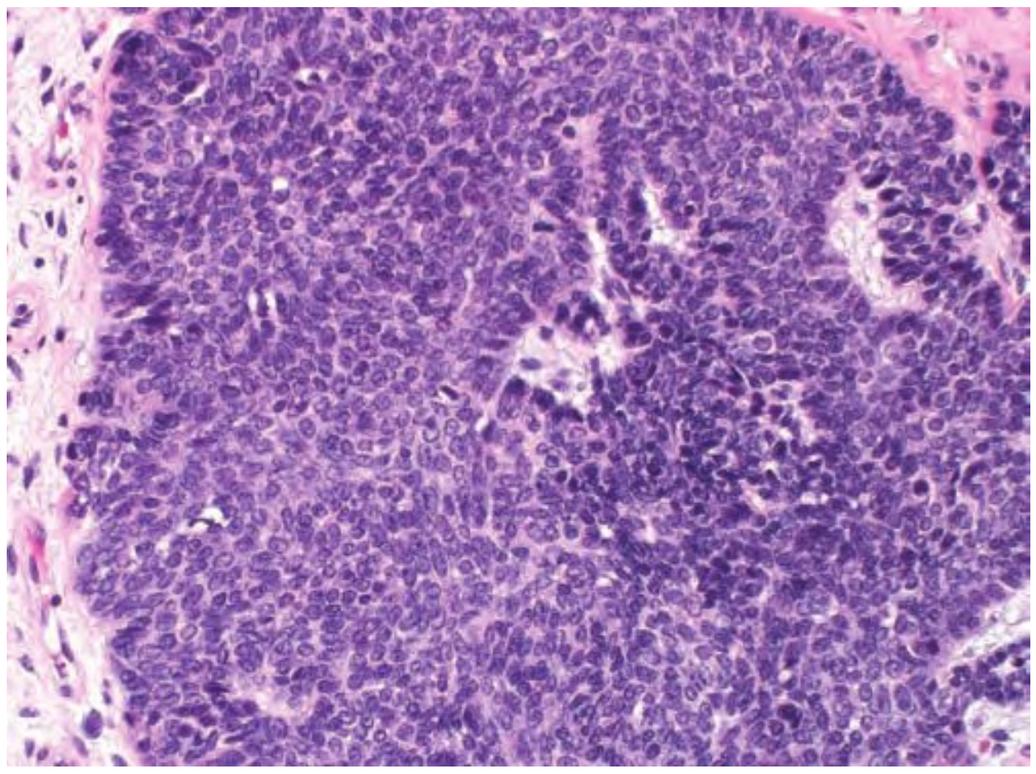


FIGURE 30-19. Trichoblastoma. Higher power showing epithelial structures reminiscent of follicular germs and occasional mitotic activity.

Similar lesions that are infiltrative, exhibit cytologic atypia, and mitotic activity may be termed *trichoblastic carcinoma*, but these lesions may overlap with basal cell carcinoma (Figs. 30-22 and 30-23). Such problematic lesions may be signed out descriptively as *malignant adnexal neoplasm* with a description of the apparent differentiation. Criteria that may have value in distinguishing trichoblastomas and trichilemmomas from basal cell carcinomas include the following: the presence in the former of symmetry, circumscription with smooth margins and "shelling out" of the normal tissue, and follicular and "racemiform" patterns of lesional cells, the lack of a clefting

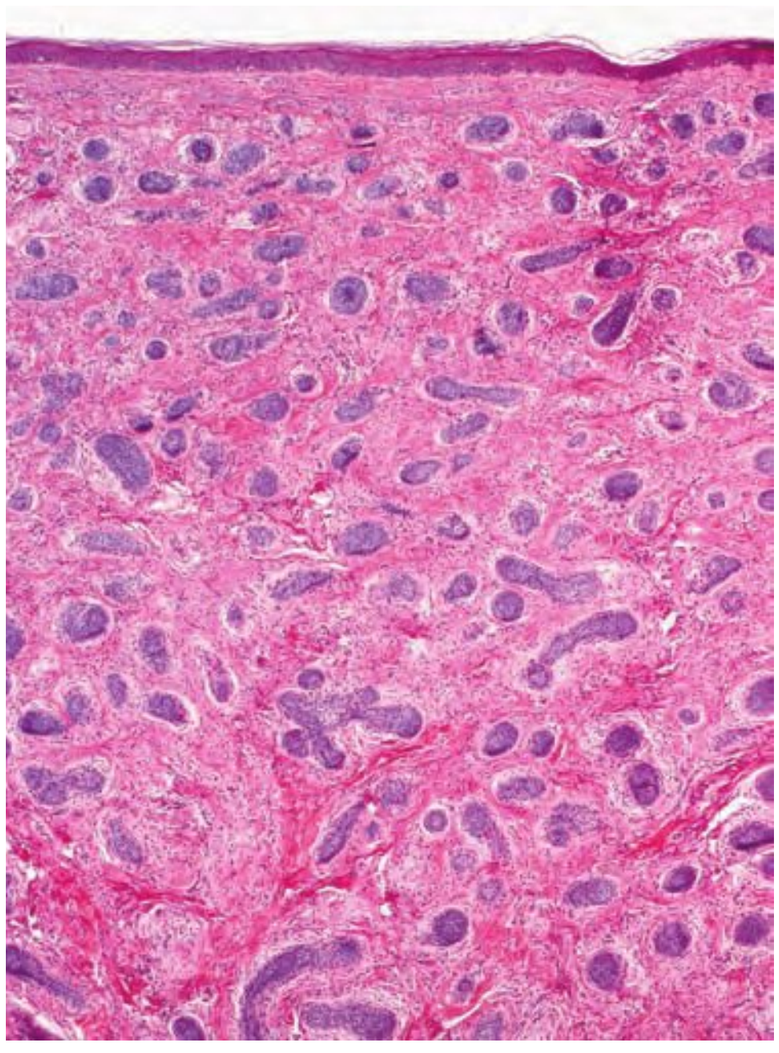


FIGURE 30-20. Trichogenic fibroma. The lesion manifests small basaloid islands in a prominent fibrotic stroma.

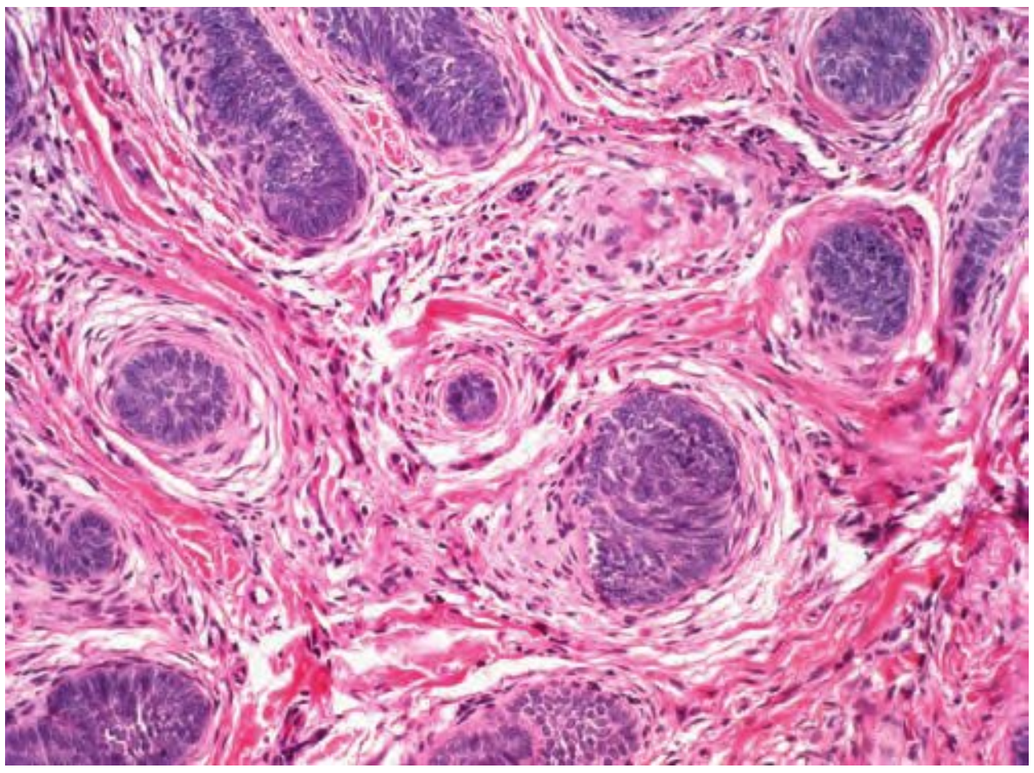


FIGURE 30-21. Trichogenic fibroma. The epithelial-stromal structures mimic those of hair follicles.

artifact between stroma and epithelium that is characteristic of basal cell carcinoma, the lack of stromal edema and lymphocytes, the formation of a delicate stroma reminiscent of that formed around immature hair follicles, and the lack of ulceration (105).

Trichoadenoma

A rare, solitary tumor first described in 1958, trichoadenoma usually occurs on the face or buttocks as a solitary nodular lesion and varies from 3 to 15 mm in diameter (106,107). It may arise anytime during adult life. It may clinically mimic basal cell carcinoma.

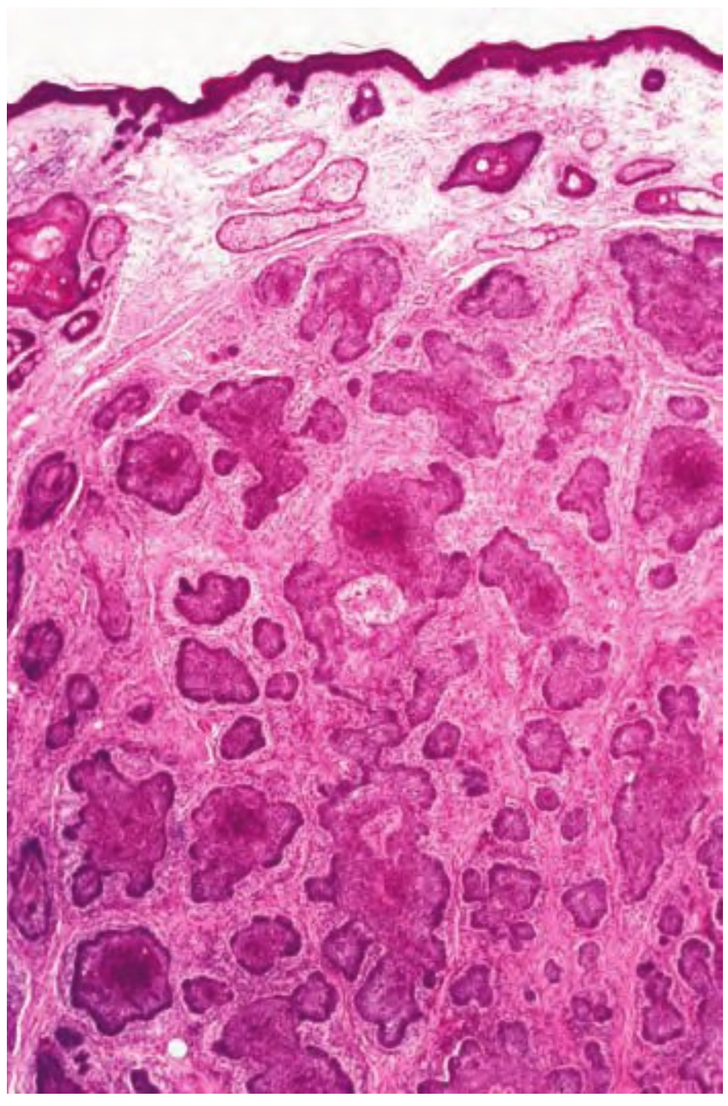


FIGURE 30-22. Trichoblastic carcinoma. A large dermal tumor comprised of irregular epithelial islands.

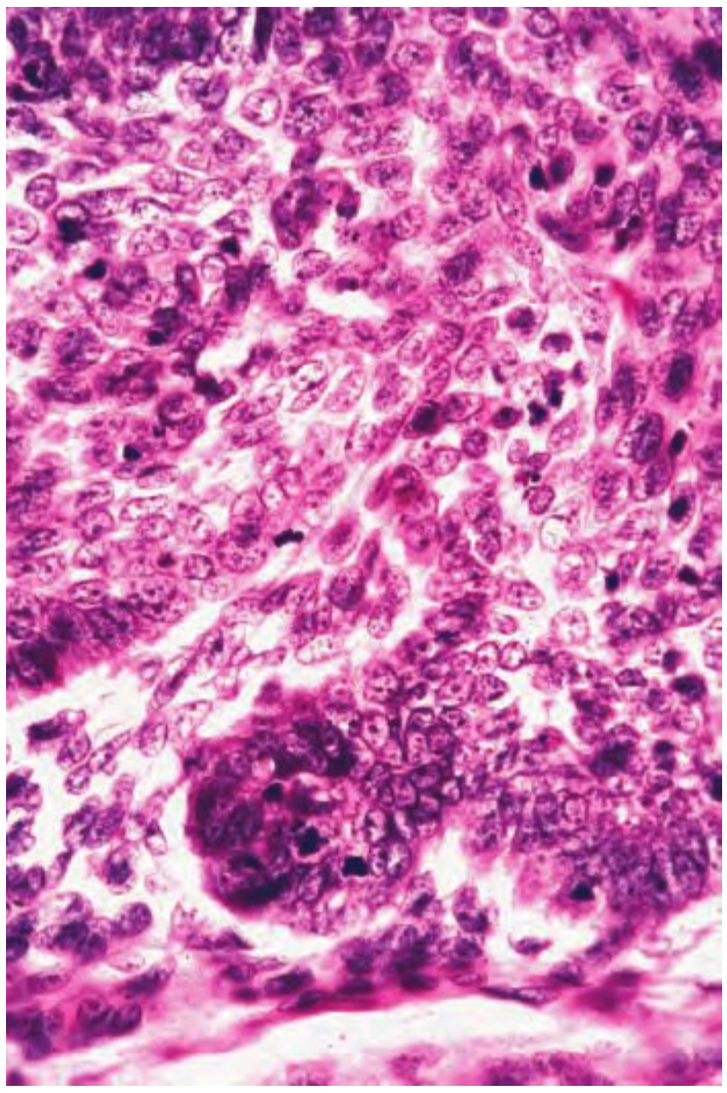


FIGURE 30-23. Trichoblastic carcinoma. Higher power demonstrates cytologic atypia, numerous mitoses, and a fibrocellular stroma.

Histopathology. Numerous horn cysts are present throughout the dermis (Fig. 30-24). They are surrounded by eosinophilic cells, which greatly resemble the eosinophilic cells that are often seen in trichoepithelioma located between the basophilic cells and the central horn cysts (Fig. 30-25). In some instances, a single layer of flattened granular cells is interpolated between the horn cysts and the surrounding eosinophilic cells (107–109). Some islands consist only of eosinophilic epithelial

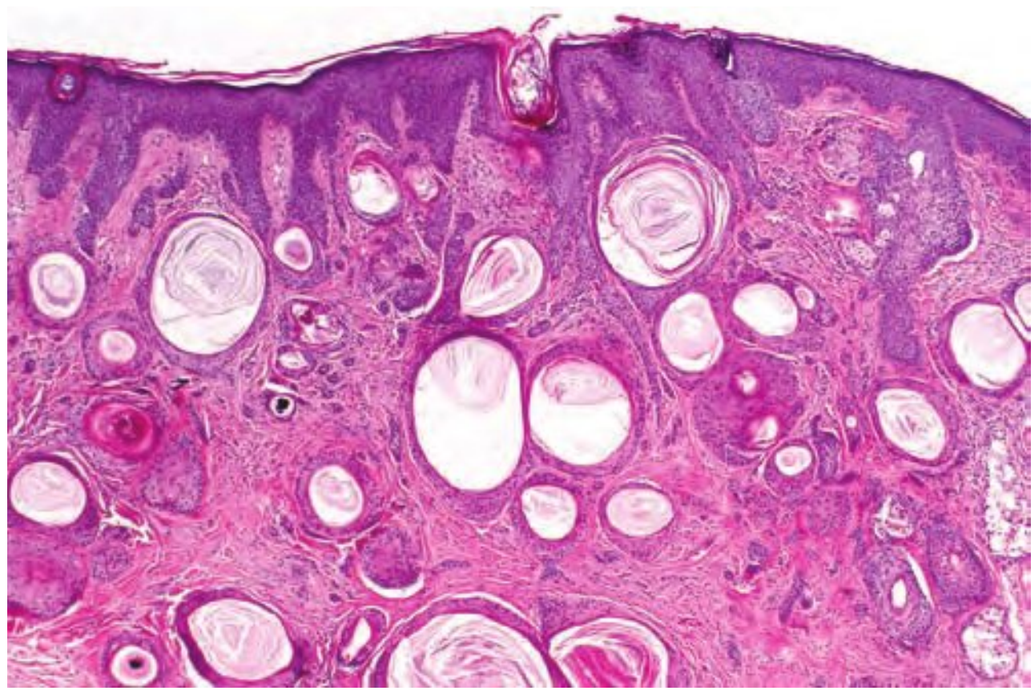


FIGURE 30-24. Trichoadenoma. Numerous horn cysts are present in the dermis.

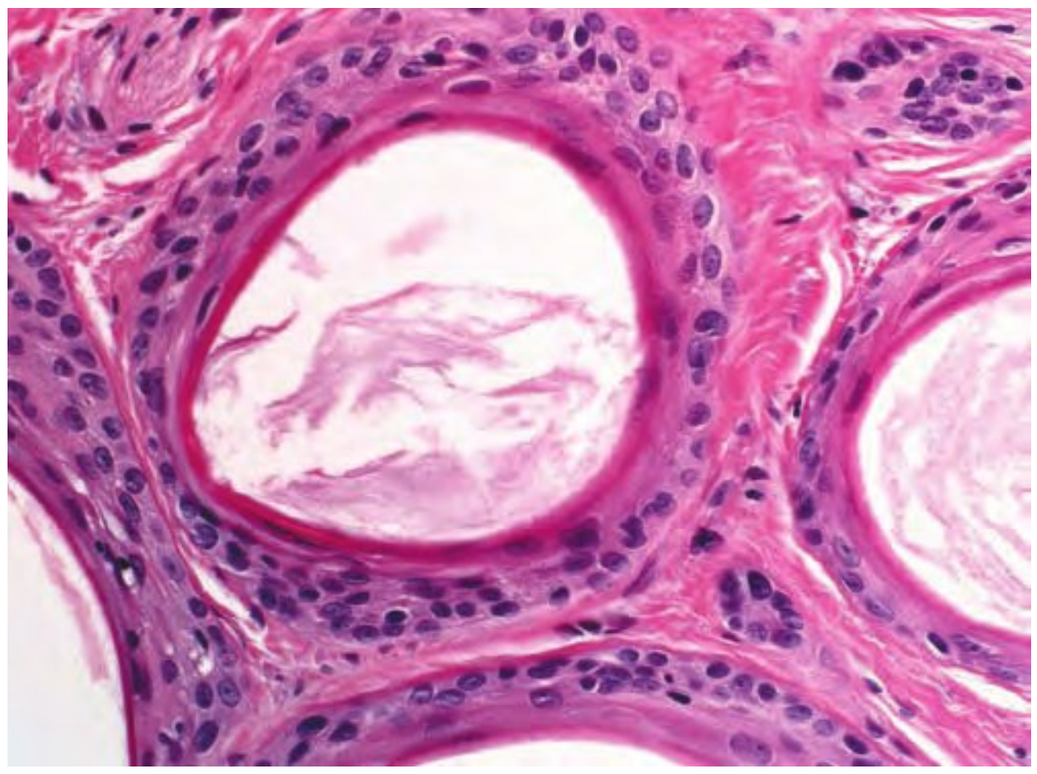


FIGURE 30-25. Trichoadenoma. The horn cysts are lined by eosinophilic cells and contain keratin.

cells without central keratinization. Sparse intercellular bridges have been observed between the eosinophilic cells. Foci of foreign-body granuloma are present at the sites of ruptured horn cysts (106). A variant has been described, termed verrucous trichoadenoma, which clinically resembles a seborrheic keratosis (110).

Additional Studies. In terms of morphologic differentiation, the trichoadenoma is situated between a trichofolliculoma and a trichoepithelioma (111). The general architecture of trichoadenoma greatly resembles that of trichoepithelioma and thus suggests the development of immature hair structures. However, because the cyst wall consists of epidermoid cells and the keratinization may take place with formation of keratohyaline, it has been suggested that the tumor differentiates largely toward the infundibular portion of the pilosebaceous unit (107). In fact, the keratin expression pattern of trichoadenomas resembles that seen in follicular infundibula and the follicular bulge (112).

Generalized Hair Follicle Hamartoma and Basaloid Follicular Hamartoma

Only a few cases have been described of generalized hair follicle hamartoma, a distinctive condition characterized by progressive alopecia starting in adulthood, diffuse papules and plaques of the face, and an association with myasthenia gravis (113–116).

Basaloid follicular hamartoma was originally described as a localized patch of alopecia on the scalp (117). Solitary and multiple familial lesions have since been described (118,119). A few rare syndromes have been described that among their many manifestations have lesions reminiscent of basaloid follicular hamartomas (113,120). An autosomally dominant inherited form with multiple basaloid follicular hamartomas has been described and named *dominantly inherited generalized basaloid follicular hamartoma syndrome*. Generalized lesions have been described without other associated abnormalities (121). These syndromes all may represent contiguous gene syndromes or different allelic forms of the same gene mutation (122,123).

Histopathology. In both hamartomas, the hair loss is the result of damage inflicted on each hair follicle by gradually growing "hair follicle hamartomas."

In the generalized hair follicle hamartoma, areas of alopecia without papules or plaques reveal more or less advanced replacement of the hair follicles by a lacelike network of basaloid cells with follicular differentiation resembling trichoepithelioma (113,115). The papules and plaques of the face show a complete lack of hair structures and extensive proliferations of basaloid cells embedded in a cellular stroma with formation of horn cysts in some areas. The histologic appearance is indistinguishable from that of trichoepithelioma (114).

The basaloid follicular hamartoma reveals strands and cords of small, basaloid cells emanating from the infundibular portion of the hair follicle (Figs. 30-26 and 30-27) (123,124). The tumor stroma is mildly fibrocellular. There is no significant cleft-ing between tumor and stroma, and mitotic activity is rare (Fig. 30-27). These lesions may have a similar appearance to infundubulocystic basal cell carcinoma, but usually they can be distinguished on clinical and histologic grounds (123,125,126).

Differential Diagnosis. Linear unilateral basal cell nevus shows similar basaloid proliferations, some of which may resemble trichoepithelioma and basal cell carcinoma, but the clinical picture is different because the lesion is congenital and unilateral (127).

Additional Studies. Transgenic mice with increased epidermal expression of *smoothened* demonstrate activation of the Sonic Hedgehog signaling pathway and exhibit lesions similar to basaloid follicular hamartomas (128).

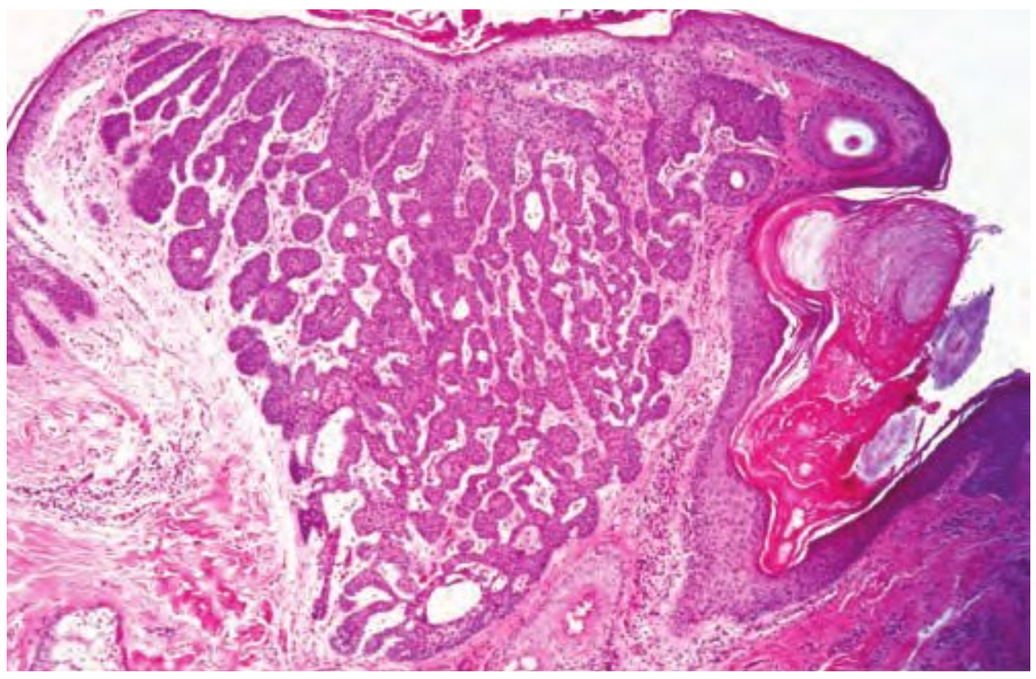


FIGURE 30-26. Basaloid follicular hamartoma. Present is a small, well-circumscribed lesion comprised of strands of epithelial cells with scattered cystic structures.

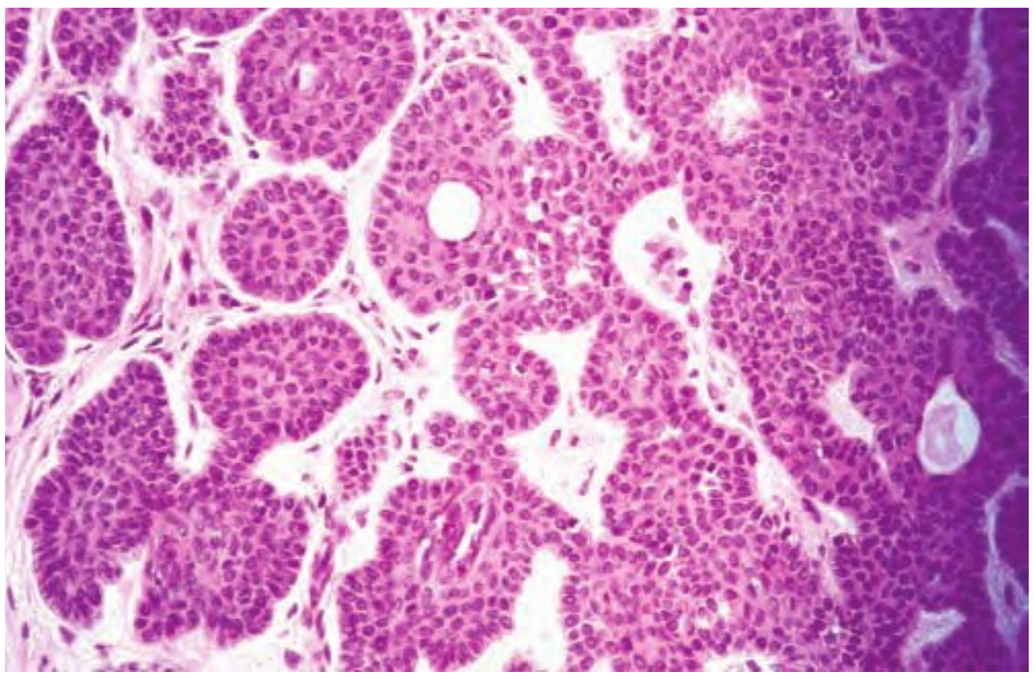


FIGURE 30-27. Basaloid follicular hamartoma. The lesion exhibits small basaloid cells lacking necrosis or mitotic activity. A mildly fibrocellular stroma is seen.

Pilomatricoma

Pilomatricoma (pilomatrixoma), or calcifying epithelioma of Malherbe, is a tumor with differentiation toward hair cells, particularly hair cortex cells. Pilomatricoma occurs usually as a solitary lesion. The face and the upper extremities are the most common sites. Generally, the tumor varies in diameter from 0.5 to 3.0 cm, but it may be as large as 5 cm. The tumors may arise in persons of any age, but about 40% of them arise in children younger than 10 years of age, and about 60% in persons in the first two decades of life (129).

It frequently presents as a firm, deep-seated nodule that is covered by normal skin. Occasionally, however, the tumor is more superficially located, causing a blue-red discoloration of the overlying skin, and, rarely, it protrudes as a sharply demarcated, dark-red nodule. Rapid enlargement of a pilomatricoma may occur as the result of formation of a hematoma (130). Perforation may take place with extrusion of parts of the contents (131). Although, as a rule, pilomatricoma is not hereditary, there are a few instances of familial occurrence, and in some of these cases the tumor is associated with myotonic dystrophy (132,133). Pilomatricoma-type changes can be seen in the epidermal cysts of Gardner's syndrome (134). Unusual clinical variants include large, extruding, or perforating examples, multiple eruptive cases, familial cases, and malignant examples termed *pilomatrix carcinoma* (see text following) (135–139).

Histopathology. The tumor is sharply demarcated and often surrounded by a connective tissue capsule (Fig. 30-28). It is usually located in the lower dermis and extends into the subcutaneous fat. Embedded in a rather cellular stroma are irregularly shaped islands of epithelial cells. As a rule, two types of cells, *basophilic cells* and *shadow cells*, compose the islands (Fig. 30-29) (140). In some tumors, however, basophilic cells are absent. The basophilic cells possess round or elongated, deeply basophilic nuclei and scanty cytoplasm, so that the nuclei lie close together (Fig. 30-29). The cellular borders of the basophilic cells often are indistinct, so that it appears as if

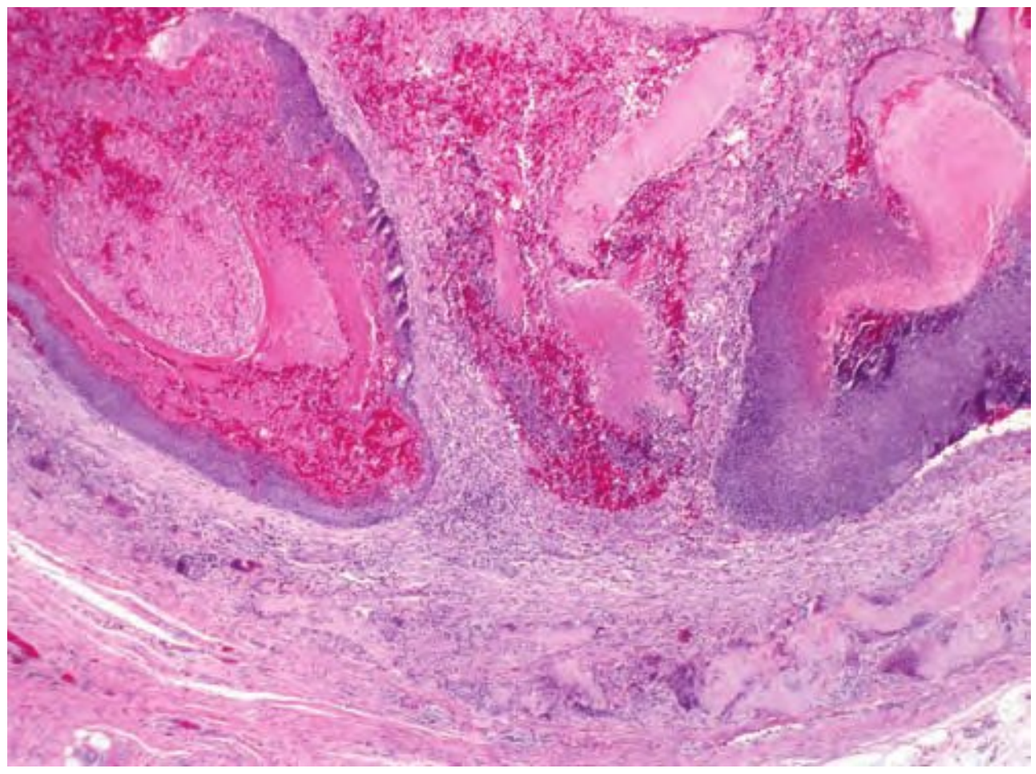


FIGURE 30-28. Pilomatricoma. The tumor is often well circumscribed and composed of epithelial islands embedded in a cellular stroma. Two types of cells comprise the islands: basophilic cells and shadow cells. The basophilic cells resemble hair matrix cells. The shadow cells show a central unstained shadow at the site of the lost nucleus. In the center of the field, one can see transformation of the basophilic cells into shadow cells.

the nuclei were embedded in a contiguous mass. The basophilic cells are arranged either on one side or along the periphery of the tumor islands. In some areas, the transition of basophilic cells into shadow cells is abrupt, whereas in others the transition is gradual. In areas of gradual transition there are cells showing a gradual loss of nuclei and ultimately appearing as faintly eosinophilic, keratinized shadow cells. The shadow cells have a distinct border and possess a central unstained area as a shadow of the lost nucleus. In tumors of recent origin, numerous areas of basophilic cells usually are present. As the lesion ages, the number of basophilic cells decreases because of

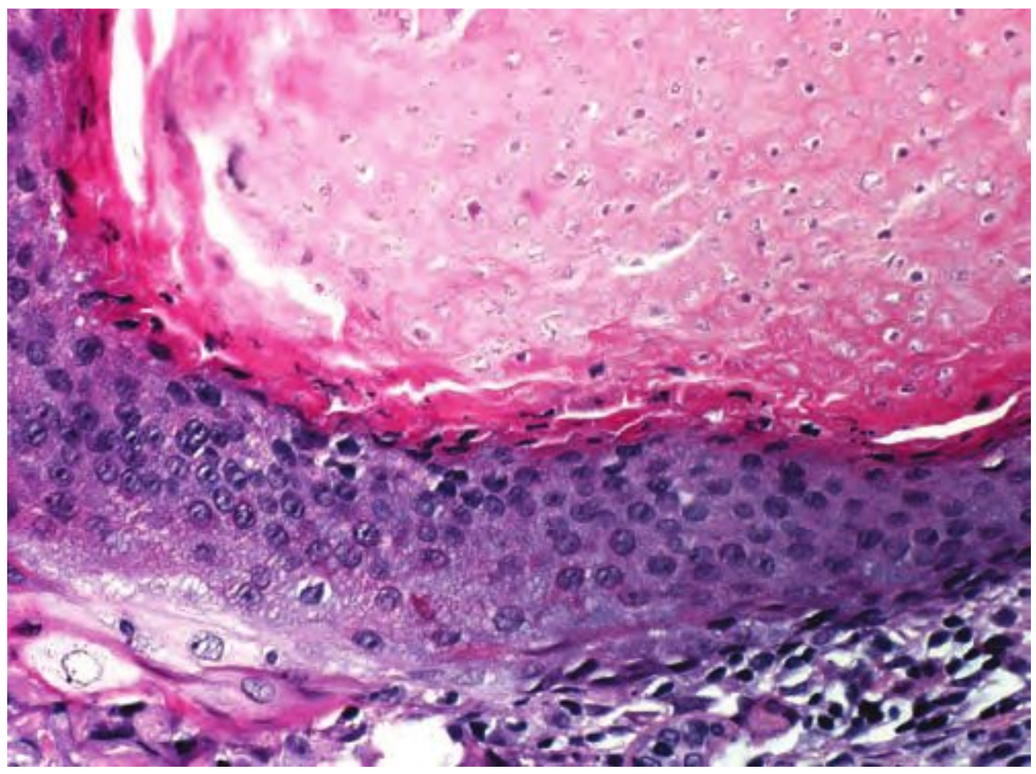


FIGURE 30-29. Pilomatricoma. The transformation of basaloid cells into shadow cells is associated with loss of nuclei.

development into shadow cells, and in tumors of long standing few or no basophilic cells remain.

In many tumors, small, round, eosinophilic centers of keratinization are seen within areas of basophilic cells or within aggregates of shadow cells. The keratinization within these centers is abrupt and complete (141). In some tumors, melanin is present, as can be expected in tumors with differentiation toward hair bulbs. It is found most commonly in shadow cells or within melanophages of the stroma. A variant of pilomatricoma with numerous dendritic melanocytes located in the islands of basophilic cells has been described and termed melanocytic matricoma (142–144).

With the von Kossa stain, calcium deposits are found in approximately 75% of the tumors (145). Usually, the calcium is already apparent as deeply basophilic deposits in sections stained with hematoxylin-eosin. Most of the tumors containing calcium are composed largely of shadow cells. The calcium is seen either as fine basophilic granules within the cytoplasm of the shadow cells or as large sheets of amorphous, basophilic material replacing the shadow cells. Occasionally, foci of calcification are seen in the stroma of the tumors. Areas of ossification are seen in 15% to 20% of the cases (146). Ossification takes place in the stroma next to areas of shadow cells, probably through metaplasia of fibroblasts into osteoblasts. Bone morphogenic protein-2 has been shown in the cytoplasm of shadow cells but not in basophilic cells, indicating a possible role in bone formation (147). Calcium-rich shadow cells may act as inducing factors (148). The stroma of pilomatricomas often shows a considerable foreign-body reaction containing many giant cells adjacent to the shadow cells (Fig. 30-30).

Additional Studies. Pilomatricoma was originally described in 1880 as calcified epithelioma of sebaceous glands; however, it was recognized in 1942 that the cells of the tumor differentiate in the direction of hair cortex cells, a finding that was subsequently confirmed by electron microscopic studies (149,150). On this basis, the designation *pilomatricoma* was suggested (146).

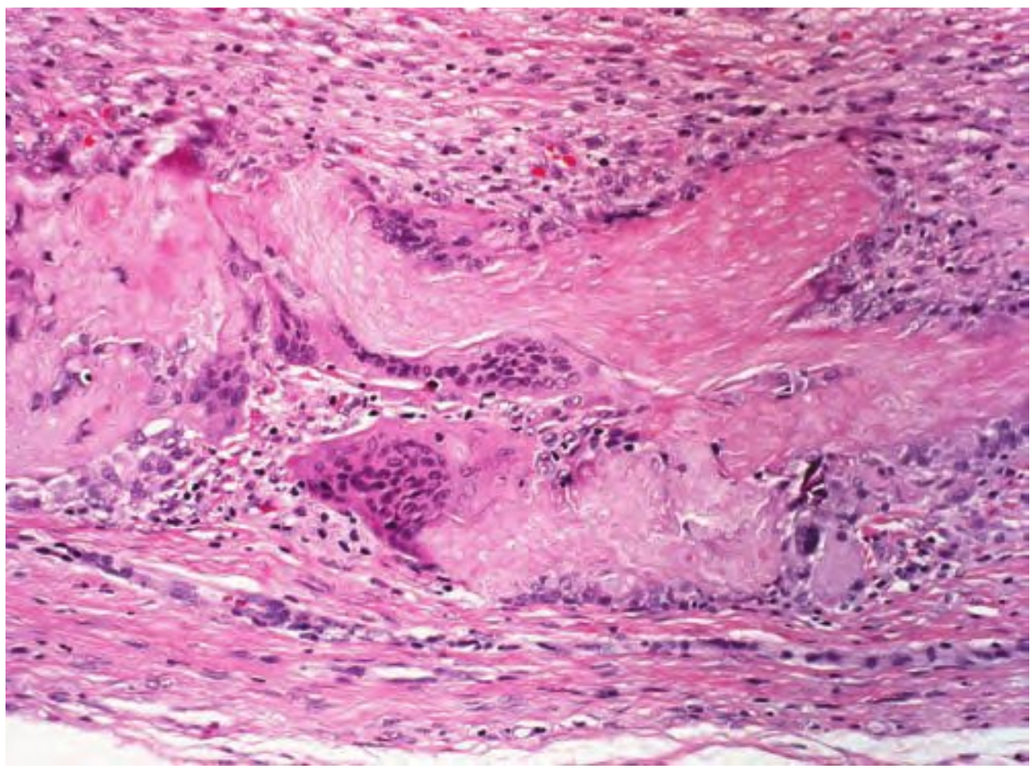


FIGURE 30-30. Pilomatricoma. The stroma often contains numerous multinucleated giant cells reacting to tumoral keratin.

Histochemical studies have revealed in most tumor cells a strongly positive reaction with the periodic acid-Schiff stain for sulfhydryl or disulfide groups. This reaction is indicative of keratinization (145,146,151). As further evidence of keratinization, the shadow cells show strong birefringence in polarized light (152). A very similar birefringence is seen in the keratogenous zone of hair (146).

Electron microscopic examination has revealed a few desmosomes and a moderate number of tonofilaments in the areas of basophilic cells (153). In cells that are in transition to shadow cells, numerous tonofilaments are seen aggregated into thick keratin fibrils. They form keratin without the appearance of keratohyaline granules. A striking resemblance exists between cells that are in transition to shadow cells and cells in the keratogenous zone of normal hair because both types of cells show thick keratin fibrils concentrically arranged around a faintly visible nucleus. Fully developed shadow cells show numerous fused, electron-dense keratin fibrils surrounding the empty nuclear area (151,153,154).

Several studies using immunohistochemistry and *in situ* hybridization with various cytokeratins and hair-specific keratins further support the notion that pilomatrixomas differentiate toward cortical cells of the normal hair shaft during their maturation process (155–157).

Mutations in the gene for β-catenin (*CTNNB1*) have been described in pilomatricomas (158,159). The resulting mutation stabilizes the β-catenin protein, which translocates into the nucleus, where it activates gene transcription through members of the Lef/Tcf family (160).

Differential Diagnosis. The wall of trichilemmal cysts also contains basophilic cells, which as they keratinize gradually lose their nuclei and often undergo calcification. The peripheral layer of basophilic cells in trichilemmal cysts, however, shows a palisading pattern, whereas the basophilic cells of pilomatricoma do not. Furthermore, shadow cells characterized by a central unstained area at the site of the disintegrated nucleus are seen only in pilomatricomas and, exceptionally, in basal cell carcinomas with foci of matrical differentiation (161).

Pilomatrix Carcinoma

Pilomatrix carcinoma is the rare malignant counterpart of pilomatricoma. The lesions have a male predominance and occur in older patients. Some pilomatricomas show apparent transformation into carcinomas (162,163). Other cases are malignant from the onset (164,165). Pilomatrix carcinomas are not necessarily larger than benign pilomatricomas. Pulmonary and bone metastases may occur (137,166,167). The lesions have a tendency to recur if not widely excised (136).

Histopathology. Pilomatrix carcinomas are asymmetric, cellular, infiltrative neoplasms (Fig. 30-31). Many areas, especially at the periphery of the tumor, show proliferations of large, anaplastic, hyperchromatic basophilic cells with numerous mitoses (Fig. 30-32); however, this can be seen in pilomatricomas on occasion (163). Toward the center of the tumor, there

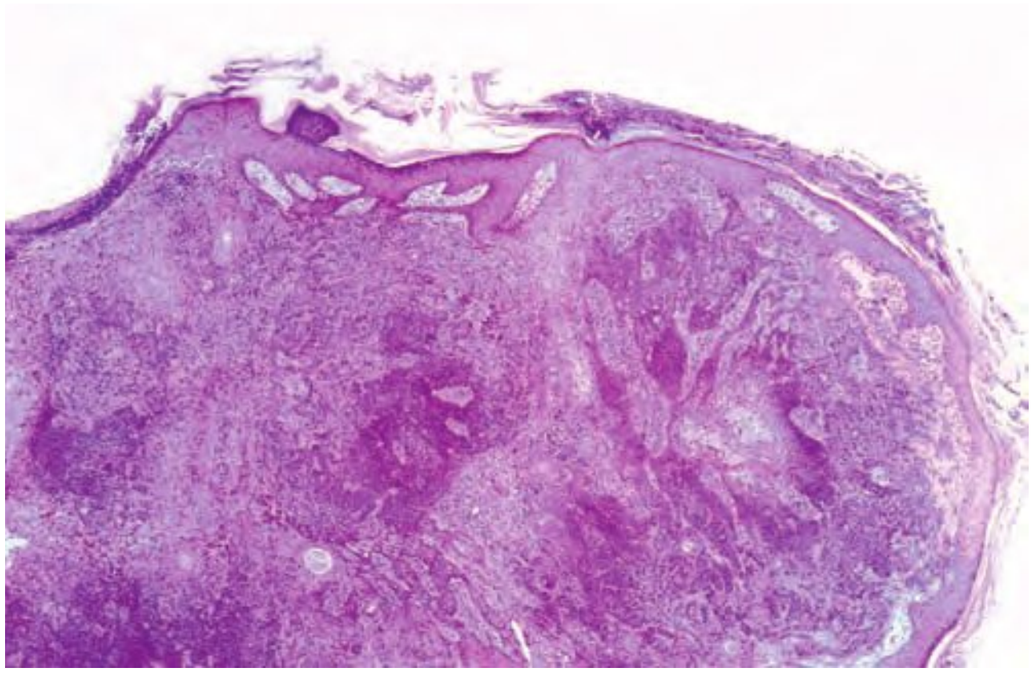


FIGURE 30-31. Pilomatrix carcinoma. There is a cellular, asymmetric, ulcerated tumor that infiltrates the dermis.

may be transformation of basophilic cells into eosinophilic shadow cells of the type seen in benign pilomatricomas, or there may be large cystic centers containing necrotic debris (165,168). Features that are helpful in making the diagnosis include asymmetry and poor circumscription, presence of several markedly sized and variably shaped basaloid aggregations of tumor cells, continuity of basaloid cells with the epidermis, extensive areas of necrosis en masse, infiltrative growth pattern, and presence of ulceration (169).

Additional Studies. Pilomatrix carcinoma has been found to express keratins 5, 14, and 17, whereas pilomatricomas typically lack these keratins (170).

Proliferating Trichilemmal Cyst

The proliferating trichilemmal cyst, also referred to as proliferating trichilemmal tumor, is typically a single lesion; rarely, there are multiple lesions (171,172). Another common designation used for this lesion is proliferating pilar tumor. About 90% of the cases occur on the scalp, with the residual 10% occurring mainly on the back. More than 80% of the patients are women, most of them elderly (173).

Starting as a subcutaneous nodule suggestive of a wen, the tumor may grow into a large, elevated, lobulated mass that may undergo ulceration and thus greatly resembles a squamous cell carcinoma (173). The tumor may occur in association with one or even several trichilemmal cysts of the scalp (174,175). There is evidence that a proliferating trichilemmal cyst may develop from an ordinary trichilemmal cyst (173,176). However, the tumor may also give rise to one or several trichilemmal cysts, which ultimately may separate from it (172). In several instances, rapid enlargement of nodular scalp lesions indicated malignant transformation (177). In such cases, metastases may arise.

Histopathology. The proliferating trichilemmal cyst, or proliferating trichilemmal tumor, usually is well demarcated from the surrounding tissue (178). It is composed of multiple, variably sized lobules of squamous epithelium, and the epithelial lining is typically thicker than that seen in pilar cysts (Fig. 30-33). Some of the lobules are surrounded by a vitreous layer and show palisading of their peripheral cell layer (172). Characteristically, the epithelium in the center of the lobules abruptly changes into eosinophilic amorphous keratin (Fig. 30-34). This amorphous keratin is of the same type as that seen in the cavity of ordinary trichilemmal cysts (179). In addition to showing trichilemmal keratinization, some proliferating trichilemmal cysts exhibit changes resembling the keratinization of the follicular infundibulum. These changes consist of epidermoid keratinization resulting in horn pearls, some of which resemble "squamous eddies" (173).

The tumor cells in many areas show some degree of nuclear atypia, as well as individual cell keratinization, which at first glance suggests a squamous cell carcinoma (Fig. 30-34) (174,180). The tumor differs from a squamous cell carcinoma by a rather sharp demarcation from the surrounding stroma, as

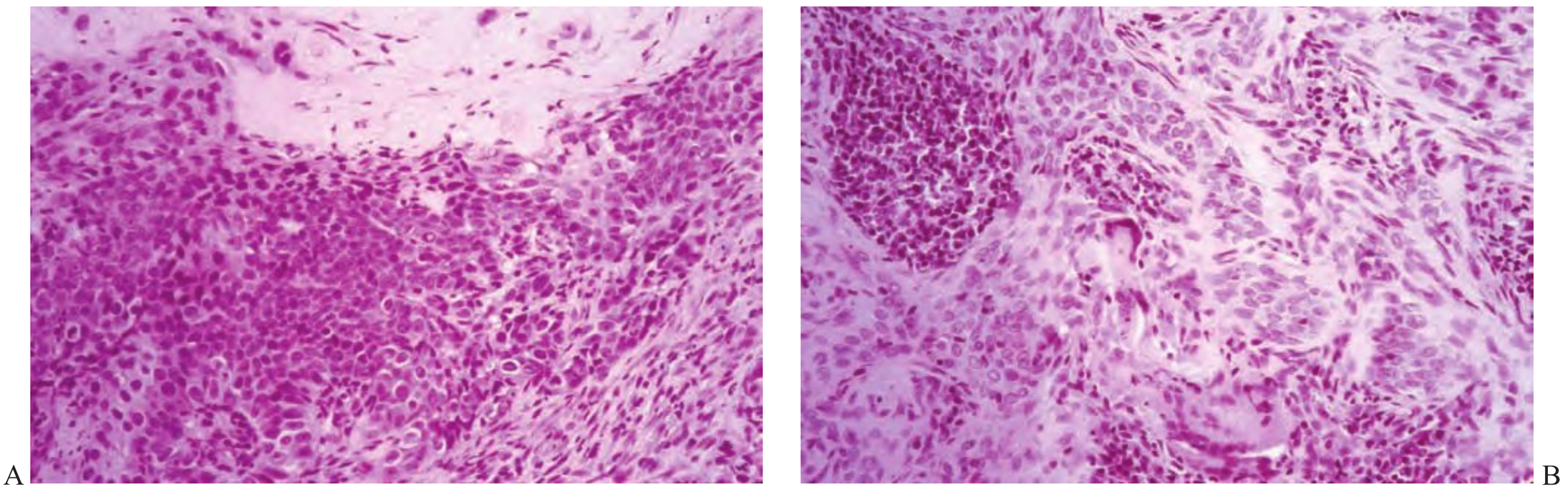


FIGURE 30-32. (A-B) Pilomatrix carcinoma. Hyperchromatic, anaplastic cells exhibit mitotic activity and transition into shadow cells.

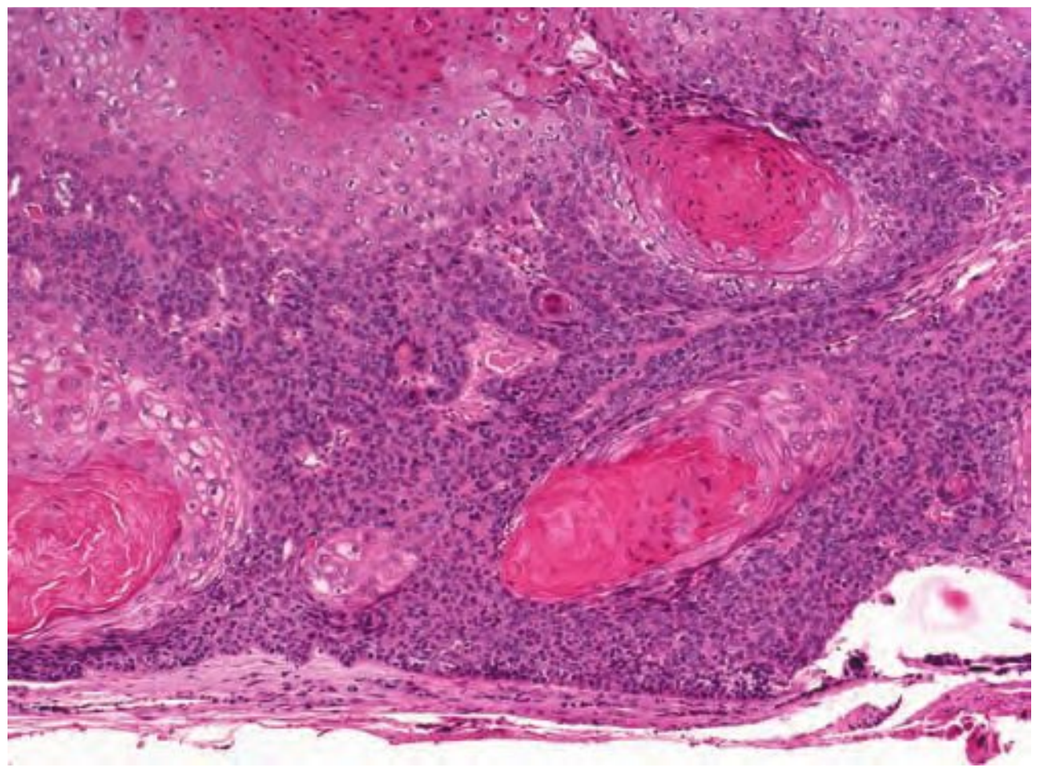


FIGURE 30-33. Proliferating trichilemmal cyst. The tumor is composed of irregularly shaped lobules of squamous epithelium undergoing an abrupt change into amorphous keratin. Central portions of the lobules demonstrate amorphous keratin.

well as an abrupt mode of keratinization (178). Foci of calcification, although generally small, are often present in the areas of amorphous keratin (175,178). Some tumors show vacuolization or clear cell formation of some of the tumor cells as a result of glycogen storage (174,179).

Differential Diagnosis. In addition to its well-circumscribed nature, the presence of numerous sharply demarcated areas of amorphous eosinophilic keratin in the center of the tumor

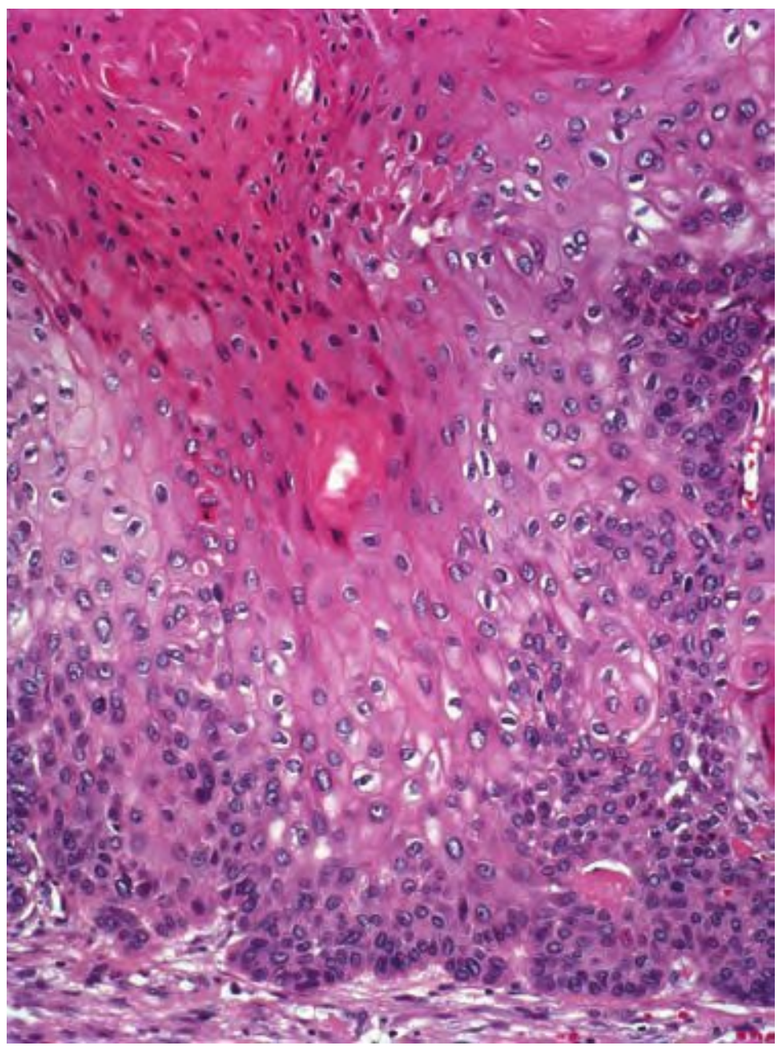


FIGURE 30-34. Proliferating trichilemmal cyst. Large, pale keratinocytes undergo abrupt keratinization without keratohyaline granules.

strands and lobules and the absence of extensive areas of severe atypia and of invasion of the surrounding tissue usually permit differentiation from squamous cell carcinoma.

Additional Studies. Keratinization in proliferating trichilemmal cysts is of the same type as in ordinary trichilemmal cysts. The "trichilemmal" keratinization in both is analogous to that of the outer root sheath as seen normally at the follicular isthmus above the zone of sloughing of the inner root sheath and in the sac surrounding the lower end of the telogen hair (174,181). Analogous to the outer root sheath, proliferating trichilemmal cysts show (a) an abrupt change of squamous epithelium into amorphous keratin, (b) vacuolated cells containing glycogen, like the cells of the outer root sheath, and (c) a prominent glassy layer of collagen surrounding some tumor formations (179). Focal calcification within the amorphous keratin is a feature that proliferating trichilemmal cysts and ordinary trichilemmal cysts have in common.

Malignant Proliferating Trichilemmal Tumor

In rare instances, malignant transformation of proliferating trichilemmal cysts takes place, indicated by rapid enlargement of the nodule (177). There have been several reported instances of metastases, most of them regional (174,182,183). In one instance, however, the metastases were generalized and fatal (184). Penetration of the tumor into cerebral sinuses has occurred, causing death (185).

Histopathology. Malignant proliferating trichilemmal tumors show extensive areas of severe atypia and invasion of the surrounding tissue (177). Even though areas of trichilemmal keratinization are still evident, tissue invasion and the presence of nuclear atypia and giant nuclei indicate malignancy (184).

Additional Studies. Unlike proliferating trichilemmal cyst, there is loss of CD34 expression (186). DNA aneuploidy and a higher proliferation index have also been observed (186). There appears to be a spectrum of cases ranging from a proliferative trichilemmal cyst to a frankly malignant proliferating trichilemmal tumor (187). In addition, similar to squamous cell carcinomas, loss of heterozygosity at chromosome 17p and increased p53 immunoreactivity have been observed in proliferating trichilemmal cysts (188,189). It has been proposed by some researchers that proliferating trichilemmal cysts may be low-grade carcinomas (190,191). Regardless, both lesions should be treated with wide local excision and adequate follow-up (187).

Trichilemmoma

Trichilemmoma is a fairly common solitary tumor. In addition, multiple facial trichilemmomas are specifically associated with Cowden's disease.

Solitary Trichilemmoma

Solitary trichilemmoma, first recognized as an entity in 1962, generally is a small tumor, 3 to 8 mm in diameter, occurring

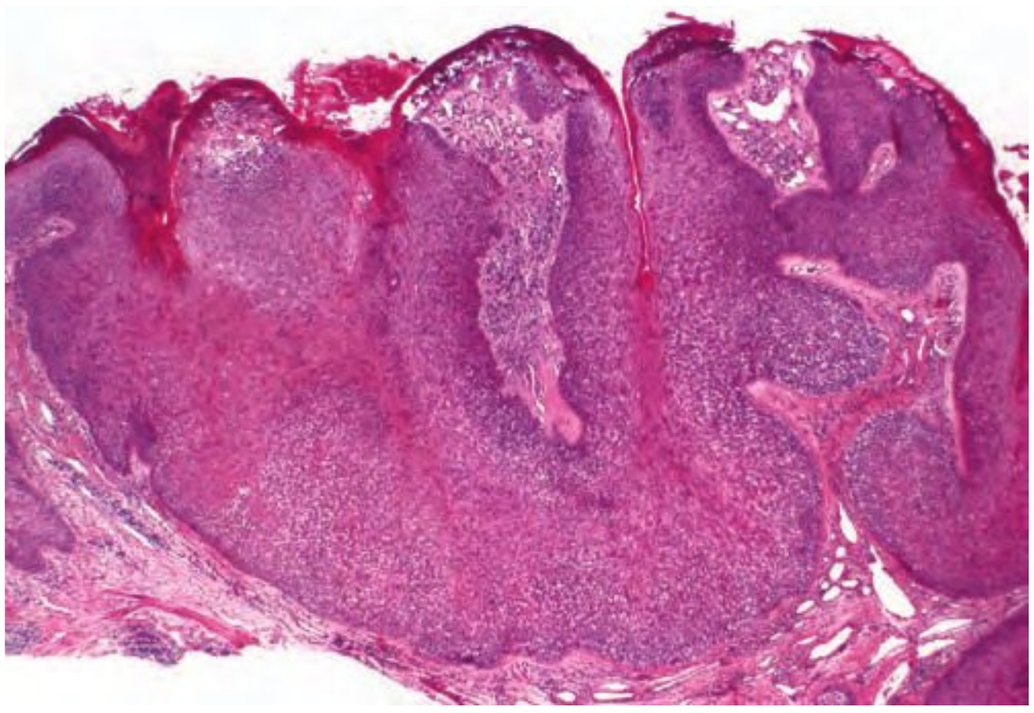


FIGURE 30-35. Trichilemmoma. The tumor shows verrucous hyperplasia with lobular formations extending into the superficial dermis. As a result of their differentiation toward outer root sheath cells, many cells appear clear.

usually on the face (192,193). Occasionally, it measures several centimeters in diameter (194). It has no characteristic clinical appearance. In some instances, it is found at the base of a cutaneous horn (195).

Histopathology. One or several lobules are seen descending from the surface epidermis into the dermis. In some instances, the lobules are oriented about a central hair-containing follicle (192). A variable number of tumor cells have the appearance of clear cells because of their content of glycogen (Figs. 30-35 and 30-36). The periphery of the tumor lobules usually shows palisading of columnar cells and a distinct, often thickened basement membrane zone resembling the vitreous layer surrounding the lower portion of normal hair follicles (Fig. 30-36) (193). Paradoxically, trichilemmomas do not show the trichilemmal type of keratinization seen in trichilemmal cysts and proliferating trichilemmal cysts. Instead, at the surface, trichilemmomas display epidermoid keratinization, which is frequently pronounced, often associated with verrucous hyperplasia, and may even lead to the formation of an overlying cutaneous horn (196).

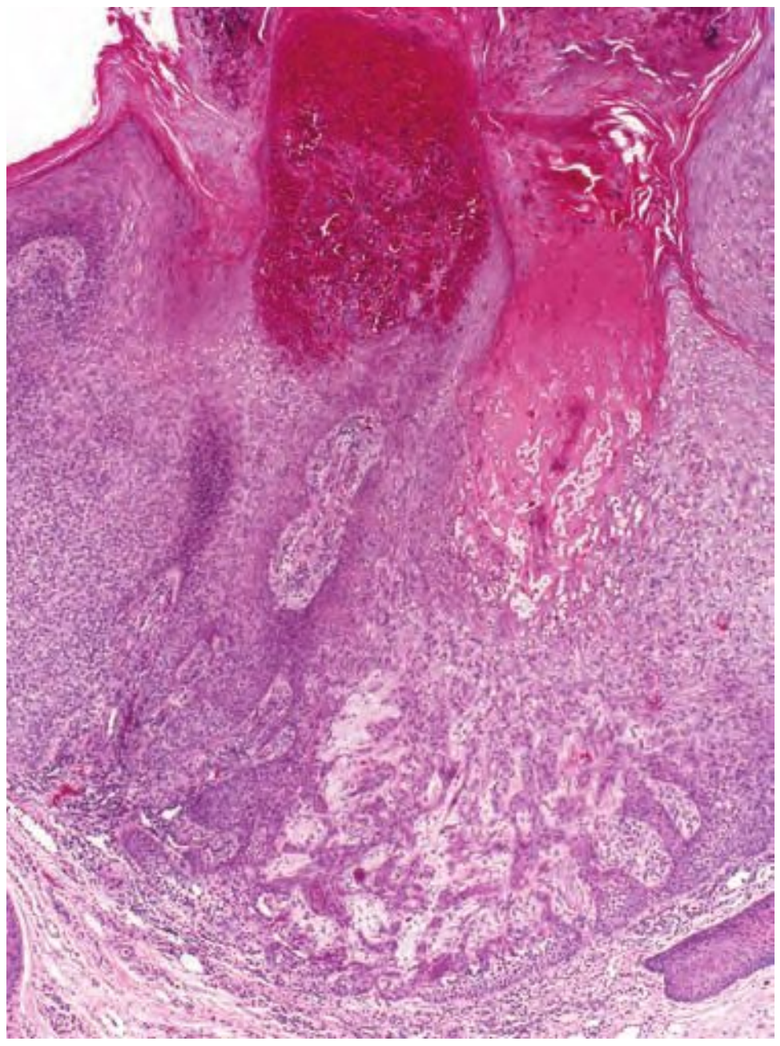


FIGURE 30-37. Desmoplastic trichilemmoma. The lesion exhibits features of a trichilemmoma with focal infiltrative growth in the dermis.

In *desmoplastic trichilemmoma* there are irregular extensions of cells of the outer root sheath type that project into sclerotic collagen bundles and mimic invasive carcinoma (Figs. 30-37 and 30-38) (197). Superficially, the lesion shows changes of a trichilemmoma, a finding that aids in the distinction from an invasive carcinoma. In addition, unlike basal cell carcinomas, desmoplastic trichilemmomas stain with CD34 (198).

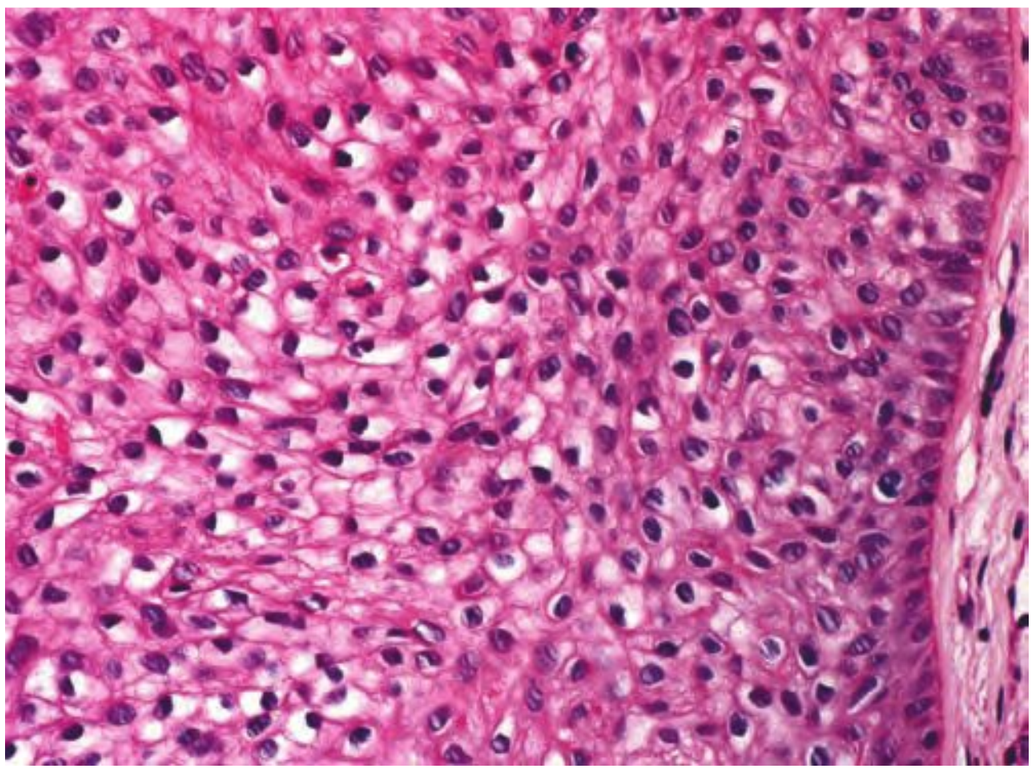


FIGURE 30-36. Trichilemmoma. Many cells demonstrate clear cytoplasm. The peripheral epithelial cells demonstrate palisading.

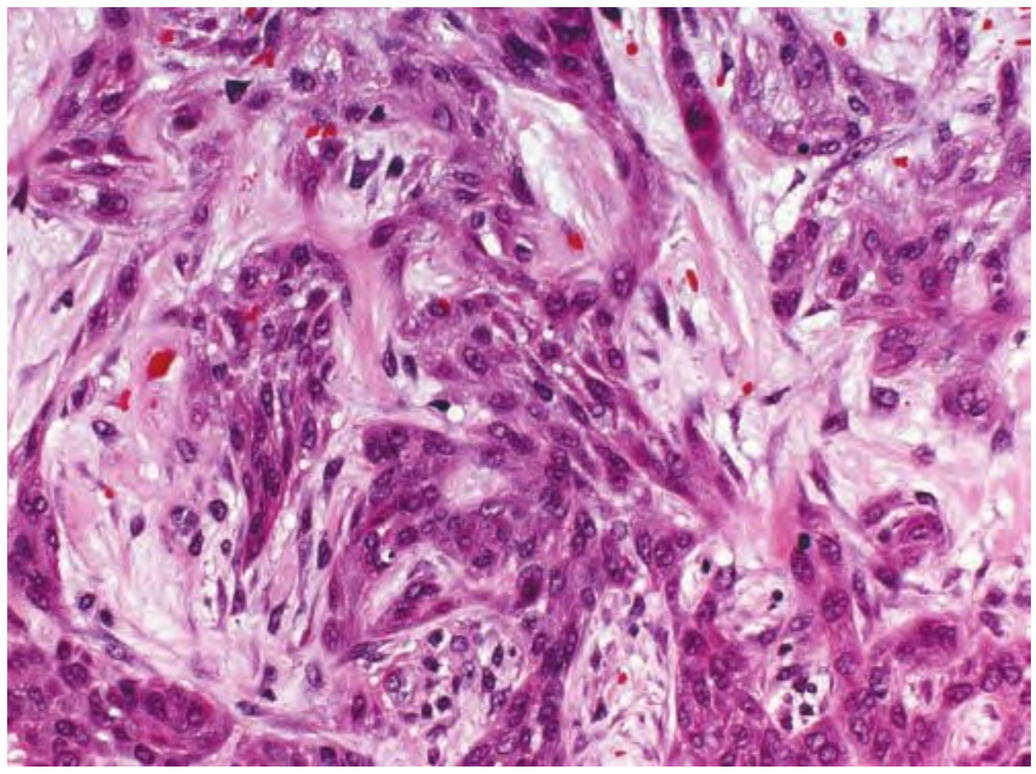


FIGURE 30-38. Desmoplastic trichilemmoma. Cords of bland epithelial cells infiltrate the dermis mimicking invasive carcinoma.

Differential Diagnosis. In instances with relatively few clear cells and marked hypergranulosis and hyperkeratosis, differentiation from a verruca vulgaris may be difficult. A PAS stain for the demonstration of glycogen may aid in differentiating these two lesions. However, old verrucae, which often lack viral cytopathic changes, may acquire cytoplasmic glycogen and mimic many features of trichilemmoma. Trichilemmomas differ from ordinary verrucae by their lobulated rather than papillary (verrucous) configuration, their localization about follicular infundibula, the presence of basaloid palisading at the periphery of tumor lobules, and the presence of a thickened, hyalinized basement membrane that can be highlighted by a PAS stain. Molecular studies have not supported the notion that all trichilemmomas result from human papillomavirus infection (199).

Multiple Trichilemmomas in Cowden's Disease

Cowden's disease, or multiple hamartoma syndrome, is an autosomal dominant genodermatosis with distinctive mucocutaneous and systemic findings (200). The syndrome is characterized by multiple hamartomas in several organ systems including the skin, breast, thyroid, gastrointestinal tract, endometrium, and brain. The mucocutaneous lesions are a near-constant manifestation and include trichilemmomas, oral papillomatoses, and acral and palmoplantar keratoses. The most frequent systemic findings include fibrocystic breast disease, breast fibroadenomas, thyroid adenomas, goiter, and intestinal polyposis (201). Individuals are at highest risk for the development of breast cancer, but other visceral malignancies, including thyroid and endometrial carcinomas, may occur (202,203). An association with Lhermitte-Duclos disease (dysplastic cerebellar gangliocytoma) and Bannayan-Riley-Ruvalcaba syndrome (macrocephaly, lipomatosis, hemangiomatosis, and speckled penis) has been noted, suggesting that they are all overlapping syndromes characterized by germline *PTEN* mutations (204–207).

Multiple trichilemmomas are found in all patients with Cowden's disease (202). They are limited to the face, where they are found mainly about the mouth, nose, and ears. They consist of flesh-colored, pink or brown papules that may resemble verrucae vulgares (208). Multiple trichilemmomas precede the development of breast cancer and thus can identify women with a high risk of developing this cancer (202). Thus, recognition of Cowden's disease is important because of the high incidence of breast cancer in women with this disease. In addition, there may be closely set oral papules, giving the lips, gingiva, and tongue a characteristic "cobblestone" appearance, as well as multiple small acral keratoses. Small hyperkeratotic papillomas are commonly found on the distal portions of the extremities (209).

The gene for Cowden's disease was localized to chromosome 10q22-23 and subsequently identified as *PTEN* (phosphatase and tensin homologue deleted on chromosome 10) (210,211). *PTEN* encodes a dual-specificity phosphatase and is the major 3-phosphatase in the phosphoinositol-3-kinase pathway, which inactivates signals from (PI-3K)/AKT kinases, an antiapoptotic pathway; therefore, loss of *PTEN* function results in increased antiapoptotic signaling in the PI-3K/AKT pathway (212). Mutational analysis has revealed germline mutations in the gene in multiple members of afflicted families (213,214).

Histopathology. Multiple biopsy specimens may be needed to find the diagnostic histologic picture of trichilemmoma in the facial lesions. Thus, in one series, only 29 of 53 facial lesions showed findings diagnostic of trichilemmoma (196).

The oral lesions may show a fibromatous nodule composed of relatively acellular fibers patterned in whorls (sclerotic fibroma) or fibrovascular tissue with acanthosis (196,209,215). The extrafacial cutaneous lesions may resemble verruca vulgaris or acrokeratosis verruciformis (see Chapters 6 and 25). Only few specimens show mild follicular hyperplasia as seen in trichilemmoma (209).

Differential Diagnosis. See Differential Diagnosis under Solitary Trichilemmoma.

Tumor of the Follicular Infundibulum

The tumor of the follicular infundibulum was first described in 1961 (216). It usually occurs as a solitary, flat, keratotic papule on the face (216). Clinically, it may resemble a basal cell carcinoma. Rarely, multiple papules are present (217). In addition, lesions may occur in Cowden's disease and nevus sebaceous (218).

Histopathology. There is a platelike growth of epithelial cells in the upper dermis extending parallel to the epidermis and showing multiple connections with the lower margin of the epidermis (Fig. 30-39). The peripheral cell layer of the tumor plate shows palisading, and the centrally located cells show a pale-staining cytoplasm as a result of their glycogen content; small cysts

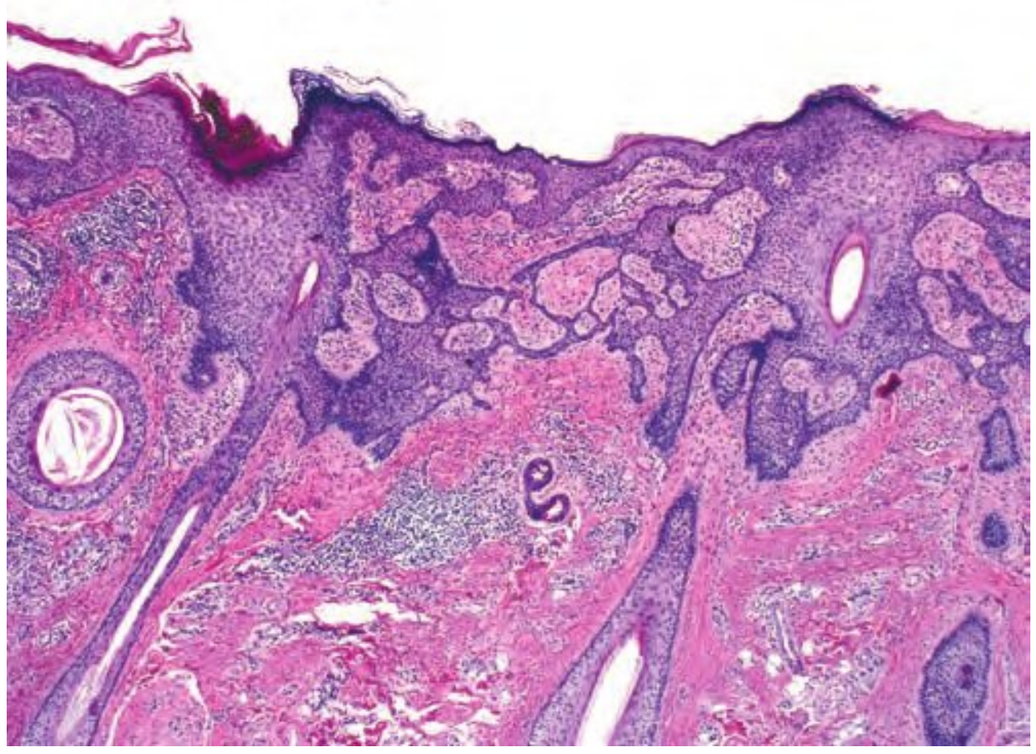


FIGURE 30-39. Tumor of the follicular infundibulum. A platelike growth of anastomosing epithelial cords extends parallel to the epidermis in the upper dermis and shows multiple connections with the epidermis.

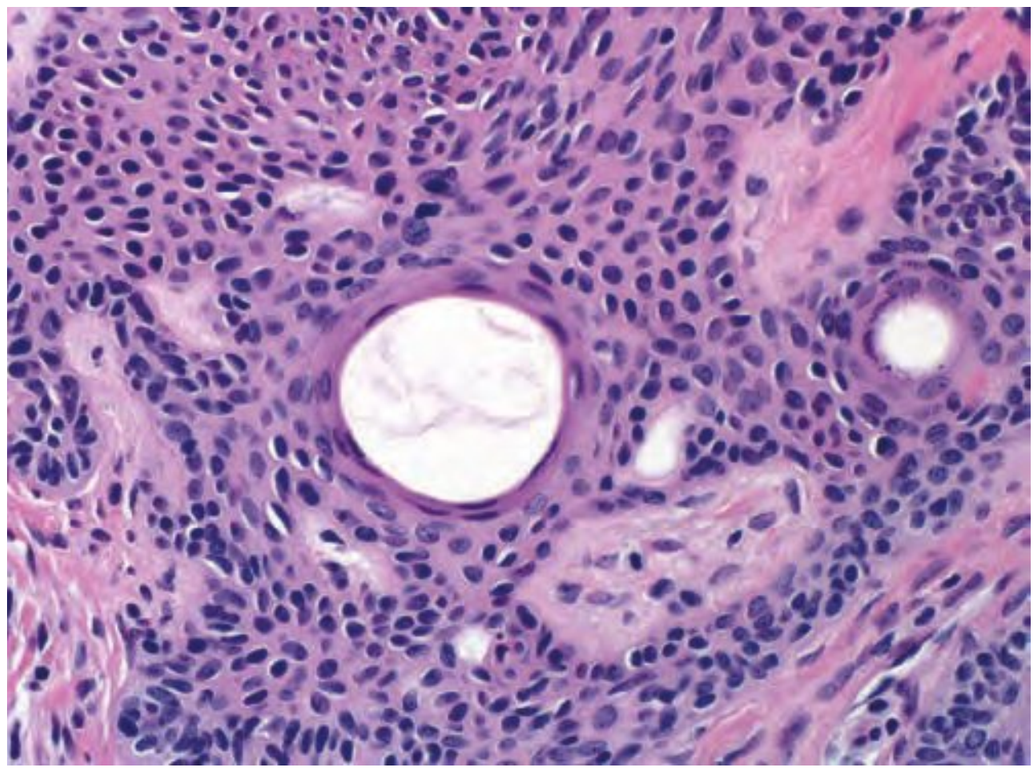


FIGURE 30-40. Tumor of the follicular infundibulum. Lesional cells demonstrate focal cytoplasmic clearing and horn cyst formation.

resembling the follicular infundibulum are seen often (Fig. 30-40). Small hair follicles enter the tumor plate from below and lose their identity and then are no longer recognizable (216). Along the lower margin of the plate, there may be invaginations that resemble hair papillae (217). Focal sebaceous differentiation and ductal proliferation have been seen (219,220).

Differential Diagnosis. The platelike growth with multiple connections to the epidermis resembles superficial basal cell carcinoma, which may also show peripheral palisading. However, the cells of the tumor of the follicular infundibulum possess a greater amount of cytoplasm, in which, furthermore, PAS-positive material is present (221). Atypia, necrosis, and mitotic activity are generally lacking. Other entities to consider are trichilemmoma, inverted follicular keratosis, and a seborrheic keratosis (172). The key histologic finding in tumor of the follicular infundibulum, as mentioned previously, is the presence of a platelike growth of epithelium with multiple connections to the epidermis.

Trichilemmal Horn; Trichilemmomal Horn

Trichilemmal and trichilemmomal horns clinically have the appearance of a cutaneous horn, as seen in several other conditions (see Chapter 29). Both are solitary. The more common trichilemmal horn may be seen in many different areas; the trichilemmomal horn occurs on the face or scalp (195,222).

Histopathology. In a *trichilemmal horn,* trichilemmal keratinization occurs. At the base of the lesion there is a prominent basement membrane zone, with palisading of the basal cell layer and a tendency of the viable epithelial cells to become large and pale staining. As trichilemmal cells, they keratinize without a granular layer (222,223). Some nuclear atypia analogous to a carcinoma *in situ* has been observed (224). A seborrheic keratosis or verruca vulgaris with exuberant trichilemmal keratinization may mimic a trichilemmal horn (225). Immunohistochemical staining with CD34 has been shown, confirming an outer root sheath origin (226).

In a *trichilemmomal horn,* a trichilemmoma is seen at the base of the lesion. At the surface, the trichilemmoma shows a cutaneous horn displaying epidermoid keratinization that is frequently pronounced, with a thick granular layer and massive hyperkeratosis (Fig. 30-37, top) (195).

Trichilemmal Carcinoma

Trichilemmal carcinoma occurs largely on the face or ears as a slow-growing epidermal papule, indurated plaque, or nodule that may ulcerate (227–231). Unlike trichilemmomas, trichilemmal carcinoma is an unusual finding in Cowden's disease (232). Recurrence and metastases are uncommon, and conservative surgical excision with clear margins is curative (227,229,233).

Histopathology. This tumor is histologically invasive and consists of cytologically atypical clear cells resembling those of the outer root sheath (19). The lesional cells have abundant glycogenated clear cytoplasm. The lesional cells form solid, lobular, or trabecular growth patterns with foci of pilar-type keratinization and with peripheral palisading of cells with subnuclear vacuolization. Cytologic atypia is prominent, and there may be pagetoid spread of lesional cells into the epidermis, mimicking melanoma. The cells have hyperchromatic, pleomorphic, very large nuclei (233). The cytoplasm contains glycogen, and this is PAS positive and diastase sensitive (231). Areas of trichilemmal keratinization are frequently present (234).

Differential Diagnosis. A trichilemmal carcinoma may resemble a trichilemmoma by showing a lobular architecture or may resemble a "tumor of the follicular infundibulum" by replacing the surface epidermis (231,233). Differentiation from other carcinomas with clear cell features such as squamous cell carcinoma, basal cell carcinoma, and sebaceous carcinoma may be difficult. Typical features of these carcinomas are usually seen adjacent to the clear cell component.

Additional Studies. The pathogenesis of trichilemmal carcinomas is unclear. The distribution of lesions suggests that sunlight may play a role. A few cases have been reported in association with a burn scar, irradiation, and xeroderma pigmentosa (230,235,236). Loss of *p53* has been shown in a trichilemmal carcinoma arising from a proliferating trichilemmal cyst (237).

TUMORS WITH SEBACEUS DIFFERENTIATION

Nevus Sebaceus

Nevus sebaceus of Jadassohn is nearly always located on the scalp or the face as a single lesion and is present often at birth. In childhood, this lesion consists of a circumscribed, slightly raised, hairless plaque that is often linear in configuration, but it may be round or irregularly shaped. In puberty, the lesion becomes verrucous and nodular (238).

Less commonly, nevus sebaceus consists of multiple extensive lesions found on the face, neck, or trunk. Usually, at least some of the lesions have a linear configuration (239). In addition, some patients with extensive nevus sebaceus show

evidence of a "neurocutaneous syndrome," epilepsy and mental retardation, neurologic defects, or skeletal deformities (240–243). In some patients, the linear nevus is a combination of a linear nevus sebaceus and a linear epidermal nevus (241,242). Thus, the "neurocutaneous syndrome" that is associated with nevus sebaceus overlaps with the abnormalities associated with the epidermal nevus syndrome, in which skeletal deformities and central nervous system abnormalities may also occur (see Chapter 6) (244). The involvement of the central nervous system that may be seen in extensive cases of both linear nevus sebaceus and linear epidermal nevus closely resembles that of tuberous sclerosis by computed tomography and x-ray studies (see Chapter 32) (245).

Histopathology. The sebaceous glands in nevus sebaceus follow the pattern of normal sebaceous glands during infancy, childhood, and adolescence. In the first few months of life, they are well developed (246). During childhood the sebaceous glands in nevus sebaceus are underdeveloped and, therefore, greatly reduced in size and number. Thus, the diagnosis of nevus sebaceus may be missed. However, the presence of incompletely differentiated hair structures is typical of nevus sebaceus. There often are cords of undifferentiated cells resembling the embryonic stage of hair follicles (238). Some hair structures consist of dilated, keratin-filled infundibula showing multiple buds of undifferentiated cells (Fig. 30-41).

At puberty, the lesion assumes its diagnostic histologic appearance. Large numbers of mature or nearly mature sebaceous glands and overlying papillomatous hyperplasia of the epidermis are seen. The hair structures remain small, except for occasional dilated infundibula. Ectopic apocrine glands develop in about two thirds of the patients at puberty and sometimes at a younger age (Fig. 30-41) (238,247). There are often buds of undifferentiated cells that resemble foci of basal cell carcinoma and represent malformed hair germs (Fig. 30-42) (247). The apocrine glands are located deep in the dermis beneath the masses of sebaceous gland lobules.

Quite commonly, in addition to the infantile and adolescent phases, there is a third stage in adulthood when various types of appendageal tumors develop secondarily within lesions of nevus sebaceus. Syringocystadenoma papilliferum has been found in 8% to 19% of the lesions of nevus sebaceus (Fig. 30-43) (238). In two large case series, the most commonly associated appendageal tumors were trichoblastoma and syringocystadenoma papilliferum (248,249). Less commonly found appendage tumors include nodular hidradenoma, syringoma, sebaceous epithelioma, chondroid syringoma, trichilemmoma, trichoade-

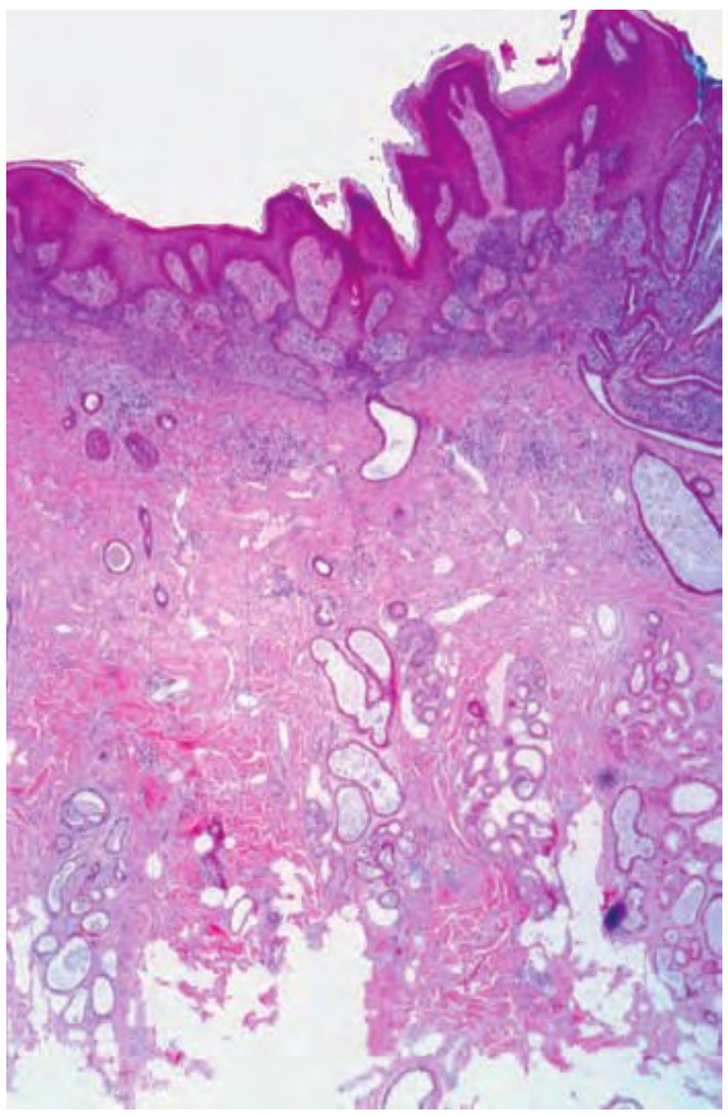


FIGURE 30-41. Nevus sebaceus. There is epidermal hyperplasia and papillomatosis. Superficially, a basaloid epithelial neoplasm is seen, and dilated apocrine glands are present in the dermis. This scalp lesion lacks anagen follicles.

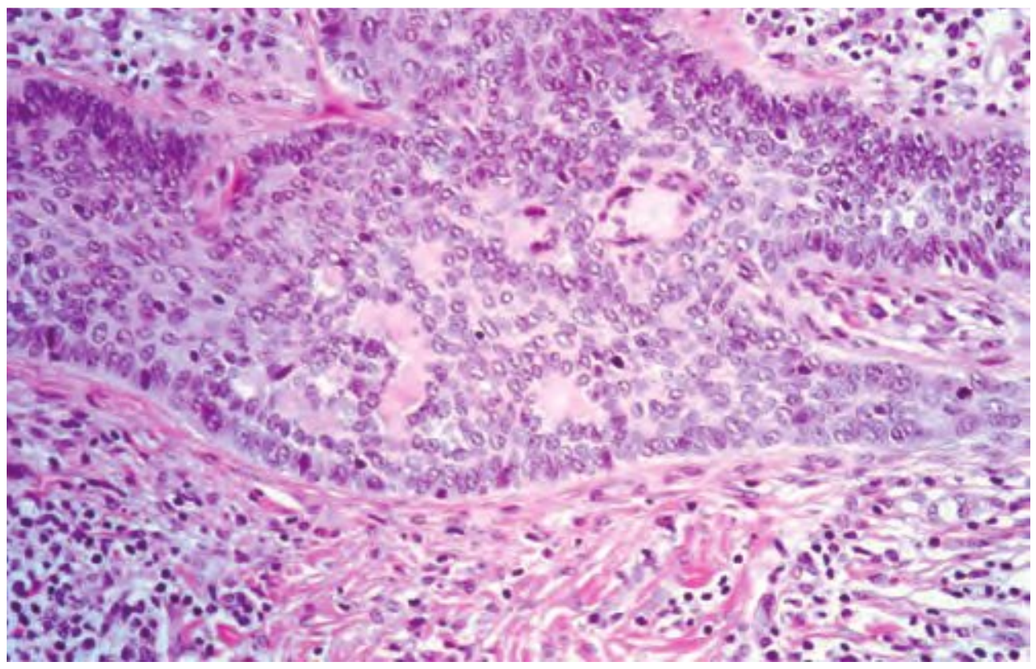


FIGURE 30-42. Nevus sebaceus. The basaloid epithelial proliferations often resemble basal cell carcinoma. However, the proliferations exhibit features of appendageal neoplasms as evidenced by the hyaline material within the lesion.

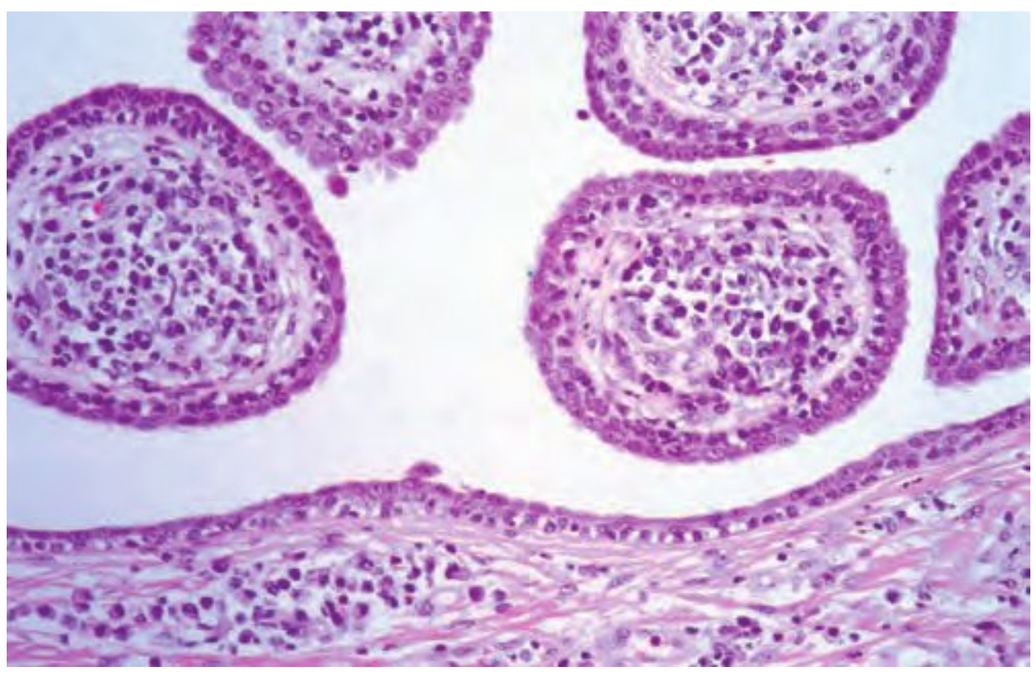


FIGURE 30-43. Nevus sebaceous. A syringocystadenoma papilliferum was also present in this lesion.

noma, sebaceous carcinoma, and proliferating trichilemmal cyst (238,250–252).

Basaloid epithelial proliferations resembling basal cell carcinoma are clinically evident in 5% to 7% of the cases of nevus sebaceus (247,253). In many instances, however, basal cell carcinomas are found that are small, clinically not apparent, and show no aggressive growth pattern (247). It is not always possible to differentiate histologically between a basal cell carcinoma and the "basaloid proliferations" that arise in as many as half of all cases of nevus sebaceus (253). As original evidence that the basal cell carcinoma–like proliferations in many instances are not true basal cell carcinomas, some proliferations contain Sudan-positive granules as an indication of sebaceous differentiation or glycogen as an indication of pilar differentiation (254). Other proliferations show follicular differentiation with formation of hair papillae and hair bulbs (255). Furthermore, in critical reviews, several groups proposed that most reported basal cell carcinomas arising in nevus sebaceus are actually trichoblastomas (248,249,256).

In only rare instances does a squamous cell carcinoma develop within a nevus sebaceus. This may be associated either with regional lymph node metastasis or with generalized metastases (257). Apocrine carcinomas and, in one instance, a malignant eccrine poroma have developed in nevi sebacei, and these lesions, too, may lead to regional or even generalized metastases (257,258).

Additional Studies. The frequent association of nevus sebaceus with other appendageal tumors and with apocrine glands suggests that nevus sebaceus is derived from the primary epithelial germ (247). Moreover, as has been reported in basal cell carcinomas, loss of heterozygosity of the human homologue of the *Drosophila* patched gene (*Ptch*) has been demonstrated in nevus sebaceus (259–261). This could partly explain the association of basal cell carcinomas and other basaloid appendageal tumors with nevus sebaceous. However, a separate study of 11 lesions of nevus sebaceus found no demonstrable loss of heterozygosity (262). The reason for the discrepancy is uncertain; however, differences such as sampling during microdissection of other cell populations may account for discrepancy (262).

Sebaceous Hyperplasia

The lesions of sebaceous hyperplasia nearly always occur on the face, chiefly on the forehead and cheeks, in elderly persons. It has also been reported in the vulva, penis, and aerola (263–266). Rarely, sebaceous hyperplasia occurs in early adult life (267). Apparent familial forms have also been reported (90,268). It clinically presents as one or, more commonly, several elevated, small, soft, yellow, slightly umbilicated papules. The usual size is 2 to 3 mm in diameter.

Histopathology. Most lesions consist of a single, enlarged sebaceous gland composed of numerous lobules grouped around a centrally located, wide sebaceous duct (Fig. 30-44). Its opening to the surface corresponds to the central umbilication of the lesion. Serial sections show that all sebaceous lobules grouped around the central duct are connected with that duct. Large lesions may consist of several enlarged sebaceous glands and contain several ducts, with sebaceous lobules grouped around each of them. Although some sebaceous gland lobules appear fully mature, others show more than one peripheral row of undifferentiated, germinative cells in which there are few or no lipid droplets (269).



FIGURE 30-44. Sebaceous hyperplasia. The lesion consists of an enlarged sebaceous gland lying in close proximity to the epidermis.

Additional Studies. Labeling with tritiated thymidine has shown that the migration of sebocytes from the basal cell area to the center of the sebaceous lobules and into the sebaceous duct is distinctly slower in cases of sebaceous hyperplasia than in normal sebaceous glands (269). Microsatellite instability has been detected in very few cases of sebaceous hyperplasia as compared to other sebaceous neoplasms (270,271) (see Muir-Torre syndrome). Immunohistochemical staining for androgen receptors has been shown to be fairly specific for sebaceous lesions as compared to basal cell carcinomas, squamous cell carcinomas, and clear cell acanthomas (272).

Differential Diagnosis. In rhinophyma, which also shows large sebaceous glands and ducts, there is no grapelike grouping of the sebaceous lobules around the ducts, and the lesion is not sharply demarcated. In nevus sebaceus, ductal structures are less apparent than in sebaceous hyperplasia, and apocrine glands are often found beneath the sebaceous glands.

Fordyce's Spots and Montgomery's Tubercles

In Fordyce's spots, groups of minute, yellow, globoid lesions are observed on the vermilion border of the lips or on the oral mucosa. The incidence of the disorder increases with age, so that 70% to 80% of elderly persons show such lesions, which represents ectopic sebaceous glands (273). Montgomery's tubercles are ectopic mature sebaceous glands located on the areola of the breast (274).

Histopathology. Each lesion consists of a group of small but mature sebaceous lobules situated around a small sebaceous

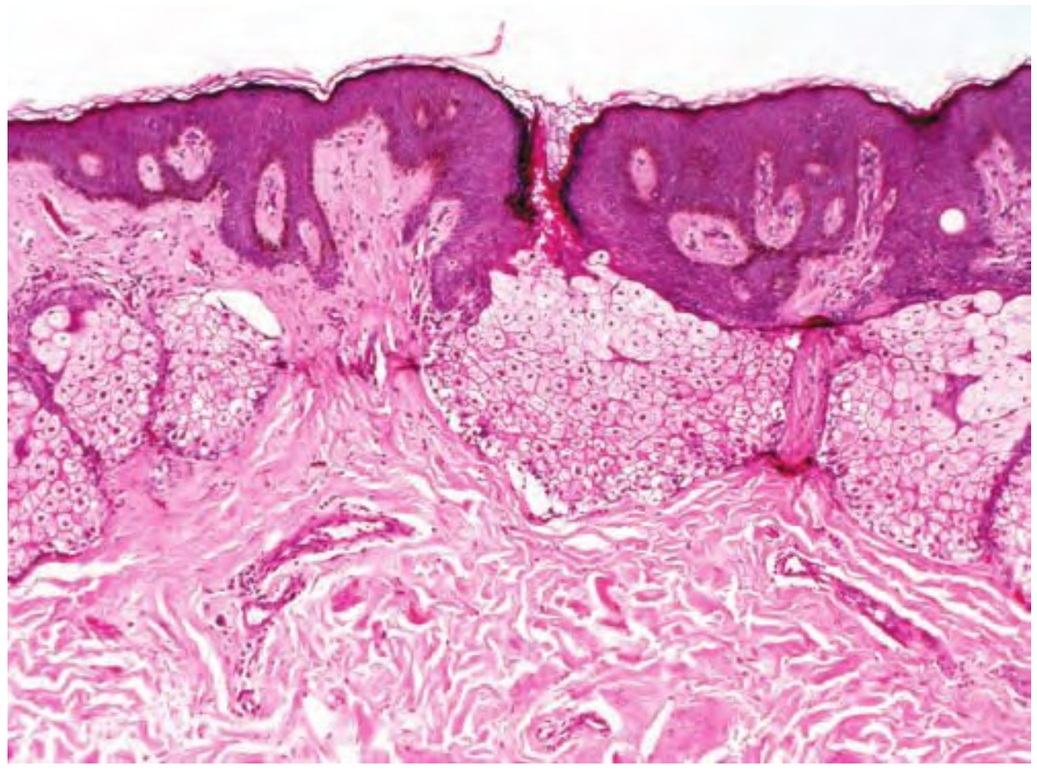


FIGURE 30-45. Montgomery's tubercle. A mature sebaceous lobule in continuity with the epidermis is seen.

duct leading to the surface epithelium (Fig. 30-45) (273,275). Because of the small size of the sebaceous duct, serial sections may be required to demonstrate the duct.

Sebaceous Adenoma

Sebaceous adenoma presents as a yellow, circumscribed nodule located on either the face or scalp. Prior to 1968, sebaceous adenoma was regarded as a rare solitary tumor, and there were few publications about it (276–278). Since then, however, both solitary and multiple lesions have been well documented in patients with Muir-Torre syndrome (see text following).

Histopathology. On histologic examination, sebaceous adenoma is sharply demarcated from the surrounding tissue. It is composed of incompletely differentiated sebaceous lobules that are irregular in size and shape (Fig. 30-46). Two types of cells are present in the lobules. The cells of the first type are identical to the cells present at the periphery of normal sebaceous glands and represent undifferentiated basaloid cells (Fig. 30-47). The cells of the second type are mature sebaceous cells (Fig. 30-47). In addition, there often are some cells in a transitional stage between these two types (279). Distribution of the basaloid and sebaceous cells within the lobules varies. Some lobules contain mainly sebaceous cells and thereby resemble mature sebaceous lobules. Frequently, the proportion of mature sebaceous cells exceeds that of the surrounding basaloid cells (Fig. 30-47). However, at most the two types of cells occur in approximately equal proportions. Fat stains, on properly preserved specimens, reveal the presence of lipid material in the sebaceous and transitional cells. Some large lobules contain cystic spaces in their center formed by the disintegration of mature sebaceous cells. In addition, there may be foci of squamous epithelium with keratinization. These foci probably represent areas with differentiation toward cells of the infundibulum. Cystic sebaceous adenomas seem to occur exclusively in patients with Muir-Torre syndrome (280).

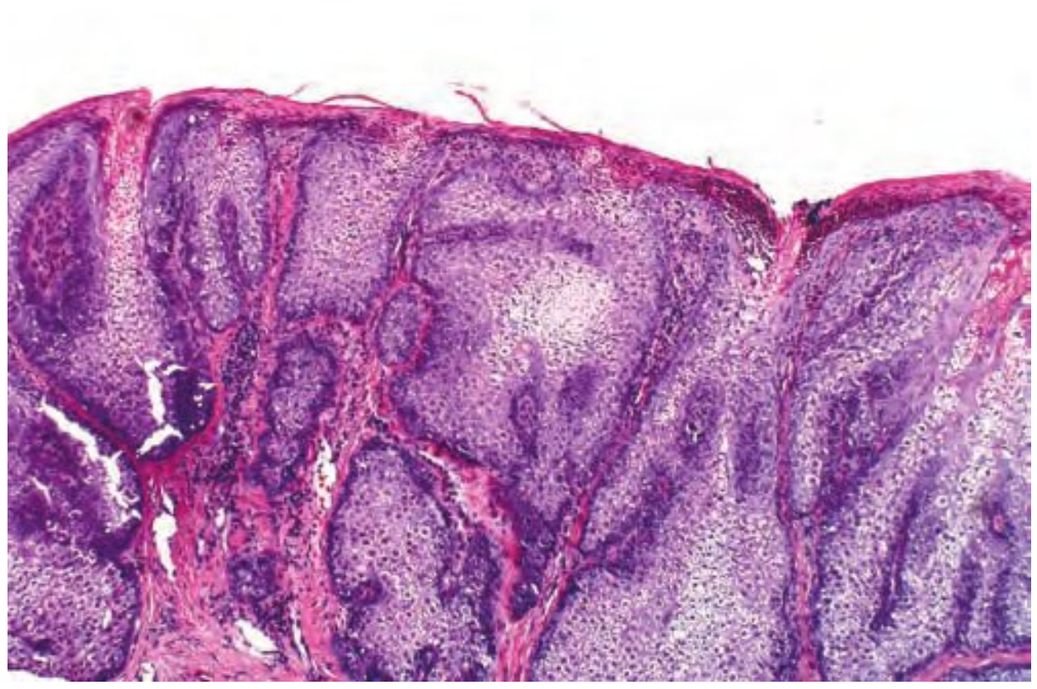


FIGURE 30-46. Sebaceous adenoma. The tumor is composed of enlarged sebaceous lobules of varying size and shape.

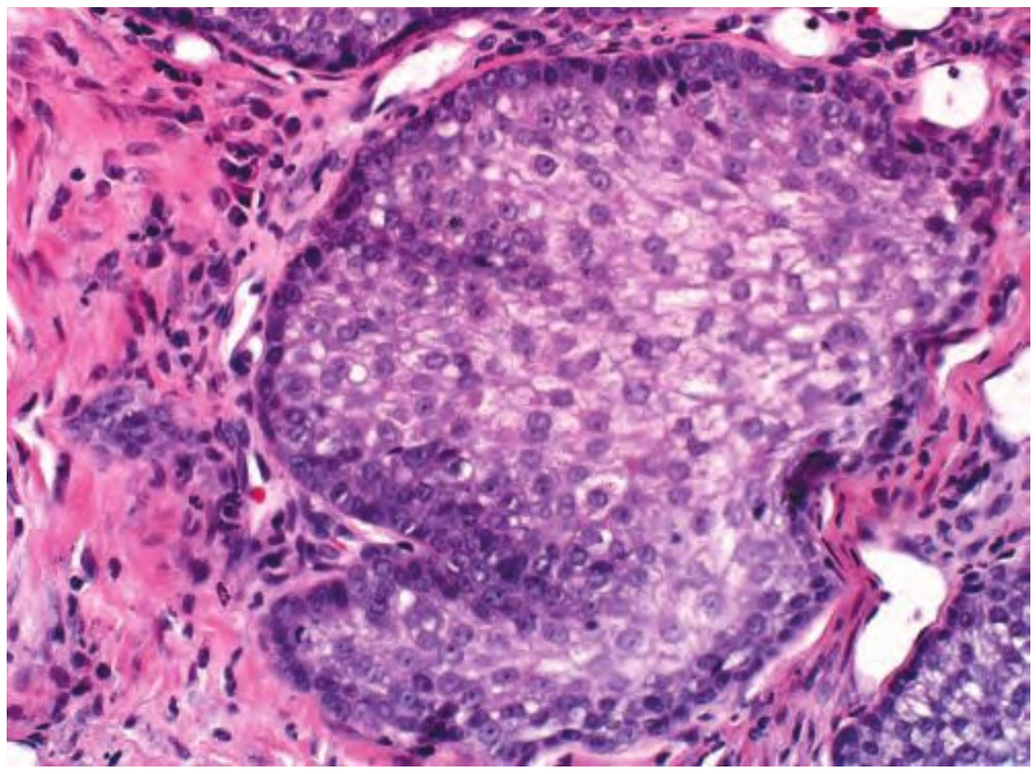


FIGURE 30-47. Sebaceous adenoma. In the lobules, two types of mature cells can be recognized: basaloid and sebaceous cells. However, sebaceous cells predominate. Cytologic atypia is not seen.

Differential Diagnosis. In terms of differentiation, sebaceous adenoma stands between sebaceous hyperplasia, in which sebaceous lobules appear fully or nearly fully matured, and sebaceous epithelioma or sebaceoma (see text following), in which the tumor is composed predominantly of irregularly shaped cell masses and the percentage of tumor cells with sebaceous differentiation is less than 50%. Sebaceous adenoma and sebaceous epithelioma lack nuclear atypia and invasive, asymmetric growth patterns, which are hallmarks of sebaceous carcinoma. Considerable mitotic activity in the basaloid regions, however, may be present in either lesion.

Sebaceoma (Sebaceous Epithelioma)

Clinically, sebaceoma, or sebaceous epithelioma, varies from a circumscribed nodule to that of an ill-defined plaque. Some of

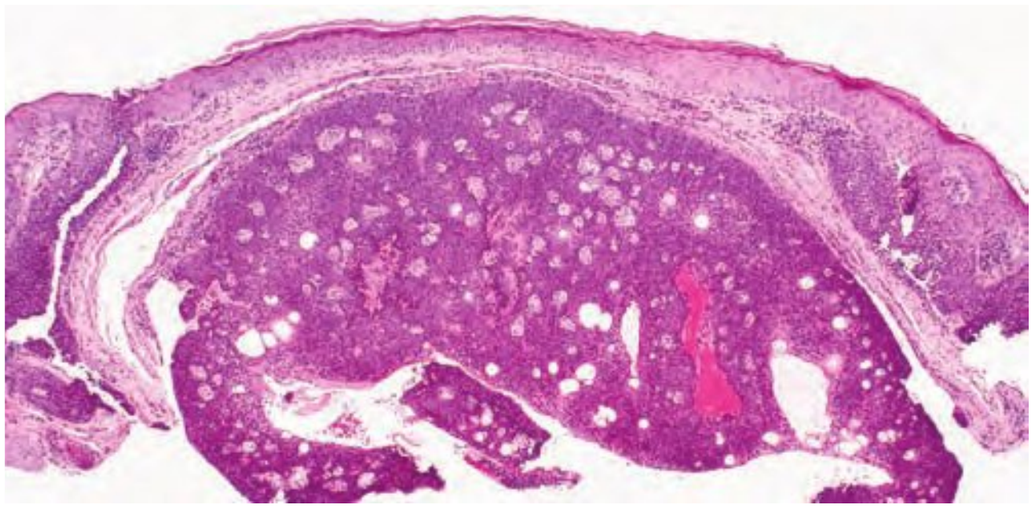


FIGURE 30-48. Sebaceoma. The tumor is a well-circumscribed nodule and comprised of basaloid epithelial cells. Scattered areas of clearer (sebaceous) cells are seen.

the lesions are yellow (281). Most lesions are located on the face or scalp. In addition to occurring as a primary lesion, a sebaceus epithelioma occasionally arises within a nevus sebaceus (238,247). Sebaceous epitheliomas may also be found among the multiple sebaceous neoplasms that occur in association with multiple visceral carcinomas and are referred to as Muir-Torre syndrome (see text following).

Histopathology. The histologic spectrum extends from that seen in sebaceous adenoma to lesions that may be difficult to distinguish from sebaceous carcinoma. Generally, a sebaceoma shows either a well-circumscribed nodule or irregularly shaped cell masses in which more than half of the cells are undifferentiated basaloid cells but in which there are significant aggregates of mature sebaceous cells and of transitional cells (Figs. 30-48 and 30-49) (282). Disintegration of sebaceous cells is seen in some areas (281). Lesions verging on a sebaceous carcinoma show some degree of irregularity in the arrangement of the cell masses, and, although the majority of cells are basaloid cells, many cells show differentiation toward sebaceous cells

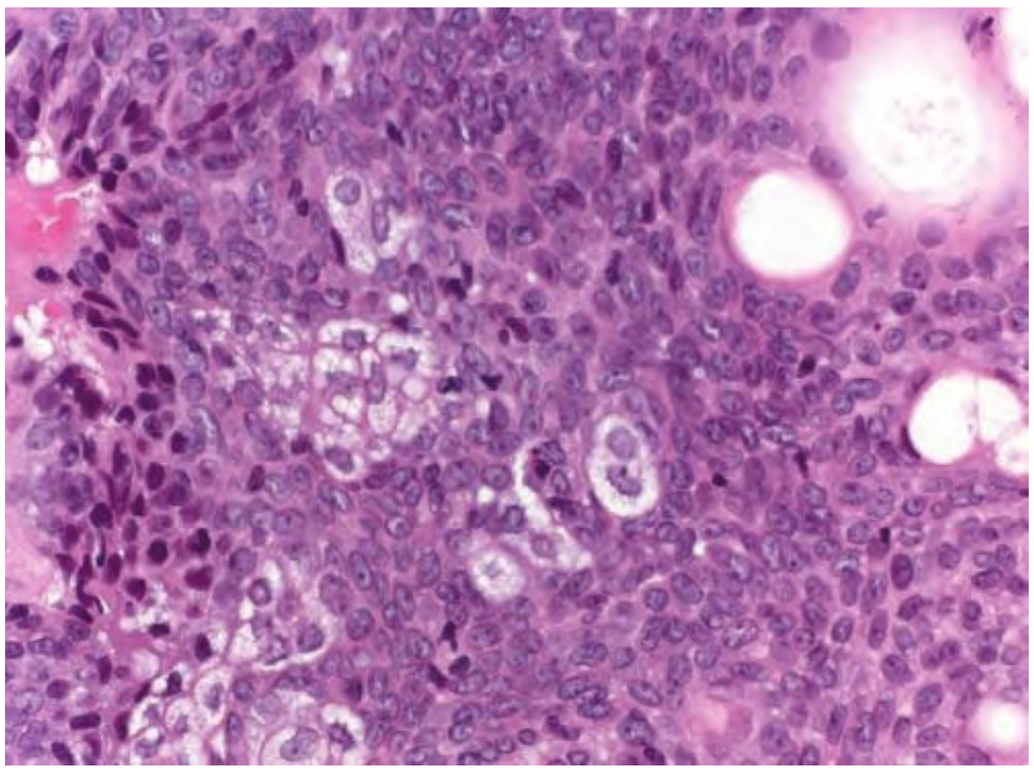


FIGURE 30-49. Sebaceoma. The majority of the lesion is composed of undifferentiated basaloid cells with islands of sebaceous cells and occasional sebaceous ducts.

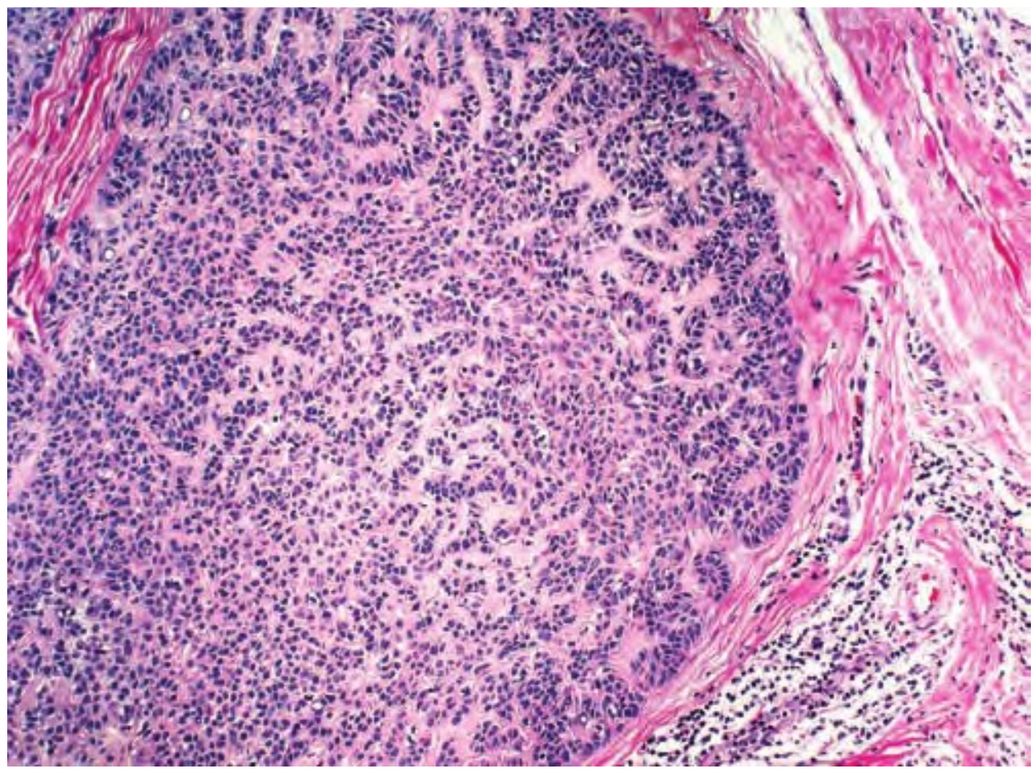


FIGURE 30-50. Rippled-pattern sebaceoma. Parallel arrangements of cells and nuclei are seen at low power.

(283). A verruca/seborrheic keratosis type of sebaceoma has been described, in which the upper part of the lesion mimics a verruca or seborrheic keratosis (284).

Differential Diagnosis. Criteria that may be of assistance in differentiating sebaceous adenoma from sebaceoma include the often greater size and depth of the latter and the lack of structures resembling normal sebaceous lobules. Nuclear atypia is "rare," and mitoses may be numerous in sebaceomas, in contrast to adenomas, in which they are few or absent (285).

Rippled-Pattern Sebaceoma. This variant of sebaceoma exhibits a unique arrangement of small, monomorphous, cigar-shaped basaloid cells in linear rows parallel to one another, resembling Verocay bodies; this arrangement of cells produces the rippled pattern (Fig. 30-50). Scattered sebaceous cells and ducts are also typically seen (Fig. 30-51) (286–289).

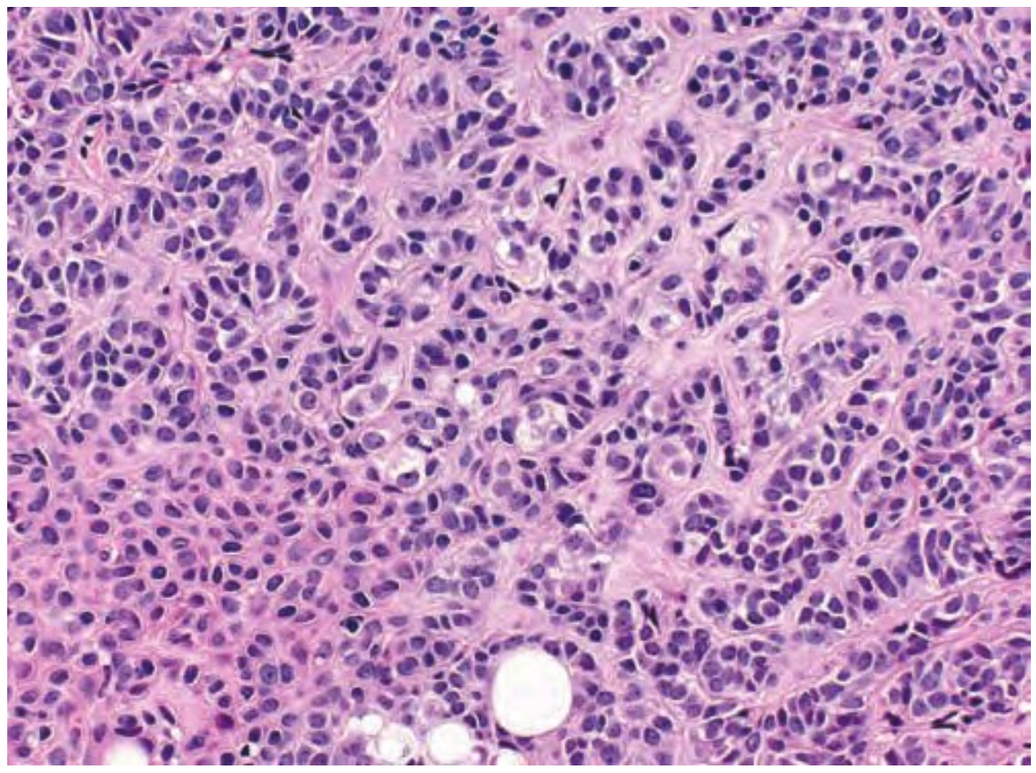


FIGURE 30-51. Rippled-pattern sebaceoma. The lesion is composed of undifferentiated basaloid cells with occasional sebaceous cells and sebaceous ducts.

Muir-Torre Syndrome

The Muir-Torre syndrome is defined by the combined occurrence of at least one sebaceous skin tumor and one internal malignancy in the same patient. Since 1967, when the first publication by Muir appeared concerning the coexistence of frequently multiple sebaceous tumors and usually multiple visceral carcinomas, scores of cases have been reported (290,291). Keratoacanthomas also have occurred in these patients, in some cases without sebaceous lesions, in association with visceral malignancies (292,293). The cutaneous lesions can often precede the first manifestation of internal malignancy (294).

Among the internal malignancies, colon carcinoma is the most common malignancy, although a wide tumor spectrum exists, including carcinomas of the genitourinary tract (including bladder, renal, pelvis, ovary, and uterus), breast, head and neck, small intestinal, and lymphoma (291,294). Adenomatous colonic polyps are also common. Many of the malignant tumors are of relatively low malignancy, with only a slight tendency to metastasize (295).

Cutaneous lesions vary from just 1 to more than 100 lesions (296). Although the lesion in many instances is recognizable as a sebaceous tumor by its color or as a keratoacanthoma by its crater, histologic examination may be required to establish a diagnosis.

Histopathology. Sebaceous adenomas are the most distinctive cutaneous markers of the Muir-Torre syndrome. They may be solid, cystic, or keratoacanthoma like (279). Cystic sebaceous adenomas seem to occur exclusively in patients with Muir-Torre syndrome (280,297). Although ordinary keratoacanthomas occur in the Muir-Torre syndrome, often they have an accompanying sebaceous proliferation (298). In addition to sebaceous adenomas, sebaceomas, and basal cell carcinomas with sebaceous differentiation, there are tumors with unusual appearance, so that a hard-to-classify sebaceous proliferation should be considered as a possible manifestation of the Muir-Torre syndrome (298). In addition, sebaceous carcinomas occur, but no metastases have been reported (296,299).

Genetics. A genetic predisposition was described in some cases of the Muir-Torre syndrome, and the Muir-Torre syndrome has been found in association with the "cancer family syndrome," now known as hereditary nonpolyposis colorectal carcinoma (291,300). Muir-Torre syndrome shares several clinical and pathologic characteristics with hereditary nonpolyposis colorectal carcinoma syndrome (300). Microsatellite instability was demonstrated in a subset of patients with Muir-Torre syndrome (301). Subsequently, germline mutations in the DNA mismatch repair genes *hMLH1* and *hMSH2* were found (302–304). The presence of microsatellite instability in sebaceous neoplasms and even benign skin lesions is helpful in the detection of an underlying inherited DNA mismatch repair defect (270,305). Moreover, immunohistochemical staining for MSH2 or MLH1 protein expression in Muir-Torre syndrome–associated skin tumors can also be used as a diagnostic screening tool to identify patients with germline mutations (306,307).

Sebaceous Carcinoma

Sebaceous carcinomas have been traditionally classified into ocular and extraocular types. The ocular type most frequently occurs on the eyelids, typically originating from the meibomian glands and less commonly from the glands of Zeis. Extraocular sebaceous carcinoma has been reported most commonly on the head and neck, but also on the vulva, penis, and rarely other locations (308–310). On the eyelids, sebaceous carcinoma may be easily mistaken for chronic blepharoconjunctivitis or a chalazion (311). On extraocular sites, sebaceous carcinoma usually manifests as a nodule that may or may not be ulcerated (283,312).

Sebaceous carcinomas of the eyelids quite frequently cause regional metastases. In addition, there may be orbital invasion, and in 22% of the cases reported in one study, death resulted from visceral metastases (313). Extraocular sebaceous carcinomas also may cause regional metastases (314–316). However, death resulting from visceral metastasis in extraocular sebaceous carcinomas originally was believed to be uncommon (312,317). It has been suggested that extraocular sebaceous carcinoma can widely metastasize and cause death just as frequently as ocular types (318). The sebaceous carcinomas that may be found among the multiple sebaceous neoplasms occurring in association with multiple visceral carcinomas in the Muir-Torre syndrome do not metastasize, although the visceral malignant tumors may (319). In some instances, a sebaceous carcinoma represents the only cutaneous manifestation of the syndrome (320).

Histopathology. The irregular lobular formations show great variations in the size of the lobules (Fig. 30-51). Although many cells are undifferentiated, distinct sebaceous cells showing a foamy cytoplasm are present in the center of most lobules (Figs. 30-52 and 30-53) (312). Many undifferentiated cells and sebaceous cells appear atypical, showing considerable nuclear and nucleolar pleomorphism (Fig. 30-53) (316). In addition,

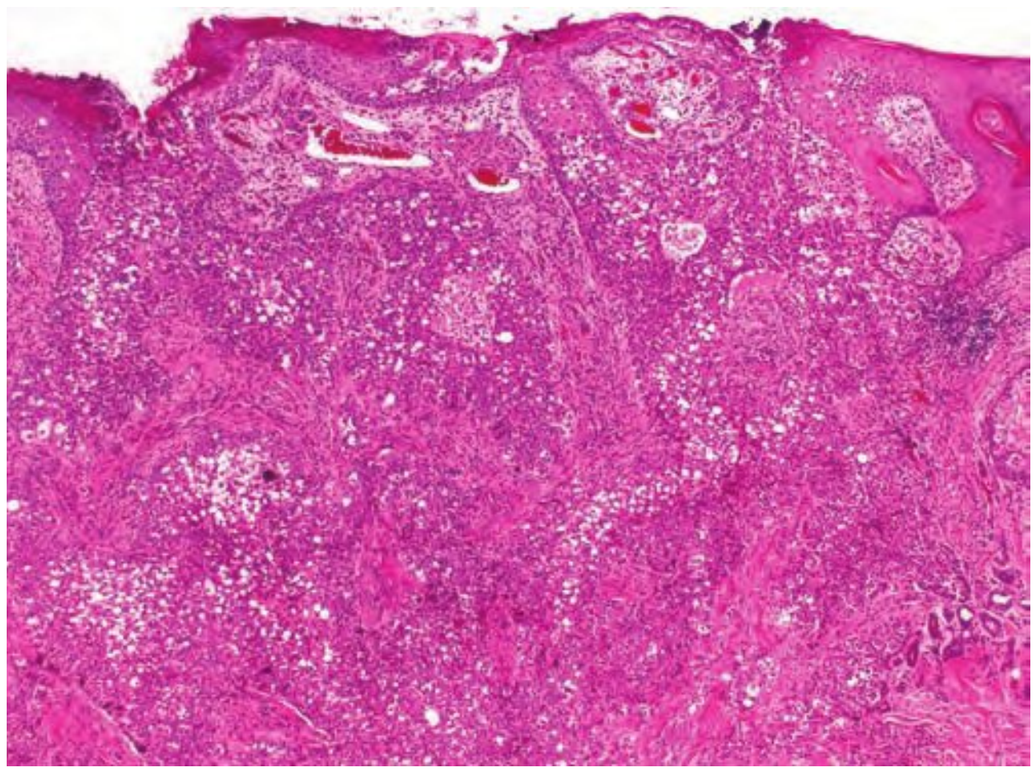


FIGURE 30-52. Sebaceous carcinoma. Irregular epithelial lobules are associated with epidermal ulceration and an infiltrative growth pattern in the dermis.

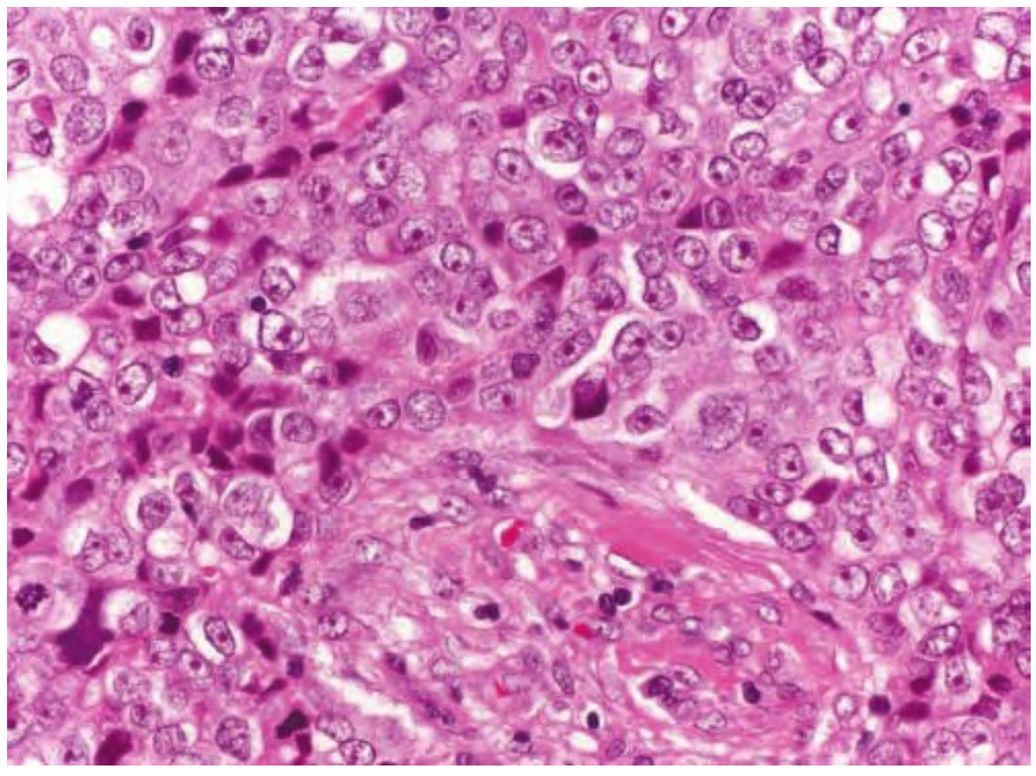


FIGURE 30-53. Sebaceous carcinoma. Lesional cells demonstrate marked cytologic atypia, mitotic activity, and focal sebaceous differentiation.

many of the undifferentiated cells have an eosinophilic cytoplasm, and when fat stains are used on frozen sections, the cells are found to contain fine lipid globules (311). Some of the large lobules show areas composed of atypical keratinizing cells, as seen in squamous cell carcinoma (283).

Sebaceous carcinomas of the eyelids in nearly half of the cases examined showed a pagetoid spread of malignant cells in the conjunctival epithelium or the epidermis of the skin of the lid or both (313). These changes are seen very rarely in extraocular sebaceous carcinoma (317). The pagetoid cells contain no mucopolysaccharides but stain positively for fat with oil red O (313). Recognition of the pagetoid growth pattern in biopsy material can be essential to recognition of the existence of an underlying sebaceous carcinoma (321).

Additional Studies. Certain strains of human papillomavirus have been implicated in the pathogenesis of sebaceous carcinoma (322). Mutations in the *p53* gene have been seen in invasive but not *in situ* sebaceous carcinoma, and immunohistochemical staining for proliferating cell nuclear antigen and p53 seem to have some prognostic value (323,324).

Differential Diagnosis. The tumor cells in sebaceous carcinoma are often large and squamoid in appearance or show basaloid differentiation with only inconspicuous lipidization. In the latter case, the tumor must be distinguished from basal cell carcinomas with sebaceous differentiation, and in the former case the differential diagnosis includes squamous cell carcinomas with hydropic changes (325,326). Other malignant neoplasms with clear cells must also be considered, including metastatic lesions (318).

Sebaceous carcinomas do not show the typical changes seen in basal cell carcinomas. Instead, the undifferentiated cells of sebaceous carcinoma show a more eosinophilic cytoplasm, greater cytologic atypia, and greater invasiveness (327). Clear-cell squamous cell carcinoma usually shows evidence of keratinization in the form of dyskeratotic cells and squamous parakeratotic whorls. Using an immunohistochemical battery, including epithelial membrane antigen (EMA), anti–BCA-255 (BRST-1), and CAM 5.2, can be helpful in distinguishing sebaceous carcinoma from basal cell carcinoma and squamous cell carcinoma (328).

The malignant neoplasms with clear cells do not show sebaceous differentiation. The cytoplasmic clearing is due to glycogen accumulation, which causes the nuclei to be positioned eccentrically. In contrast, neoplastic cells with sebaceous differentiation show scalloped, centrally situated nuclei and microvacuolated cytoplasm secondary to lipid deposits. When sebaceous carcinoma is suspected or found at frozen section, additional sections should be saved for fat stains. Sebaceous ductal differentiation consists of ductal structures lined by an eosinophilic corrugated cuticle similar to that of the normal sebaceous duct. Finally, metastases to the skin from malignant neoplasms composed of clear cells, namely renal, breast, bladder, and prostatic carcinoma or melanoma, also may mimic sebaceous carcinoma. Histochemical and immunohistochemical methods can help in narrowing the differential diagnosis appropriately (328).

As in other malignant adnexal neoplasms, zones of necrosis, marked nuclear atypia, and abnormal mitotic figures are common in sebaceous carcinoma (Fig. 30-53). Pagetoid proliferation of tumor cells in the epidermis or conjunctiva may extend widely and confers a poorer prognosis. Other adverse prognostic attributes include multicentric involvement, poor differentiation (i.e., sparse lipid), necrosis, paucity of reactive lymphocytes, extensive local invasion, and vascular or bony invasion (324). Metastases first involve regional lymph nodes of the periauricular, submaxillary, and cervical chains. Visceral spread may occur and lead to death. Additional criteria that may be of assistance in differentiating sebaceous carcinoma and sebaceoma are that carcinomas are larger, asymmetric, infiltrative, and poorly circumscribed, whereas sebaceomas may extend into the subcutis but are circumscribed and symmetric. Carcinomas may ulcerate the epidermis, and there may be extensive necrosis ("necrosis en masse"). The ratio of differentiated (vacuolated) to undifferentiated (nonvacuolated) sebocytes varies but tends to be higher in sebaceomas. Nuclear atypia is often striking, and mitotic figures are numerous and sometimes atypical in carcinomas. Sebaceomas, in contrast, lack striking nuclear atypia but may have few or many mitoses (285).

TUMORS WITH APOCRINE DIFFERENTIATION

Apocrine Nevus

Large numbers of mature apocrine glands are frequently present in lesions of nevus sebaceus and syringocystadenoma papilliferum. However, the pure apocrine nevus is a rare tumor. Apocrine nevi have presented as papules, facial nodules, and, most frequently, soft tissue masses of the axillae (329–333).

Histopathology. These lesions comprise increased numbers of apocrine glands, usually situated in the reticular dermis with occasional extension into subcutaneous tissue (329–337).

Immunohistochemistry. Studies demonstrate positive staining for carcinoembryonic antigen, gross cystic disease fluid protein, epithelial membrane antigen, and low–molecular-weight keratins (331,337,338). Lesions are typically negative for S100 and high–molecular-weight keratins.

Apocrine Hidrocystoma

Apocrine hidrocystoma occurs usually as a solitary, translucent cystic nodule (330–341). The term "apocrine cytsadenoma" has also been used to describe these lesions (339). Lesional diameter usually ranges from 1 to 15 mm; however, "giant" lesions, measuring 20 mm, have been described (342). Frequently, the lesions have a blue hue and can resemble a blue nevus (Fig. 30-54). The usual location of apocrine hidrocystoma is on the face, but it is occasionally seen on the ears, scalp, chest, shoulders, or vulva (341,343–348). Multiple apocrine hidrocystomas are rarely encountered (349,350). Lesions described as occurring on the penis have been reclassified as median raphe cysts (see Chapter 29) (351).

The blue color in some of the cysts is not fully explained. According to most authors, it is a Tyndall effect caused by the scattering of light in a colloidal system and the resultant reflection of blue light (343,349).

Histopathology. The dermis contains one or several large cystic spaces into which papillary projections often extend (Fig. 30-55). The inner surface of the cyst and the papillary projections are lined by a row of columnar secretory cells of variable height showing "decapitation" secretion indicative of apocrine secretion (Fig. 30-56). Peripheral to the layer of secretory cells are elongated myoepithelial cells, their long axes running parallel to the cyst wall (343). In some cases, one finds superficially located lumina lined by a double layer of ductal epithelium in addition to the cysts lined by secretory cells (339).

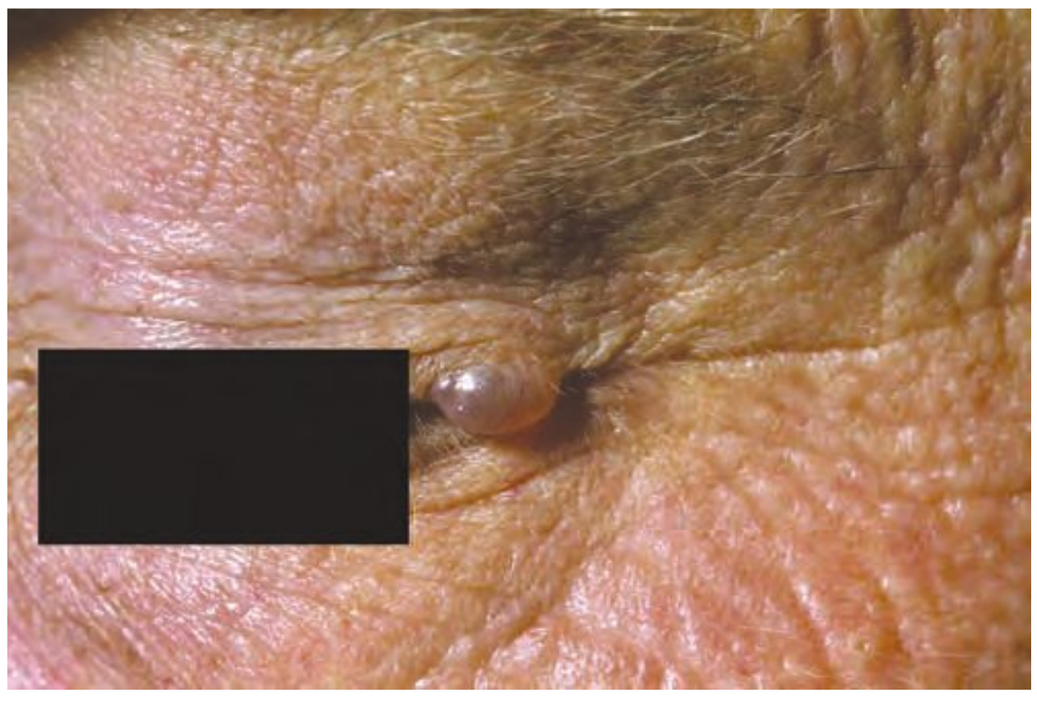


FIGURE 30-54. Apocrine hidrocystoma. A translucent cystic lesion with a bluish hue is noted.

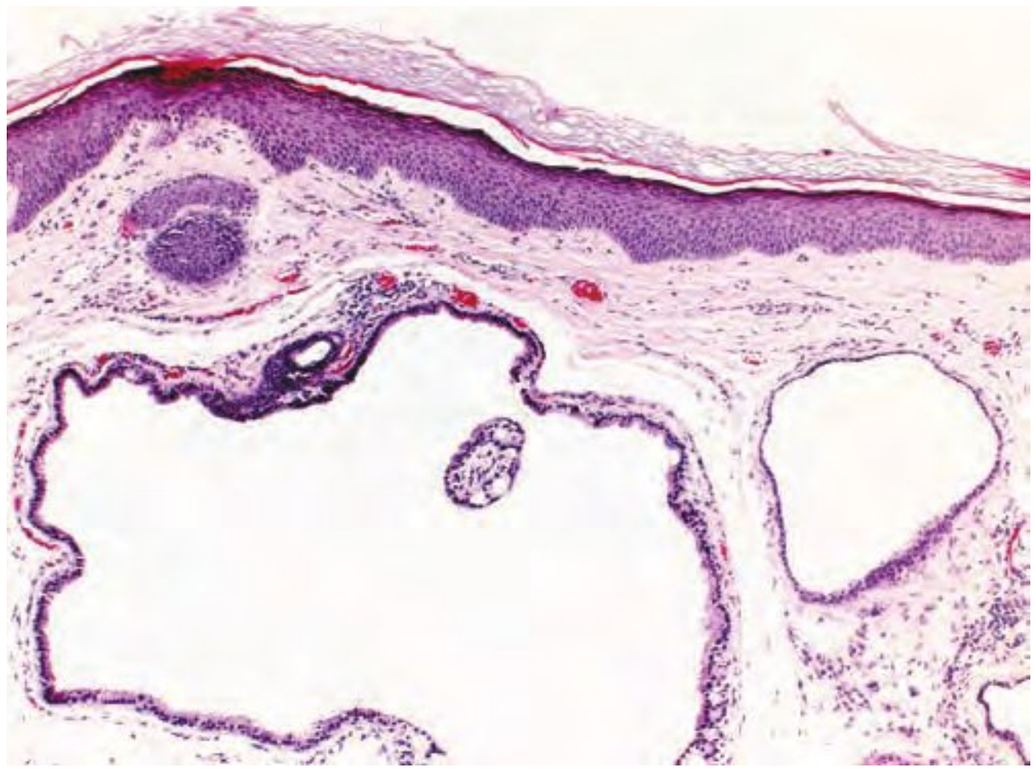


FIGURE 30-55. Apocrine hidrocystoma. The dermis contains a multiloculated cystic lesion lined by epithelial cells with occasional papillary projections.

Additional Studies. The apocrine nature of the secretion of the luminal cells has been demonstrated by the presence of numerous large PAS-positive, diastase-resistant granules in the secretory cells and by electron microscopy. Electron microscopic examination shows abundant secretory granules of moderate density and uniform internal structure in the secretory cells of apocrine hidrocystoma, particularly in their luminal portion, and evidence of apocrine secretion (352–354).

The apocrine hidrocystoma can be regarded as a cystic adenoma rather than as a retention cyst because the secretory cells do not appear flattened, as they would be in a retention cyst, and because papillary projections can extend into the lumen of the cystic spaces (339).

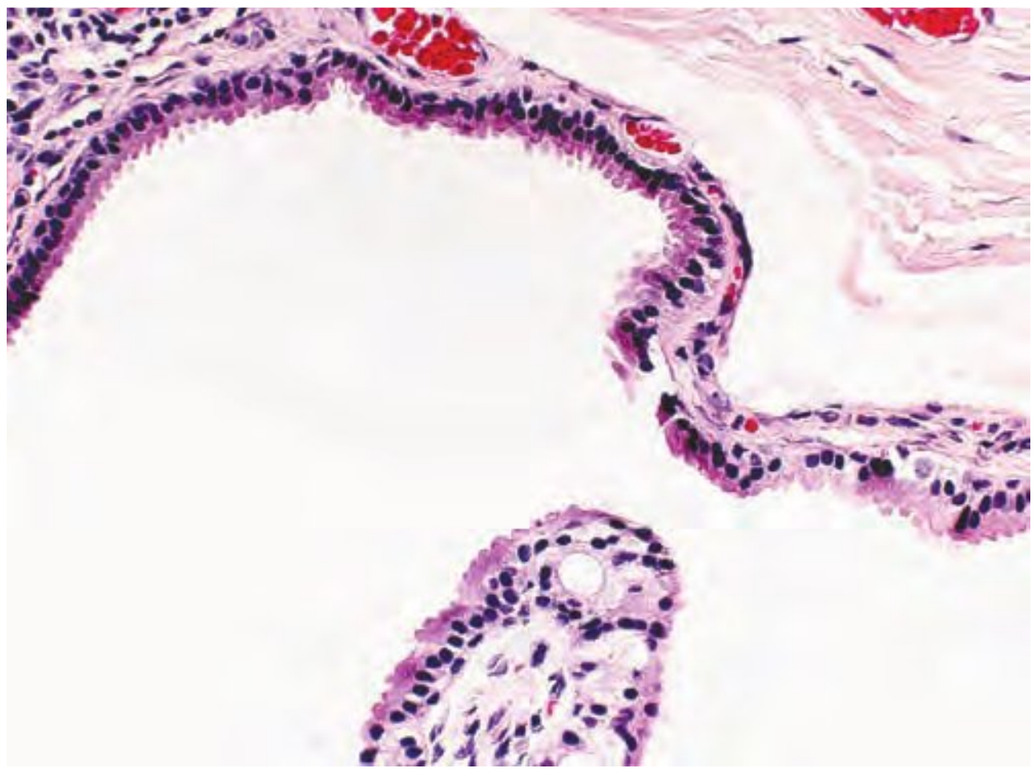


FIGURE 30-56. Apocrine hidrocystoma (cystadenoma). The cyst is lined by a single row of columnar cells showing decapitation secretion. Peripheral to the row of secretory cells are elongated myoepithelial cells.

Differential Diagnosis. Eccrine hidrocystomas, which are lined by ductal cells, differ from apocrine hidrocystomas by the absence of decapitation secretion, of PAS-positive granules, and of myoepithelial cells. However, those portions of an apocrine hidrocystoma in which the cystic spaces are lined by ductal epithelium have the same appearance as the cystic spaces in eccrine hidrocystomas, except that the latter usually are unilocular and apocrine hidrocystomas are often multilocular. Median raphe cysts of the penis, which have been mistakenly reported as apocrine hidrocystomas, show a pseudostratified columnar cyst wall without evidence of decapitation secretion and without a row of myoepithelial cells (351).

Hidradenoma Papilliferum

Hidradenoma papilliferum usually occurs in women, usually on the labia majora or in the perineal or perianal region (355–358). In males, it has been reported as a perineal lesion or ectopically as an arm lesion (359,360). Occurrences on the upper eyelid and in the external ear canal have been reported (361,362). The tumor is covered by normal skin and measures only a few millimeters in diameter. Malignant changes have been reported in hidradenoma papilliferum, as aggressive adenosquamous or squamous cell carcinomas (363,364).

Histopathology. The tumor represents an adenoma with apocrine differentiation (365). It is located in the dermis, is well circumscribed, is surrounded by a fibrous capsule, and shows no connection with the overlying epidermis (Fig. 30-57). Some tumors have a peripheral epithelial wall showing areas of keratinization (197). Within the tumor, one observes tubular and cystic structures (Fig. 30-58). Papillary folds project into the cystic spaces. The lumina are lined occasionally with only a single row of columnar cells, which show an oval, pale-staining nucleus located near the base, a faintly eosinophilic cytoplasm, and active decapitation secretion as seen in the secretory cells of apocrine glands (Fig. 30-58) (365). Usually, the lumina are surrounded by a double layer of cells consisting of an inner layer of secretory cells and an outer layer of small cuboidal cells with deeply basophilic nuclei that are myoepithelial cells (Fig. 30-58) (366).

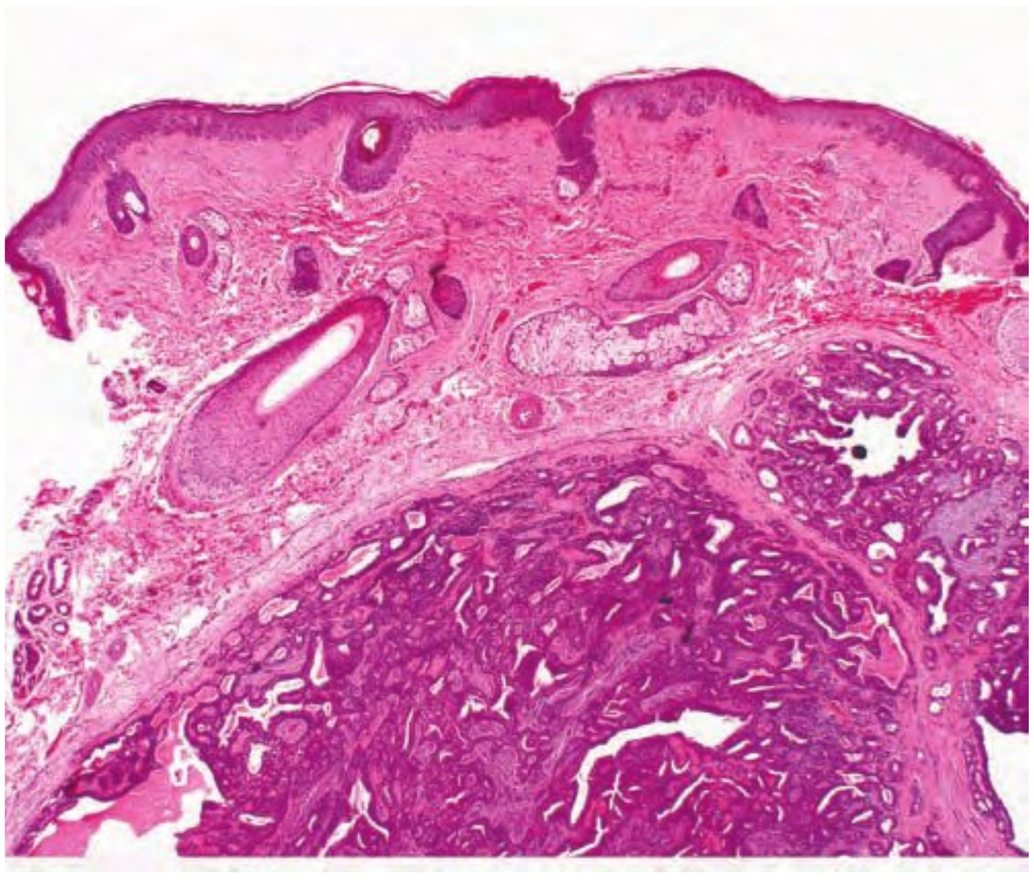


FIGURE 30-57. Hidradenoma papilliferum. The tumor consists of a well-circumscribed dermal nodule with scattered cystic and branching spaces.

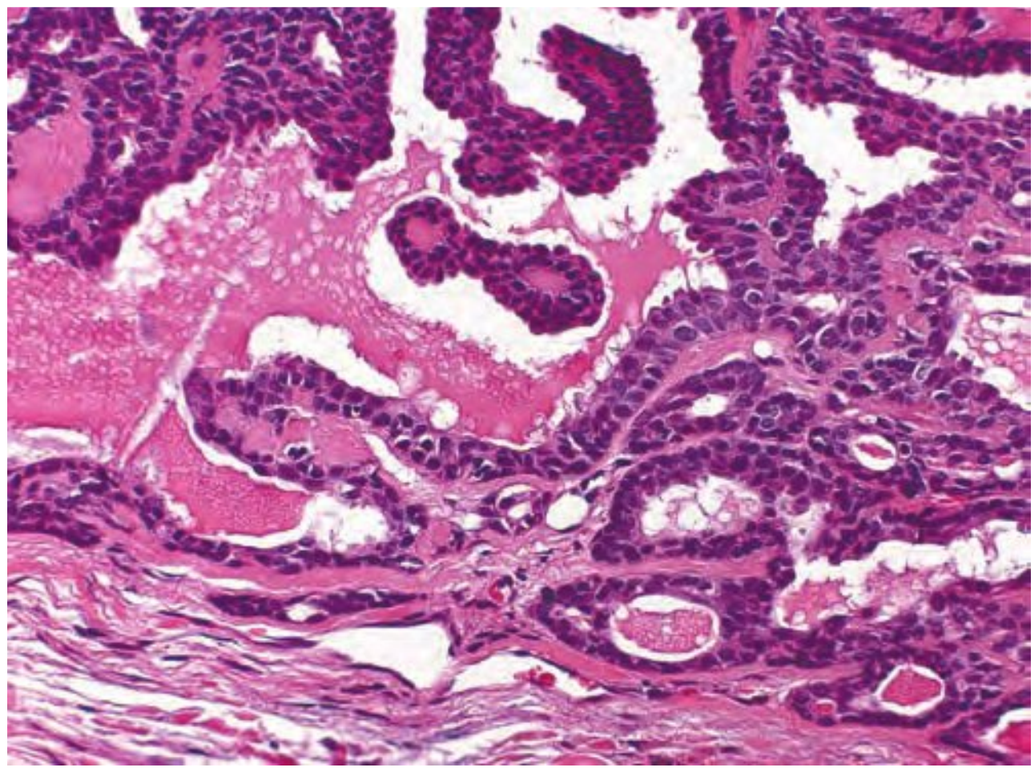


FIGURE 30-58. Hidradenoma papilliferum. Numerous papillary projections are seen within the lesion. The papillary folds are lined by one layer of high cylindric cells, which show evidence of active "decapitation" secretion like that seen in apocrine glands. A basal layer of small cuboidal cells is also present.

Additional Studies. The apocrine nature of the secretion in hidradenoma papilliferum has been established by histochemical, enzyme histochemical, and electron microscopic examinations.

Histochemically, the luminal cells contain many large, PAS-positive, diastase-resistant granules as seen in the secretory cells of apocrine glands. In addition, the luminal cells are positive for nonspecific esterase and acid phosphatase, the so-called apocrine enzymes, and negative for phosphorylase, a typical eccrine enzyme. Furthermore, the outer row of cells stains positive for alkaline phosphatase, as myoepithelial cells normally do (365).

Electron microscopic examination demonstrates two features of the luminal cells that are regarded as characteristic for apocrine secretory cells. First, numerous membrane-limited, secretory granules that are of varying size and density and that contain lipid droplets are present in the apical portion of these cells. Second, as evidence of decapitation secretion, portions of apical cytoplasm containing large secretory granules are released into the lumen (366). The peripheral layer of cells contains numerous myofilaments.

Syringocystadenoma Papilliferum

Syringocystadenoma papilliferum occurs most commonly on the scalp or the face; however, in about one fourth of the cases,

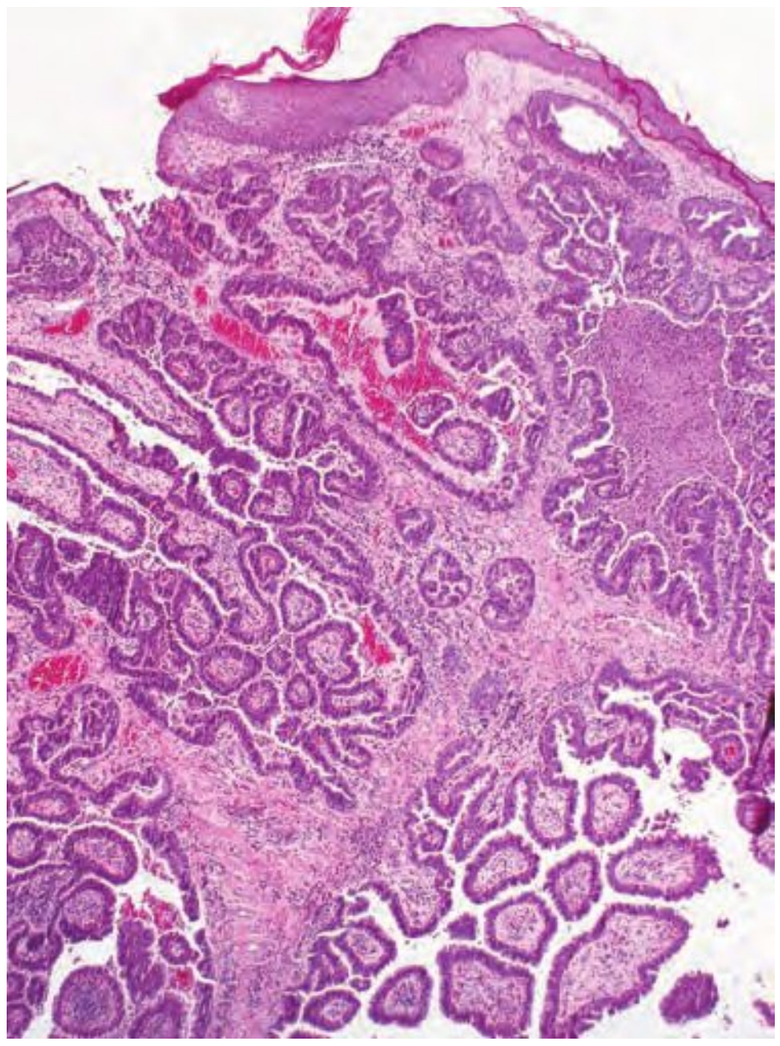


FIGURE 30-59. Syringocystadenoma papilliferum. The lesion exhibits a cystic invagination extending into the dermis, with numerous papillary projections.

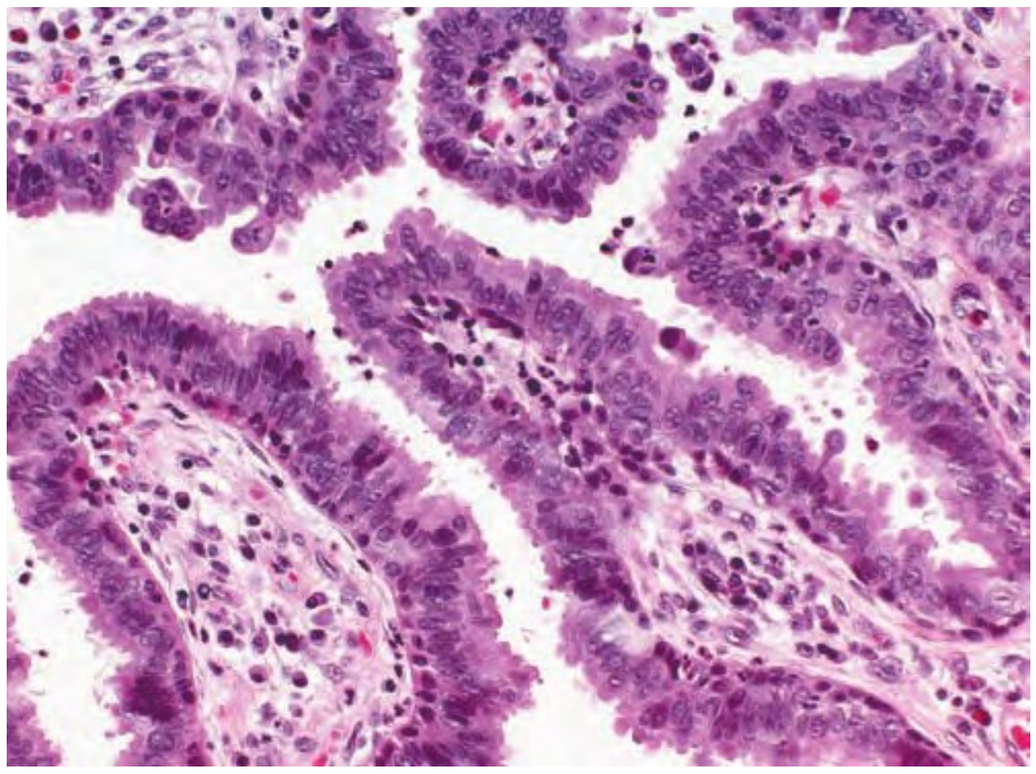


FIGURE 30-60. Syringocystadenoma papilliferum. The papillary projections are lined by two rows of cells. The luminal row of cells consists of columnar cells with evidence of active "decapitation" secretion. The outer row of cells consists of small cuboidal cells. Plasma cells are usually seen in the papillary core.

it is seen elsewhere (367–370). It is usually first noted at birth or in early childhood and presents as a papule or several papules in a linear arrangement or as a plaque. The lesion increases in size at puberty, becoming papillomatous and often crusted (371). On the scalp, syringocystadenoma papilliferum frequently arises around puberty within a nevus sebaceus that has been present since birth.

Histopathology. The epidermis shows varying degrees of papillomatosis. One or several cystic invaginations extend downward from the epidermis (Fig. 30-59). The upper portion of the invaginations and, in some instances, large segments of the cystic invaginations are lined by squamous, keratinizing cells similar to those of the surface epidermis (372). In the lower portion of the cystic invaginations, numerous papillary projections extend into the lumina of the invaginations. The papillary projections and the lower portion of the invaginations are lined by glandular epithelium often consisting of two rows of cells (Fig. 30-60). The luminal row of cells consists of high columnar cells with oval nuclei and faintly eosinophilic cytoplasm. Occasionally, some of these cells show active decapitation secretion, and cellular debris is found in the lumina (14,373). The outer row of cells consists of small cuboidal cells with round nuclei and scanty cytoplasm. In some areas, the cells of the luminal layer are arranged in multiple layers and form a lacelike pattern resulting in multiple small, tubular lumina (368).

Beneath the cystic invaginations, deep in the dermis, one can find in many cases groups of tubular glands with large lumina. The cells lining the large lumina often show evidence of active decapitation secretion, indicating that they are apocrine glands (Fig. 30-60) (14,371). Connections of the apocrine glands deep in the dermis with the cystic invaginations in the upper dermis can be traced when step sections are carried out (14).

A highly diagnostic feature is the almost invariable presence of a fairly dense cellular infiltrate composed nearly entirely of plasma cells in the stroma of this tumor, especially in the papillary projections (Fig. 30-60). These are predominantly of the immunoglobulin G (IgG) and IgA classes (374,375).

Frequently, there are malformed sebaceous glands and hair structures in the lesions of syringocystadenoma papilliferum (371). In about one third of the cases, syringocystadenoma papilliferum is associated with a nevus sebaceus. In about 10% of the cases, a basaloid epithelial proliferation resembling basal cell carcinoma develops, but this is noted only in lesions that also exhibit a nevus sebaceous (368). A few instances of transition of a syringocystadenoma papilliferum into an adenocarcinoma with regional lymph node metastases have been reported (376).

Additional Studies. Syringocystadenoma papilliferum can exhibit both apocrine and of eccrine differentiation. For example, positive immunoreactivity for gross cystic disease fluid proteins 15 and 24 and zinc α-2 glycoprotein demonstrates evidence of apocrine differentiation (338,377). On the other hand, immunohistochemical analysis of cytokeratins in syringocystadenoma papilliferum demonstrates similarities to eccrine poromas and the ductal component of eccrine glands (378). In addition, light and electron microscopic features of some lesions show evidence of eccrine differentiation (13). It is probable that syringocystadenoma papilliferum arises from undifferentiated cells with the potential to exhibit both apocrine

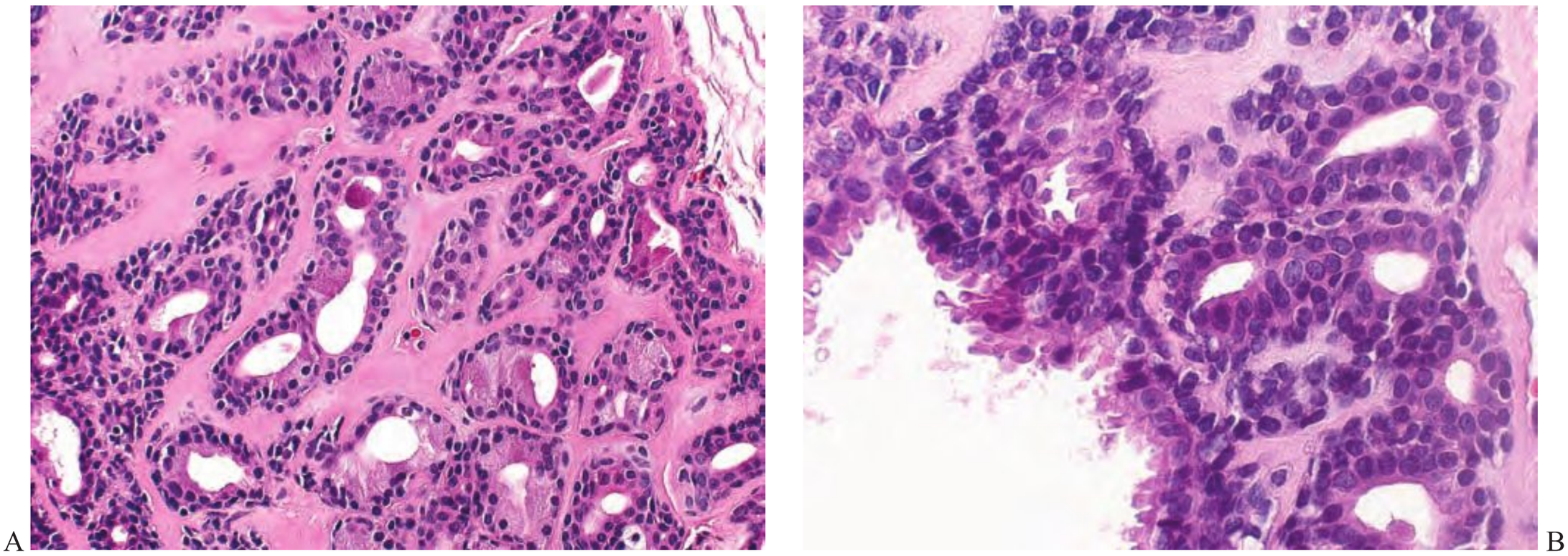


FIGURE 30-61. Tubular apocrine adenoma. A: There are numerous irregularly shaped tubular structures in the dermis. B: The tubules are usually lined by two layers of epithelial cells—an indicator of benignancy. The peripheral layer consists of cuboidal or flattened cells, and the luminal layer is composed of columnar cells. Some of the tubules have a dilated lumen with papillary projections. Eosinophilic debris can be seen in the tubular lumens.

and eccrine modes of epithelial secretion. Of interest, the view expressed by Pinkus probably is correct: Most lesions of syringocystadenoma papilliferum exhibit apocrine differentiation; however, some demonstrate eccrine features (371). Studies have demonstrated loss of heterozygosity for Patched and p16, a negative regulator of the cell cycle, in syringocystadenoma papilliferum, suggesting that these molecules may play a role in the pathogenesis of these lesions (379).

Tubular Apocrine Adenoma

First described in 1972 (380), additional cases of tubular apocrine adenoma have been reported (381–385). The tumor typically presents as a well-defined nodule that is located on the scalp. Most tumors are less than 2 cm in diameter, although one reported lesion located on the scalp measured 7 by 4 cm (380).

Histopathology. This tumor manifests numerous irregularly shaped tubular structures that are usually lined by two layers of epithelial cells (Fig. 30-61). The peripheral layer consists of cuboidal or flattened cells, and the luminal layer is composed of columnar cells (380). Some of the tubules have a dilated lumen with papillary projections extending into it (Fig. 30-61). Decapitation secretion of the luminal cells is seen in many areas. In addition, cellular fragments and eosinophilic granular debris are seen in some lumina. In some cases, tubular apocrine adenomas can arise in association with syringocystadenoma papilliferum (SCAP), and often the SCAP is situated in the superficial portion of the "combined" lesion (382,384,386).

Additional Studies. Electron microscopy has revealed secretory granules and evidence of apocrine-type decapitation secretion in the luminal cells (380,383). In contrast to hidradenoma papilliferum, the peripheral cell layer contains no myofilaments. Enzyme histochemistry is also consistent with apocrine differentiation (380).

Differential Diagnosis. In tubular apocrine adenomas with marked papillary proliferations, there may be some nuclear pleomorphism, which suggests sweat gland carcinoma or a metastatic adenocarcinoma. However, the presence of a peripheral layer of cuboidal or flattened cells is a feature favoring benignity (381).

Tubular apocrine adenomas resemble papillary eccrine adenoma, and these two tumors were once regarded as identical (384). Because of their differences in decapitation secretion, in enzyme histochemistry, and in electron microscopy, the suggestion was made that they be referred to as *tubulopapillary hidradenoma*, with apocrine or eccrine differentiation, as the case may be (387). For a description of papillary eccrine adenomas, see page 890. The term *tubulopapillary hidradenoma* may be considered to conceptualize a spectrum of lesions that includes tubular apocrine adenoma and papillary eccrine adenoma, and these are also closely related to syringocystadenoma papilliferum (388,389).

Apocrine Adenoma; Apocrine Fibroadenoma

Rare variants of apocrine adenomas can occur in apocrine areas, such as in the axilla (390) and in the perianal region (391,392).

Histopathology. Apocrine lumina are readily recognized by the presence of decapitation secretion. In addition, there may be cystically dilated spaces (390,391). A stromal component resembling that in fibroadenomas of the breast has been described (392).

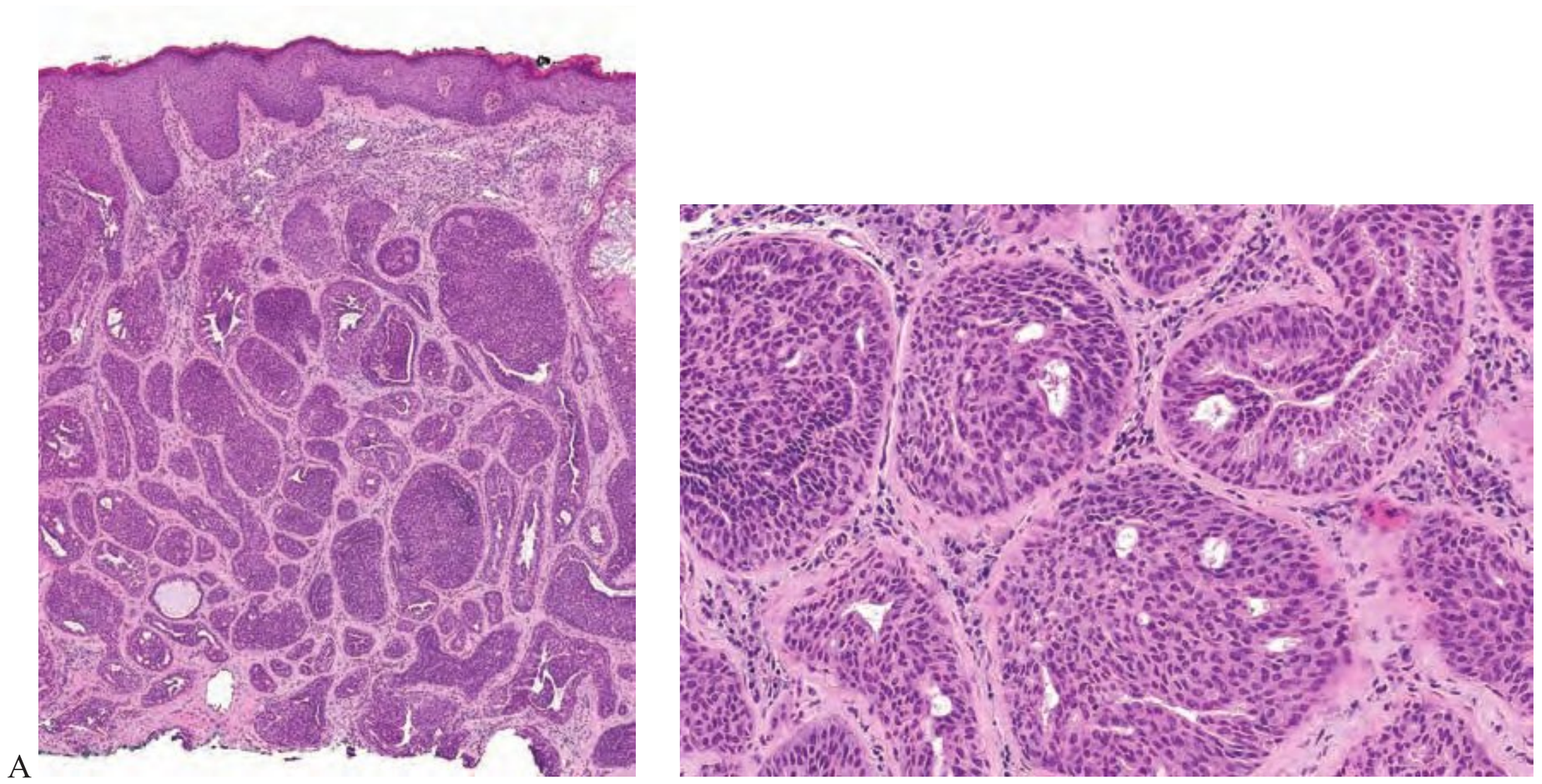


FIGURE 30-62. Erosive adenomatosis of the nipple. A: Dilated tubular structures are present at the dermal–epidermal junction and throughout the dermis. B: The dilated tubules are lined by a peripheral layer of cuboidal cells and a luminal layer of columnar cells that occasionally exhibit decapitation secretion. Other tubules exhibit a more solid proliferation resembling "papillomatosis" of mammary duct epithelium.

Erosive Adenomatosis of the Nipple

Erosive adenomatosis (papillary adenoma, florid papillomatosis) of the nipple represents an adenoma of the major nipple ducts (393–396). In the early lesions, the nipple appears eroded and inflamed, often with a serous discharge. During this early erosive phase, clinical differentiation from Paget's disease of the breast may be impossible. Later, the nipple shows nodular thickening; differentiation from Paget's disease is then easier. Peak incidence for erosive adenomatosis is in the fifth decade of life; cases in girls as young as 8 years of age have been reported (397).

Histopathology. Extending downward from the epidermis are irregular, dilated tubular structures resembling those seen in tubular apocrine adenoma (Fig. 30-62) (393). These tubules are lined by a peripheral layer of cuboidal cells and a luminal layer of columnar cells that occasionally demonstrate secretory projections at their luminal border (393). Some of the tubules demonstrate papillary proliferations of columnar cells that extend into the lumen; these proliferations may be so pronounced as to nearly fill the entire lumen. In other areas, detached, partially necrotic cells may be seen in the tubular lumina. In some lesions, considerable acanthosis of the epidermis is seen, with extension of squamous epithelium into some of the superficial ductal structures.

Differential Diagnosis. Erosive adenomatosis of the nipple must be differentiated from intraductal carcinoma, which shows larger cuboidal cells and uniform atypicality of the nuclei, frequently with necrosis. Immunohistochemical studies have demonstrated myoepithelial cells within lesions of erosive adenomatosis, which would help to differentiate these lesions from intraductal carcinoma (398). Hidradenoma papilliferum, in contrast to erosive adenomatosis of the nipple, shows no connections of the tubular structures with the surface epidermis (399).

Cylindroma

Cylindroma occurs more often as a solitary lesion than as multiple lesions (400). Cases with multiple lesions are dominantly inherited and show numerous dome-shaped, smooth nodules of various sizes on the scalp. Occasionally, scattered nodules are also present on the face and, in rare instances, on the trunk and the extremities (401). The lesions begin to appear in early adulthood and increase in number and size throughout life. The tumors present as scalp nodules ranging in size from a few millimeters to several centimeters (Fig. 30-63). Nodules on the scalp may be present in such large numbers as to cover the entire scalp like a turban. For this reason, they are referred to occasionally as *turban tumors*.

The association of multiple lesions of cylindroma with multiple lesions of trichoepithelioma is quite common (400,402–405). In these cases, the lesions of the scalp are cylindromas, and those elsewhere are partially cylindromas and partially trichoepitheliomas. Brooke-Spiegler syndrome refers to a dominantly inherited disorder in which patients demonstrate multiple cylindromas, spiradenomas, and trichoepitheliomas (403,405–408). In several instances, multiple cylindromas have been found in association with eccrine spiradenoma (400,409,410).



FIGURE 30-63. Cylindroma. The lesions typically present as scalp nodules.

Sporadic, solitary cylindromas are not inherited; they appear in adulthood and occur either on the scalp or the face. Their histologic appearance is the same as that of multiple cylindromas (400).

Histopathology. Cylindromas represent a tumor that may manifest both apocrine and eccrine differentiation; however, features of apocrine differentiation usually predominate (400). The tumors of cylindroma are composed of numerous islands of epithelial cells. Varying considerably in size and shape and lying close together, separated often only by their hyaline sheath and a narrow band of collagen, the islands of epithelial cells seem to fit together like pieces of a jigsaw puzzle (Figs. 30-64 and 30-65). The hyaline sheath surrounding the tumor islands like a cylinder is quite variable in thickness. In addition, droplets of hyalin are present in many islands, and some islands consist largely of hyalin and contain only a few cells. The hyalin is PAS positive and diastase resistant (373).

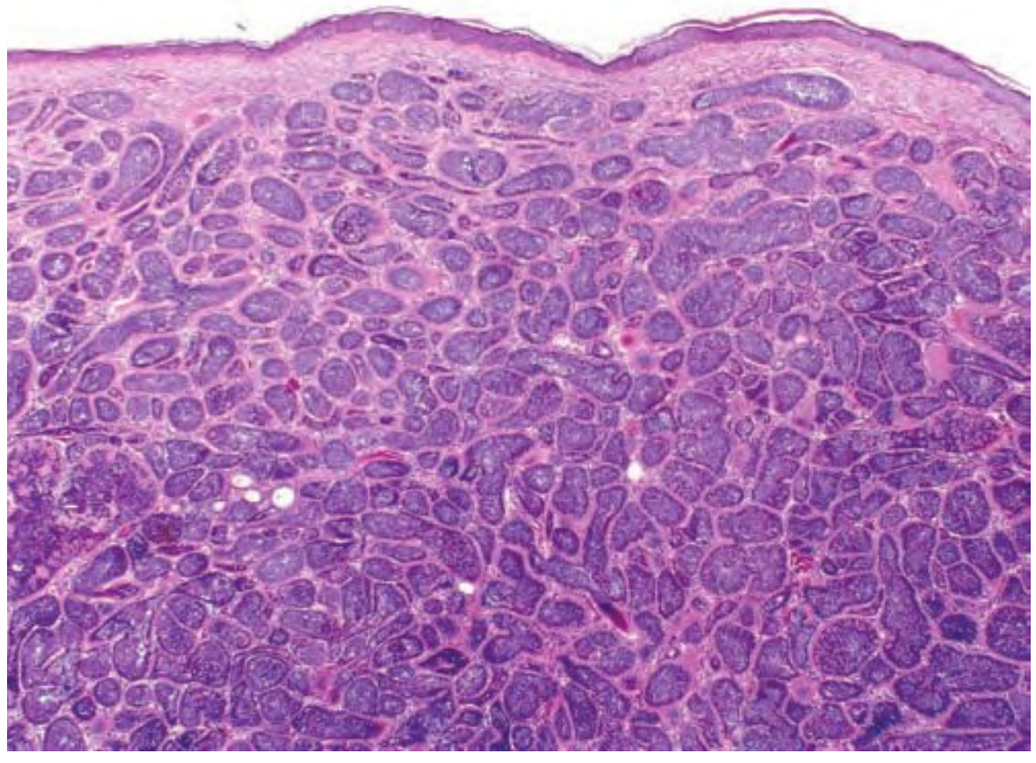


FIGURE 30-64. Cylindroma. The tumor is composed of irregularly shaped islands that fit together like pieces of a jigsaw puzzle. The islands are surrounded by a hyaline sheath.

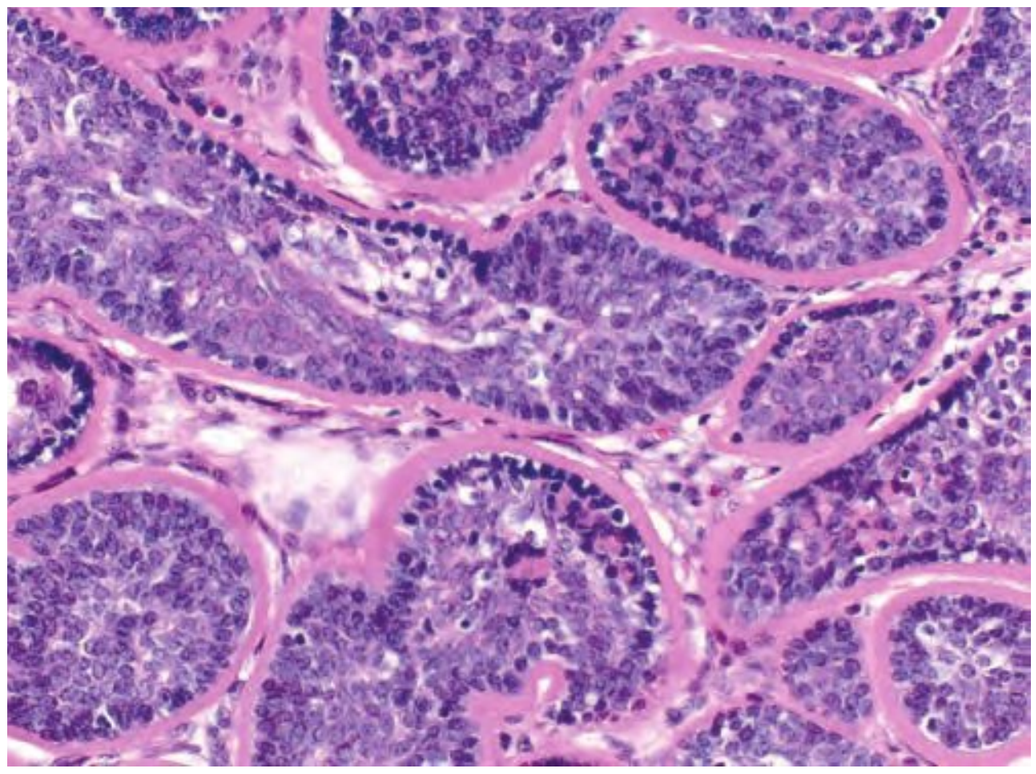


FIGURE 30-65. Cylindroma. Two types of epithelial cells comprise the islands: cells with small dark nuclei representing undifferentiated cells, and cells with large pale nuclei representing cells with a certain degree of differentiation toward ductal or secretory cells. Droplets of hyaline material are seen in the islands.

Two types of cells constitute the islands: Cells with small, dark-staining nuclei are present predominantly at the periphery of the islands, often in a palisade arrangement, and cells with large, light-staining nuclei lie in the center of the islands (Fig. 30-65). In addition, tubular lumina are often present. In some cases, they are quite numerous, whereas in others only a few are found after a thorough search. The lumina are lined by cells that usually have the appearance of ductal cells (411). Occasionally, however, the luminal cells show active secretion, like the secretory cells of apocrine glands (14). Often, amorphous material is found within the lumina; it contains both neutral and acid mucopolysaccharides, as demonstrated by positive staining with the PAS reaction and Alcian blue (373).

Additional Studies. The ultrastructural and immunohistochemical features best fit differentiation toward the intradermal coiled duct region of eccrine sweat glands (412–414), with myoepithelial cell participation (415).

Electron microscopic examination, similar to examination by light microscopy, has revealed two major types of cells: undifferentiated basal cells with small, dark nuclei, and differentiating cells with large, pale nuclei. Most of the differentiating cells still appear immature as "indeterminate cells," but some show a certain degree of differentiation toward secretory or ductal cells and are in part arranged around lumina (411,416,417).

Of interest, an early study of two large pedigrees led to the conclusion that cylindromas and trichoepitheliomas are different manifestations of the same disorder and not merely examples of genetic linkage (405). Genetic studies have identified a single gene, *CYLD1*, on 16q12-q13 as being altered in familial cylindromatosis syndrome (Brooke-Spiegler) (11). Loss of heterozygosity at the 16q12-q13 locus has been demonstrated in

familial cylindromatosis and sporadic cylindromas (11). The CYLD1 gene has been cloned; the molecule contains cytoskeletal binding domains and domains similar to ubiquitin hydrolases (418). Frameshift mutations in the CYLD1 gene have also been associated with familial cylindromatosis (419). The various tumors associated with familial cylindromatosis may arise from different types of mutations in the CYLD1 gene; however, this has not been definitively demonstrated (419).

The thick hyaline band surrounding the tumor islands of cylindroma is composed mainly of an amorphous substance identical to the subepidermal lamina densa. It is connected with the tumor cells by half-desmosomes. Enmeshed in it are aggregated anchoring fibrils and thin collagen fibrils (13). This thick hyaline membrane and also the particles of hyaline present between the cells of the tumor islands react positively to staining with antibodies against type IV collagen and laminin, analogous to the subepidermal lamina densa. This hyaline is synthesized by the tumor cells and is similar to the deposits of basement membrane protein demonstrated in hyalinosis cutis et mucosae (420).

Malignant Cylindroma

Cylindromas rarely undergo malignant degeneration; however, a number of cases have been reported (421–427). In most of these patients, there were multiple cylindromas of the scalp, but in several cases a single tumor was present (421–429). Usually only one tumor was malignant, but in some cases malignant progression had occurred in several tumors (430,431).

Death usually ensued through visceral metastases, but in a few patients it occurred as the result of invasion of the skull with ensuing hemorrhage or meningitis. Local excision of the tumors of the scalp may result in a cure.

Histopathology. Areas of malignant degeneration are characterized by islands of cells showing marked nuclear anaplasia and pleomorphism, many atypical mitotic figures, loss of the hyaline sheath, loss of palisading at the periphery, and invasion into the surrounding tissue.

TUMORS WITH ECCRINE DIFFERENTIATION

Eccrine Nevus

Eccrine nevi are very rare. They may show a circumscribed area of hyperhidrosis (432,433), a solitary sweat-discharging pore (434), or papular lesions in a linear arrangement (435).

In the so-called eccrine angiomatous hamartoma, there may be one or several nodules (436) or a solitary large plaque (437). The lesions are generally present on an extremity at birth. Hyperhidrosis and/or pain may be apparent (438).

Histopathology. Eccrine nevi show an increase in the size of the eccrine coil or in both the size and the number of coils. In other cases there is ductal hyperplasia consisting of thickening of the walls and dilation of the lumina.

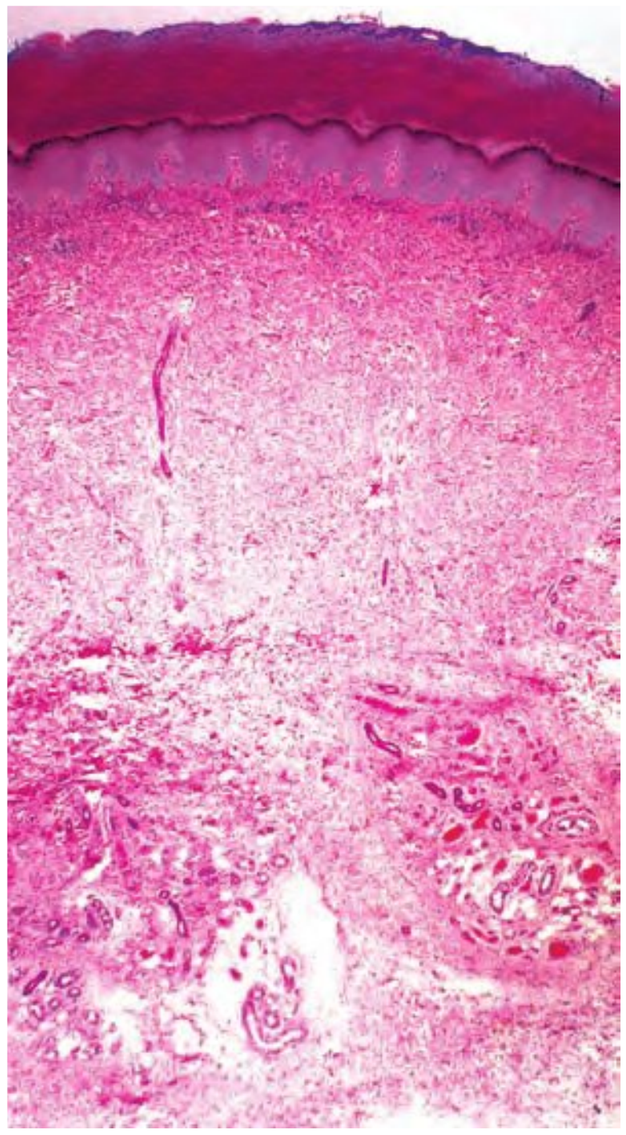


FIGURE 30-66. Eccrine angiomatous hamartoma. There is an increased number of eccrine structures and capillary channels in the deep dermis.

Eccrine angiomatous hamartomas usually lie in the deep dermis and contain increased numbers of eccrine structures and numerous capillary channels surrounding or intermingled with the eccrine structures (Figs. 30-66 and 30-67) (439). These hamartomas may also contain fatty tissue and pilar structures (440,441).

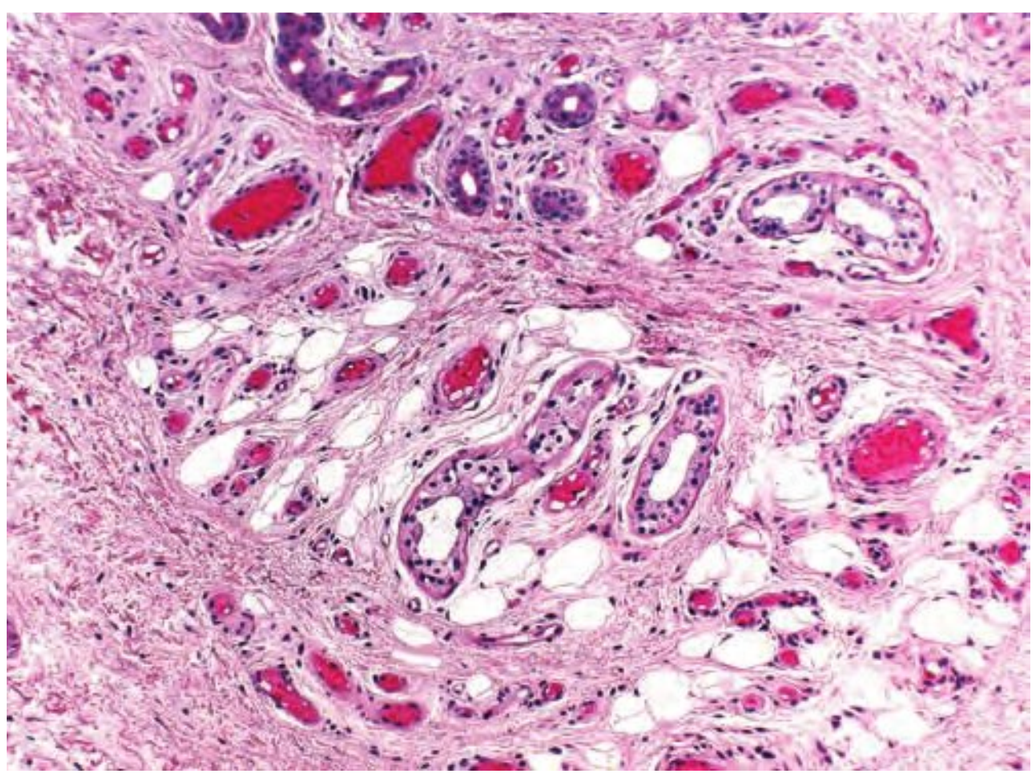


FIGURE 30-67. Eccrine angiomatous hamartoma. The eccrine coils and capillaries are associated with fatty tissue.

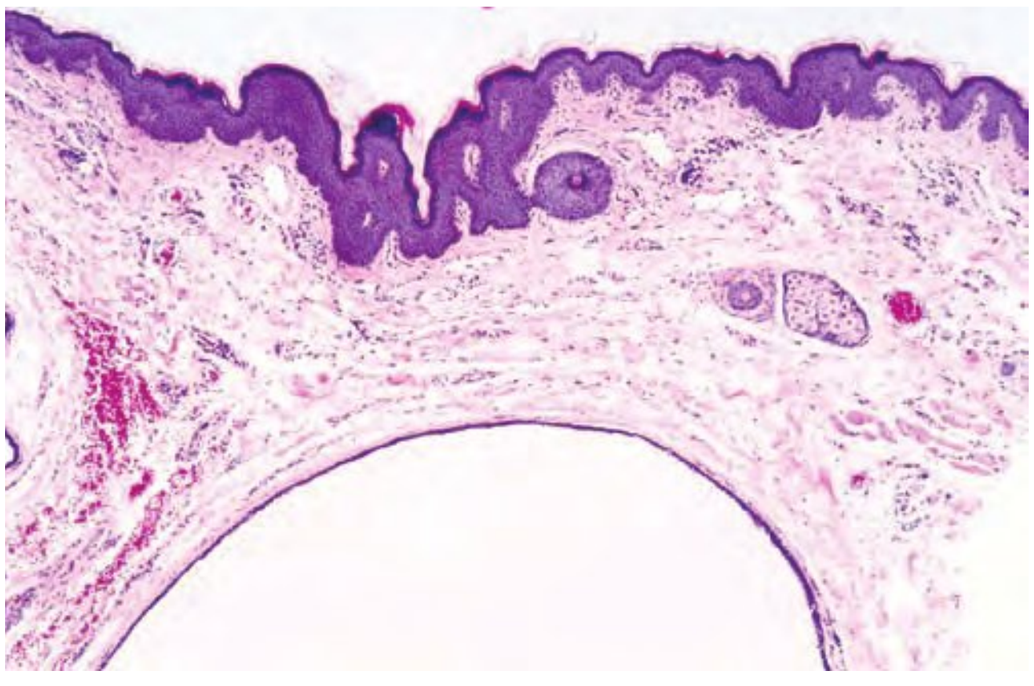


FIGURE 30-68. Eccrine hidrocystoma. A solitary cystic lesion is seen in the dermis.

Eccrine Hidrocystoma

In this condition, usually one lesion, but occasionally several, and rarely numerous lesions are present on the face (442). As in apocrine hidrocystoma, the lesion consists of a small, translucent, cystic nodule 1 to 3 mm in diameter that often has a bluish hue. In some patients with numerous lesions, the number of cysts increases in warm weather and decreases during winter (443).

Histopathology. Eccrine hidrocystoma shows a single cystic cavity located in the dermis (Fig. 30-68). The cyst wall usually shows two layers of small, cuboidal epithelial cells (Fig. 30-69) (442). In some areas, only a single layer of flattened epithelial cells can be seen, their flattened nuclei extending parallel to the cyst wall. Small papillary projections extending into the cavity of the cyst are observed only rarely (444). Eccrine secretory tubules and ducts are often located below the cyst and in close approximation to it, and, on serial sections, one may find an eccrine duct leading into the cyst from below (416). However, typically no connection is found between the cyst and the epidermis.

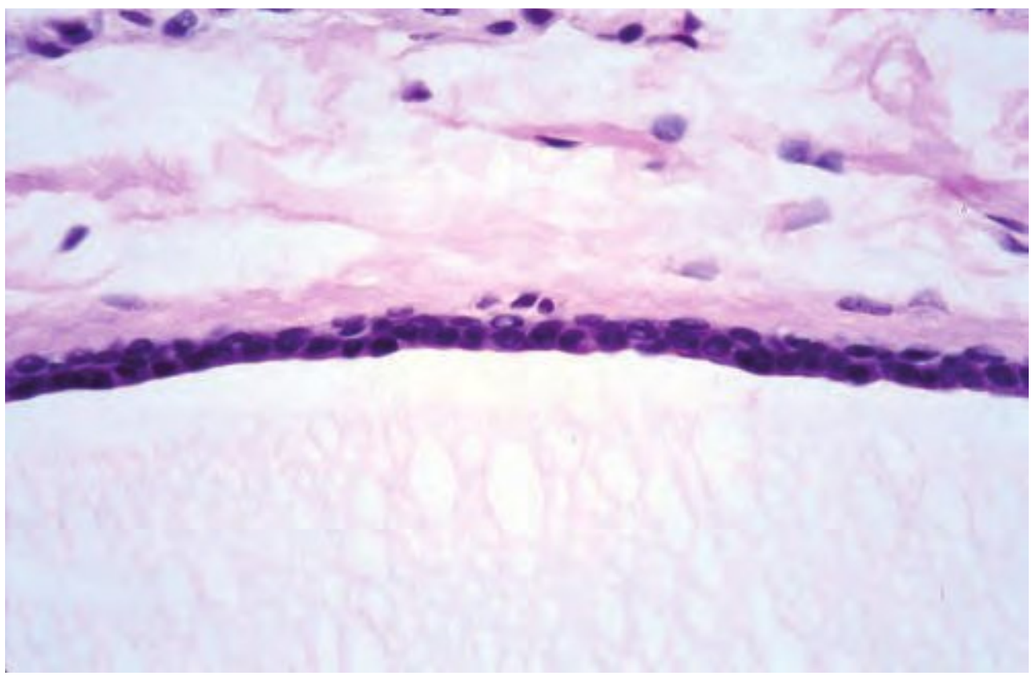


FIGURE 30-69. Eccrine hidrocystoma. The cyst is lined by a single layer of cuboidal epithelium.

Additional Studies. Electron microscopy of eccrine hidrocystoma has established that the cyst wall is composed of ductal cells, because the luminal cell membrane shows numerous microvilli and no secretory granules (445). Tonofilaments are seen in the luminal portion of the cells, and desmosomes connect the cells (446). Enzyme histochemistry in cases with numerous cysts has revealed phosphorylase and succinic dehydrogenase, which are eccrine enzymes, in the cyst walls (445,446).

It is likely that obstruction of eccrine ducts leads to either temporary or permanent retention of sweat (446).

Differential Diagnosis. For a discussion of differentiation of eccrine from apocrine hidrocystoma, see page 877.

Syringoma

Based on histochemical and electron microscopic findings, syringoma represents an adenoma of intraepidermal eccrine ducts. It occurs predominantly in women at puberty or later in life. Although occasionally solitary, the lesions usually are multiple and may be present in great numbers. They are small, skin-colored or slightly yellow, soft papules usually only 1 to 2 mm in diameter. In many patients, the lesions are limited to the lower eyelids. Other sites of predilection are the cheeks, thighs, axillae, abdomen, and vulva (285,447–450). In so-called eruptive hidradenoma or syringoma, the lesions arise in large numbers in successive crops on the anterior trunk of young persons (451). Rarely, the lesions of syringoma show a unilateral, linear arrangement (452). In rare instances, occult syringomas of the scalp are associated with diffuse thinning of the hair (453) or with cicatricial alopecia. Inapparent syringoma has been found incidentally in close approximation to basal cell carcinoma (454).

Histopathology. Embedded in a fibrous stroma are numerous small ducts (Fig. 30-70), the walls of which are lined usually by two rows of epithelial cells (Fig. 30-71). In most instances, these cells are flat. Occasionally, the cells of the inner row appear vacuolated. The lumina of the ducts contain amorphous debris (Fig. 30-71). Some of the ducts possess small,

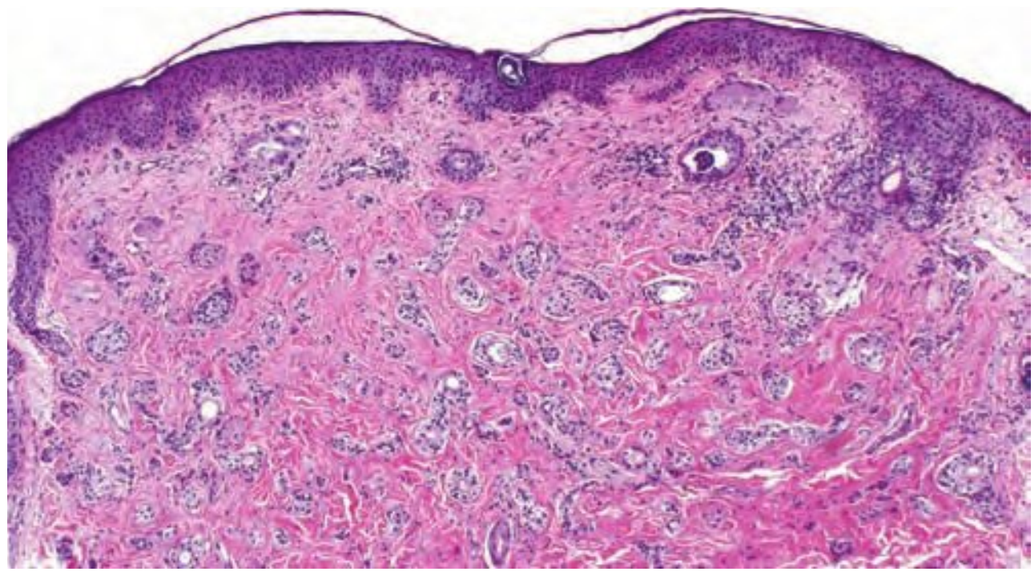


FIGURE 30-70. Syringoma. In the dermis, numerous tubular structures are embedded in a dense, collagenous stroma.

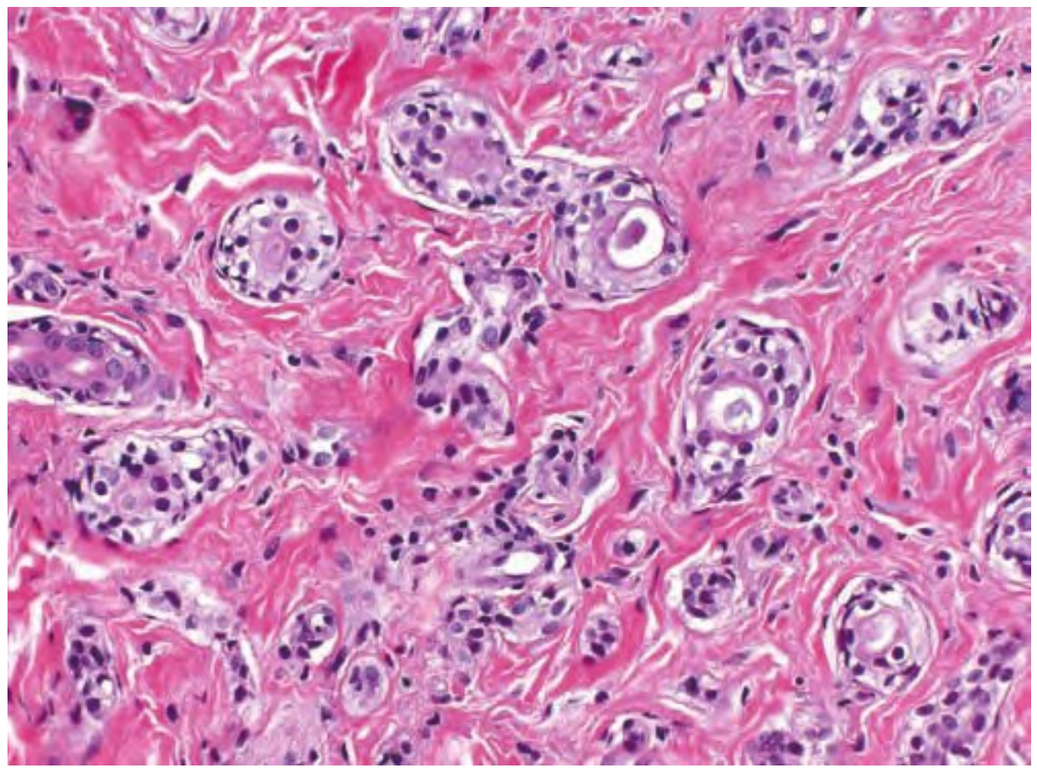


FIGURE 30-71. Syringoma. The walls of the ducts are predominantly lined by two rows of epithelial cells. Some ducts are lined by an eosinophilic cuticle, whereas others have comma-like tails. Granular eosinophilic material is seen in some ducts.

comma-like tails of epithelial cells, giving them the appearance of tadpoles. In addition, there are solid strands of basophilic epithelial cells independent of the ducts.

Near the epidermis, there may be cystic ductal lumina filled with keratin and lined by cells containing keratohyaline granules (451). These keratin cysts resemble milia. Sometimes they rupture, producing a foreign-body reaction.

In rare instances, many of the tumor cells appear as clear cells secondary to glycogen accumulation (455). Typically, one observes only a few ductal structures and epithelial cords but predominantly cell islands that are irregular in shape and size. With the occasional exception of the peripheral cell layer, these islands are usually composed entirely of clear cells and have more cell layers than are generally seen in ordinary syringomas (Fig. 30-72) (456).

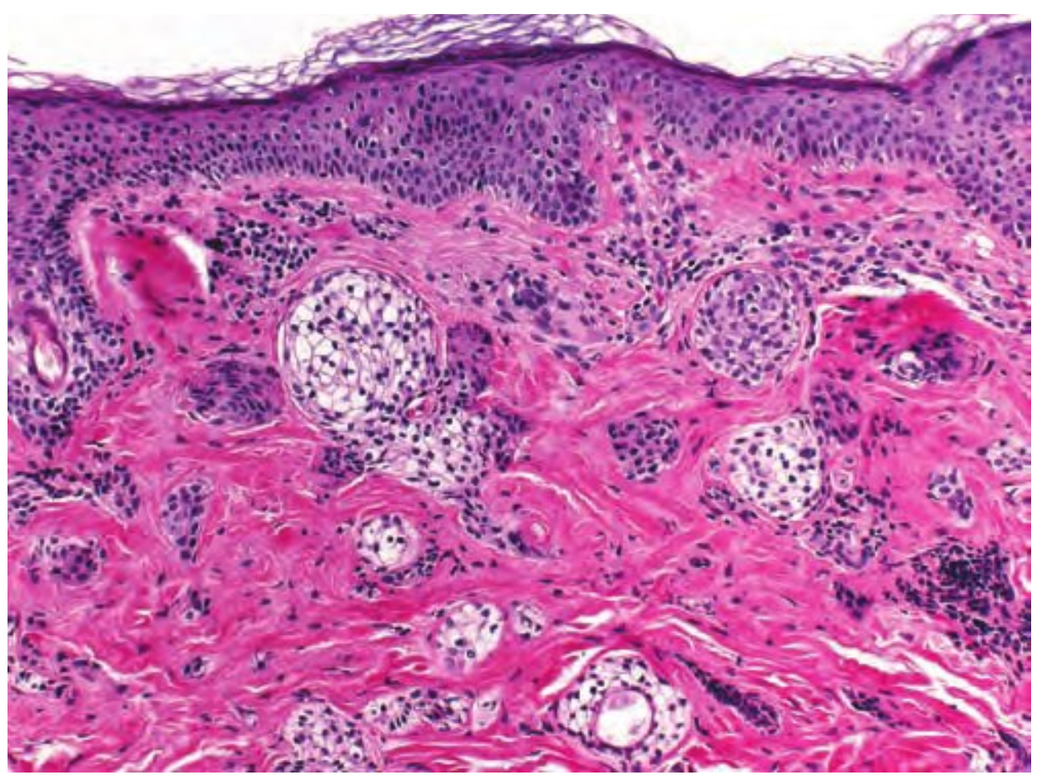


FIGURE 30-72. Clear cell syringoma. In this rare variant, the tumor islands consist largely of clear cells as a result of glycogen accumulation.

Additional Studies. Enzyme histochemical and electron microscopic studies have established syringoma as a tumor with differentiation toward intraepidermal eccrine sweat ducts (416,457). The enzyme pattern in the cells of syringoma shows a prevalence of eccrine enzymes such as succinic dehydrogenase, phosphorylase, and leucine aminopeptidase (458,459). In contrast to apocrine structures, syringomas react only weakly to lysosomal apocrine enzymes such as acid phosphatase and β-glucuronidase, except in a narrow, lysosome-rich periluminal zone (451).

Electron microscopic examination reveals that the lumina of the ducts are lined not by secretory but by ductal cells showing numerous short microvilli, interconnecting desmosomes, a periluminal band of tonofilaments, and many lysosomes. In some tumor cells, intracytoplasmic cavities are formed by lysosomal action. Coalescence of several such intracytoplasmic cavities to form an intercellular lumen is the mode by which the ductal lumina are formed in syringoma; this is identical with the mode of formation of the embryonic and the regenerating intraepidermal eccrine ducts (416,451).

The finding of cystic ductal lumina filled with keratin near the epidermis is compatible with the natural keratinizing propensity of the luminal cells of the intraepidermal eccrine sweat duct toward the upper strata of the epidermis (451).

Differential Diagnosis. The solid strands of basophilic epithelial cells embedded in a fibrous stroma seen in some cases of syringoma have an appearance similar to that of the strands seen in fibrosing basal cell carcinoma. However, fibrosing basal cell carcinoma lacks ductal structures containing amorphous material. The horn cysts near the epidermis in syringoma resemble those occurring in trichoepithelioma, and their presence in syringoma was formerly misinterpreted as the occurrence of both types of tumors within the same lesion (14). Although trichoepithelioma (including desmoplastic trichoepithelioma) shows solid strands of basophilic epithelial cells and horn cysts, it lacks ductal structures. Syringoma can be distinguished from microcystic adnexal carcinoma by its smaller size, greater symmetry, superficial dermal location, lack of prominent horn cyst formation, and infrequent single-file strand formation. In addition, microcystic adnexal carcinoma, a much larger tumor than syringoma, extends into the subcutaneous tissue (91). The diagnosis of microcystic adnexal carcinoma should always be considered in any apparently syringomatous or trichoepitheliomatous neoplasm that extends to the base of a superficial biopsy.

Eccrine Poroma

Initially described in 1956, eccrine poroma is a fairly common solitary tumor (460). In about two thirds of the cases, it is found on the sole or the sides of the foot, occurring next in frequency on the hands and fingers (461). Eccrine poroma has also been observed in many other areas of the skin, such as the neck, chest, nose, and eyelid (462–465). Eccrine poroma generally arises in middle-aged persons. The tumor has a rather firm

consistency, is raised, is asymptomatic, is often slightly pedunculated, and usually measures less than 2 cm in diameter.

An unusual clinical variant is *eccrine poromatosis*, in which more than 100 papules are observed on the palms and soles (466). In one reported case, the papular poromas, in addition to involving the palms and soles, showed a widespread, diffuse distribution (467).

Histopathology. In its typical form, eccrine poroma arises within the lower portion of the epidermis and it extends downward into the dermis as tumor masses that often consist of broad, anastomosing bands of epithelial cells (Fig. 30-73). The border between epidermis and tumor is readily apparent because of the distinctive appearance of the tumor cells: They are smaller than epidermal keratinocytes, have a uniform cuboidal appearance and a round, deeply basophilic nucleus, and are connected by intercellular bridges (Fig. 30-74). The lesional cells tend not to keratinize within the tumor, but they are able to keratinize on the surface of the tumor in instances in which the tumor has replaced the overlying epidermis. Although the border between tumor formations and the stroma is sharp, tumor cells located at the periphery show no palisading.

Characteristically, the tumor cells contain significant amounts of glycogen, which is associated with cytoplasmic clearing, usually in an uneven distribution (468). Melanocytes and melanin often are absent, although they may be present in tumors of individuals from various racial backgrounds (469–471).

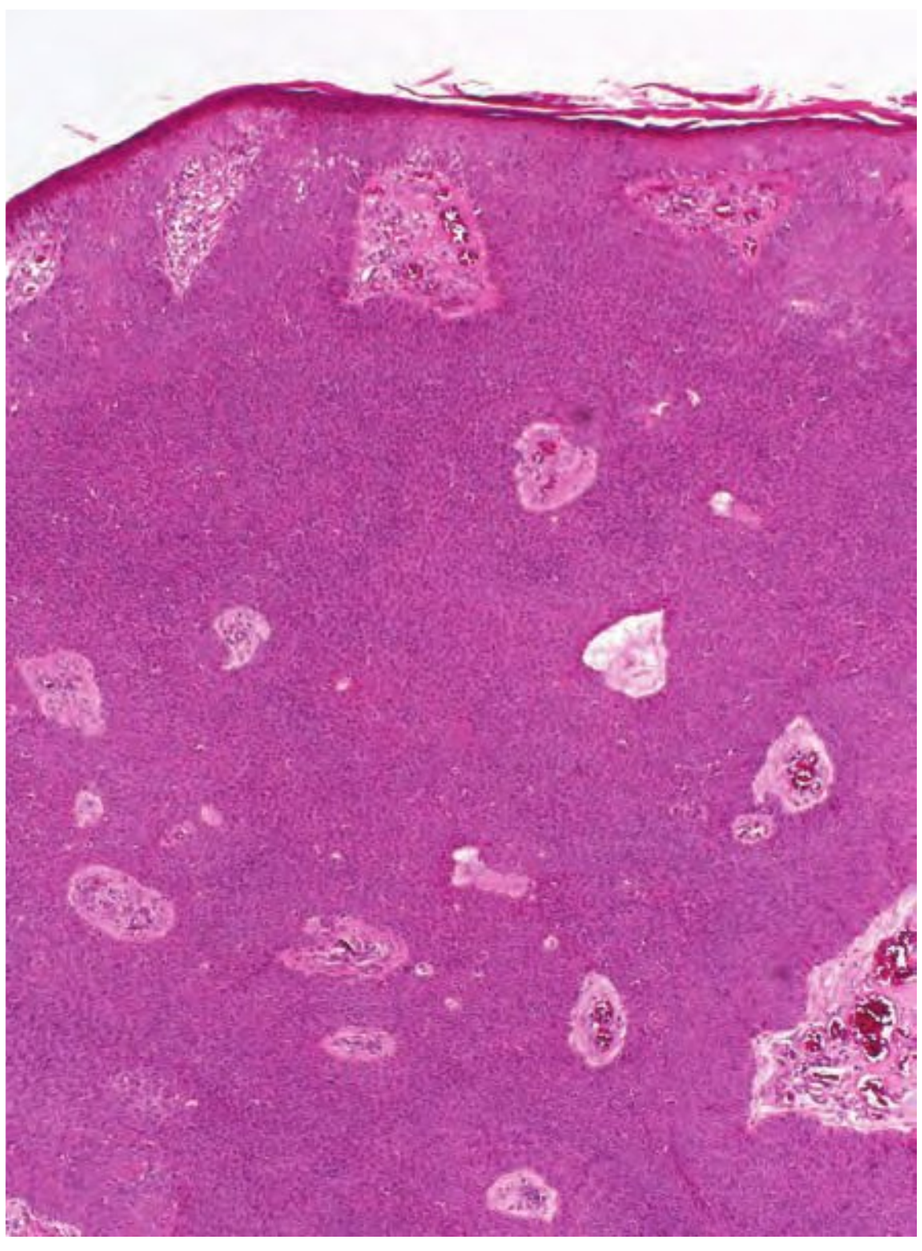


FIGURE 30-73. Eccrine poroma. The tumor consists of broad, anastomosing bands emanating from the epidermis.

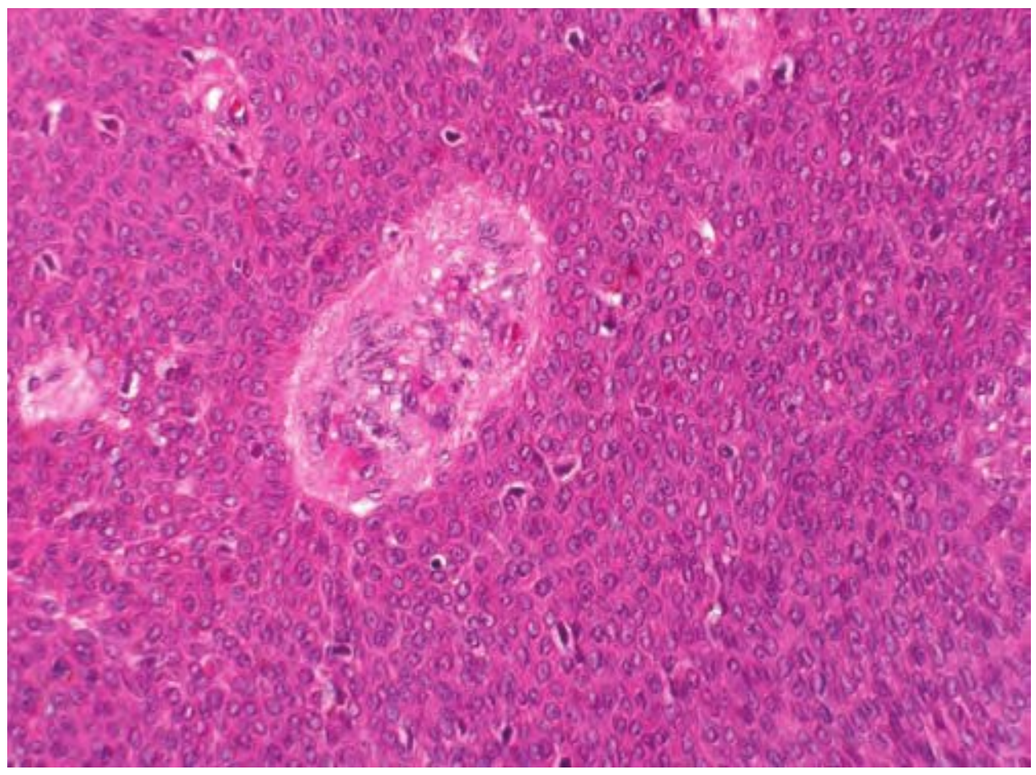


FIGURE 30-74. Eccrine poroma. The cells comprising the tumor have a uniformly small cuboidal appearance and are connected by intercellular bridges. The tumor vessels demonstrate a hyalinized stroma.

In a majority of eccrine poromas, narrow ductal lumina and occasionally cystic spaces are found within the tumor bands (468). They are lined by an eosinophilic, PAS-positive, diastase-resistant cuticle similar to that lining eccrine sweat ducts.

Poromas can be situated entirely within the epidermis, where the lesion appears as a number of distinct cellular aggregates. Such intraepidermal poromas were first described under the designation *hidroacanthoma simplex*, about the same time at which poroma was first described (Fig. 30-75) (472,473). These lesions represent one example of the so-called Borst-Jadassohn phenomenon of intraepithelial epitheliomas. A few ductal lumina lined by an eosinophilic cuticle can often be seen within the intraepidermal islands (474). Eccrine poromas may

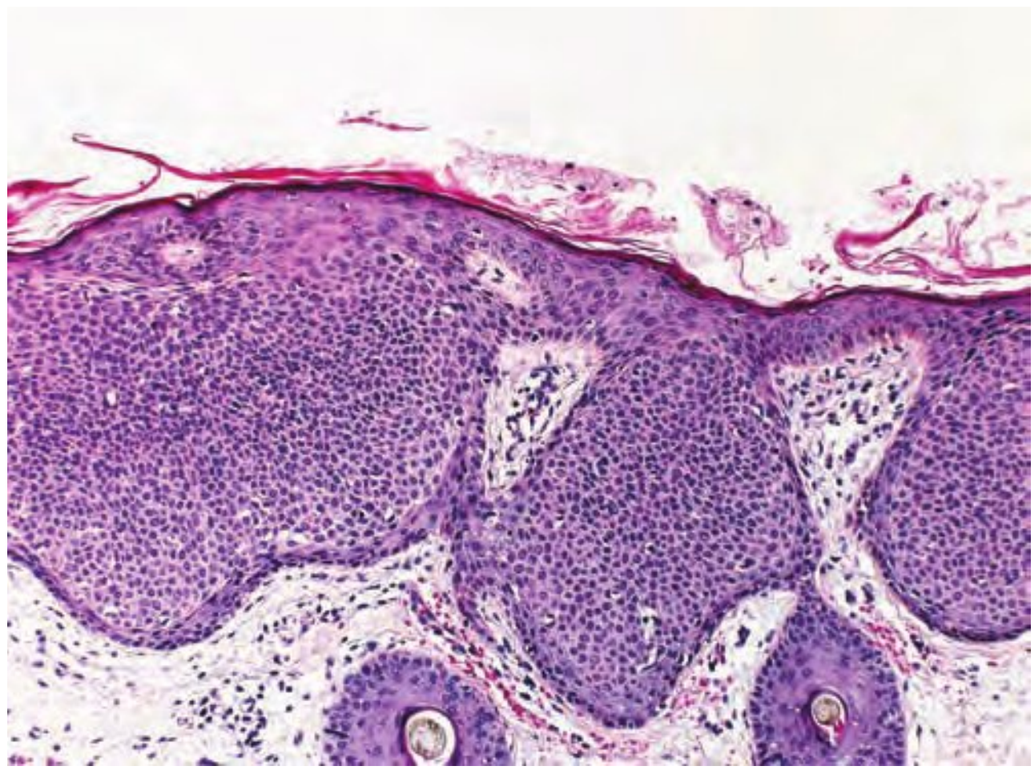


FIGURE 30-75. Hidroacanthoma simplex. There are discrete aggregates of poral cells in the epidermis, constituting one example of the so-called Borst-Jadassohn phenomenon of intraepithelial epitheliomas.

also be located largely or entirely within the dermis, where they consist of variously shaped tumor islands containing ductal lumina; these lesions are referred to as *dermal duct tumors* (475).

Syringoacanthoma of Rahbari represents a clonal variant of eccrine poroma in which variously sized nests of small, deeply basophilic, ovoid or cuboidal sweat duct–like cells are embedded within an acanthotic epidermis (476).

Additional Studies. Enzyme histochemical staining has shown the prevalence of eccrine enzymes in eccrine poromas, particularly phosphorylase and succine dehydrogenase (475,477,478).

Electron microscopic examination reveals that the tumor cells, except for the luminal cells, contain a moderate number of tonofilaments, are connected with each other by desmosomes, and appear identical to the cells that compose the outer layer of the intraepidermal eccrine duct (poral epithelial cells) (477). The luminal cells show a periluminal filamentous zone and, extending into the lumen, numerous tortuous microvilli coated with amorphous material that forms the eosinophilic cuticle seen by light microscopy. Some of the tumor cells may also exhibit features considered indicative of dermal duct differentiation (416,479).

Differential Diagnosis. Eccrine poroma must be differentiated from basal cell carcinoma and seborrheic keratosis. In basal cell carcinoma, the cells have no visible intercellular bridges, are more variable in size, often show peripheral palisading, and contain little or no glycogen. The cells of eccrine poroma greatly resemble the small basaloid cells of seborrheic keratosis, especially because they possess clearly visible intercellular bridges. However, seborrheic keratoses have an even demarcation at their lower border; moreover, their cells have the potential to keratinize, and when they keratinize, they form pseudo–horn cysts. In addition, both basal cell carcinoma and seborrheic keratosis lack ductal lumina lined with an eosinophilic cuticle. Furthermore, these two types of tumors very rarely occur on the sole of the foot.

Malignant Eccrine Poroma (Porocarcinoma)

Malignant eccrine poroma, or porocarcinoma, may arise *de novo* (480,481); however, it usually develops in a longstanding eccrine poroma (471,482–484). The tumor favors extremities, particularly legs and feet, usually in adults of either sex. In some instances, the malignant eccrine poroma is localized, manifesting itself as a nodule, plaque, or ulcerated tumor (481,482,484,485); in other cases, there are multiple cutaneous metastases, which are usually associated with visceral metastases, resulting in death (471,483–485). The propensity to form multiple cutaneous metastases is an unusual feature of malignant eccrine poroma.

Histopathology. Malignant eccrine poroma may be seen associated with an eccrine poroma or hidroacanthoma simplex (482,484). In such cases, one observes areas composed of eccrine poroma cells with a benign appearance adjacent to areas of anaplastic cells. The malignant cells have large, hyperchromatic, irregularly shaped nuclei and may be multinucleated (Figs. 30-76 and 30-77) (484). Lesional cells are rich in glycogen (480).



FIGURE 30-76. Porocarcinoma. Large islands of tumor cells are seen, many with central necrosis.

In the primary tumor, the malignant cells may be limited to the epidermis or may extend into the dermis (Fig. 30-76). Some islands of tumor cells may lie free in the dermis. The epidermis often shows considerable acanthosis as a result of the proliferation of numerous well-defined tumor cell nests within it. Cystic lumina may be seen within the epidermal and dermal tumor nests. The tumors are asymmetric, with cords and lobules of polygonal tumor cells, typically with a cribriform pattern. Nuclear atypia is evident, with frequent mitoses and necrosis

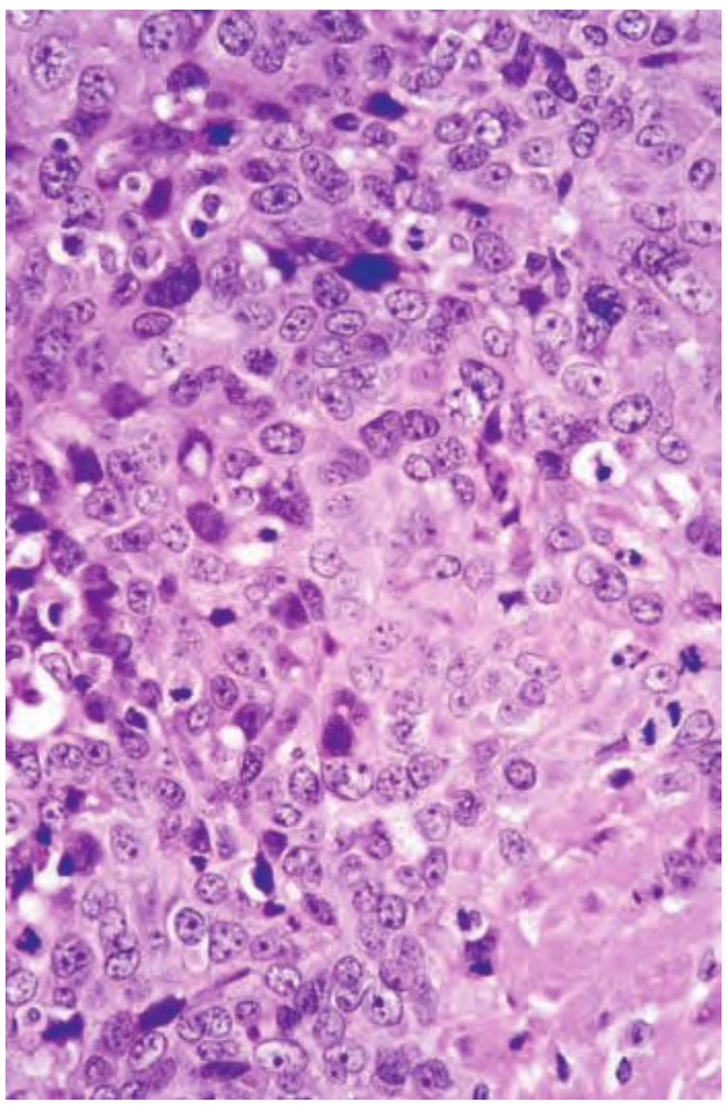


FIGURE 30-77. Porocarcinoma. Lesional cells demonstrate marked atypia, mitotic activity, and necrosis.

(Fig. 30-77). Useful clues to eccrine differentiation include spiraling ductular structures, ducts lined by cuticular material, zones of cytoplasmic glycogenation, and also intraepidermal cells in discrete aggregates, often centered on acrosyringeal pores. Foci of squamous differentiation may resemble well-differentiated squamous cell carcinoma (486). The stroma may be fibrotic, hyalinized, highly myxoid, or frankly mucinous. The distinction from metastatic adenocarcinoma, especially of breast and lung origin, can be difficult, especially for less differentiated tumors. Ductular differentiation with formation of a PAS-positive cuticle is strong evidence against a metastasis. An extracutaneous primary adenocarcinoma should be clinically ruled out.

The term *ductal eccrine carcinoma* has been used to refer to tumors that may appear in the dermis as an infiltrative poroma (porocarcinoma) or as a moderately differentiated adenocarcinoma (487). About one third of ductal eccrine carcinomas are fatal, usually because of distant metastasis (488).

Malignant eccrine poroma, analogous to its benign variant, can show a clonal ("intraepithelial epithelioma") pattern of its anaplastic acrosyringeal cells. The intraepidermal clones of such *malignant syringoacanthomas* may remain *in situ* or become invasive (476).

In cutaneous metastases, numerous nests of tumor cells may be present in both the epidermis and the dermis. In the epidermis, sharply defined small and large nests of tumor cells are seen surrounded by the squamous cells of the hyperplastic epidermis, resulting in a "pagetoid" pattern (471,480). Some of the tumor nests in the dermis are located within dilated lymphatic vessels, suggesting spread of the tumor in the lymphatics of the skin (480). From the lymphatics, the tumor cells invade the overlying epidermis because of the "epidermotropic" nature of the tumor cells.

Eccrine Syringofibroadenoma

First described in 1963, this usually is a solitary, hyperkeratotic, nodular plaque, several centimeters in diameter, on one extremity (489–491). Eccrine syringofibroadenoma and acrosyringeal nevi have many similarities, and some researchers, but not all, consider them to be equivalent lesions (489–493). In one instance, a linear lesion has been reported to extend along a lower extremity (494). Eccrine syringofibroadenomatosis has been associated with inherited palmar-plantar keratodermas, including hidrotic ectodermal dysplasia and Schopf's syndrome (495–497). Carcinomatous transformation of these lesions is rare but has been reported (498,499).

Histopathology. Slender, anastomosing epithelial cords of acrosyringeal cells, with or without formation of lumina, are embedded in a fibrovascular stroma (Figs. 30-78 and 30-79) (490). The netlike pattern of epithelial cells resembles that seen in fibroepithelioma (494). Lesions demonstrating prominent clear cell change have been described (500,501).

Additional Studies. Immunohistochemical studies and electron microscopy studies provide evidence for acrosyringeal differentiation in eccrine syringofibroadenomas (502–506).

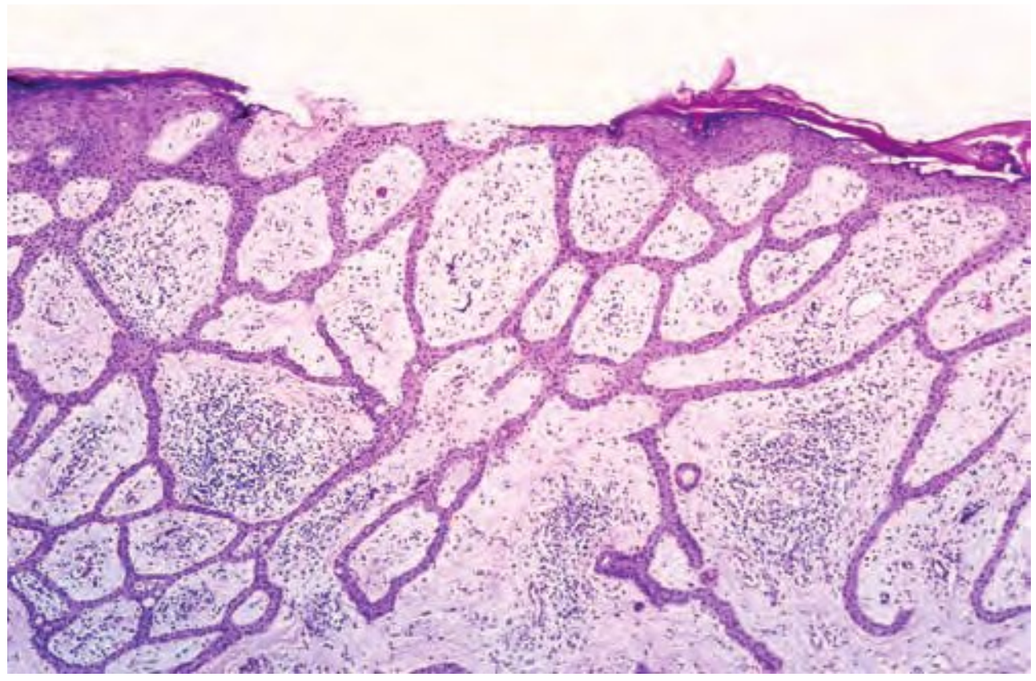


FIGURE 30-78. Eccrine syringofibroadenoma. The tumor is composed of thin, anastomosing epithelial cords associated with a fibrous stroma.

Mucinous Syringometaplasia

A rare condition first described in 1974, mucinous syringometaplasia occurs as a solitary lesion in two different forms: as a verrucous lesion in an acral location on the sole of a foot or a finger and as a plaque resembling a basal cell carcinoma in a more central location (312,507,508). With pressure, serous fluid can often be expressed (312).

Histopathology. An invagination lined by squamous epithelium extends into the dermis. One or several eccrine ducts lead into the invagination. They are lined in part by mucin-laden goblet cells (312). In addition, there may be mucinous metaplasia in the underlying eccrine coils (508,509). The epithelial mucin is PAS positive and Alcian blue reactive, suggesting that it is sialomucin.

Eccrine Spiradenoma

Eccrine spiradenoma usually occurs as a solitary intradermal nodule measuring 1 to 2 cm in diameter. Occasionally, there

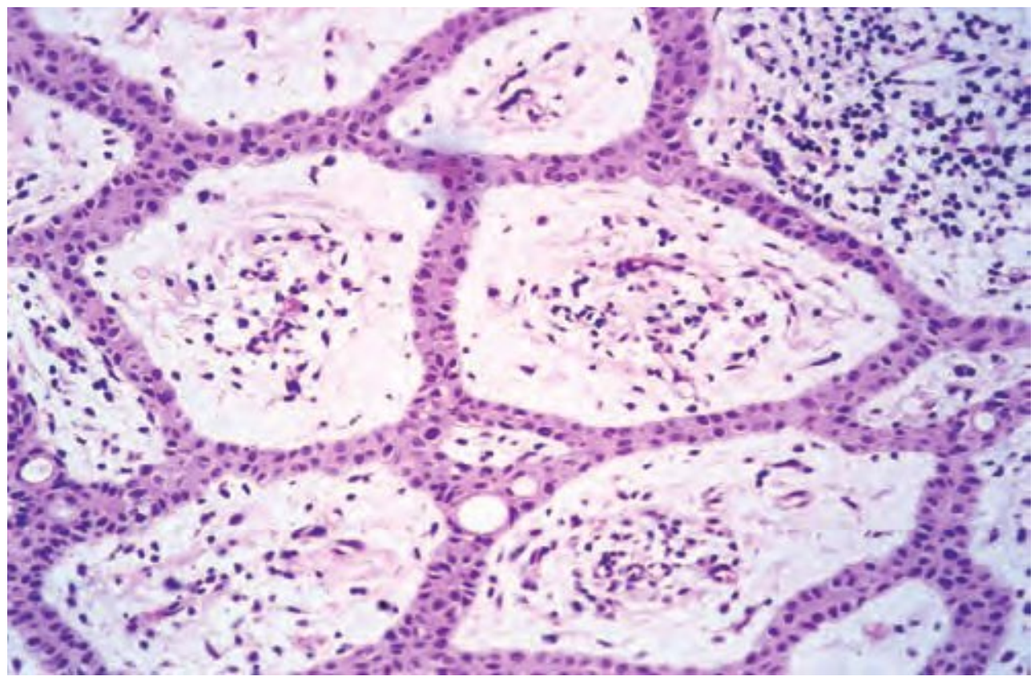


FIGURE 30-79. Eccrine syringofibroadenoma. The epithelial strands are comprised of mature acrosyringeal cells, which may form lumina and are embedded in a fibrovascular stroma.

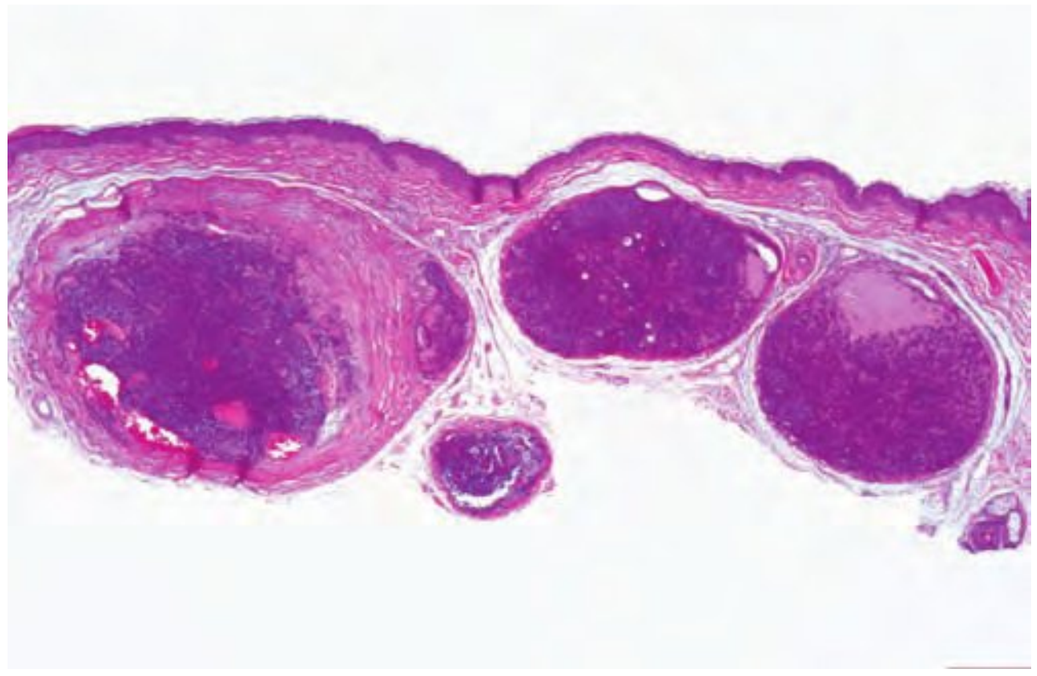


FIGURE 30-80. Eccrine spiradenoma. Well-circumscribed aggregates of blue tumor cells are seen in the dermis.

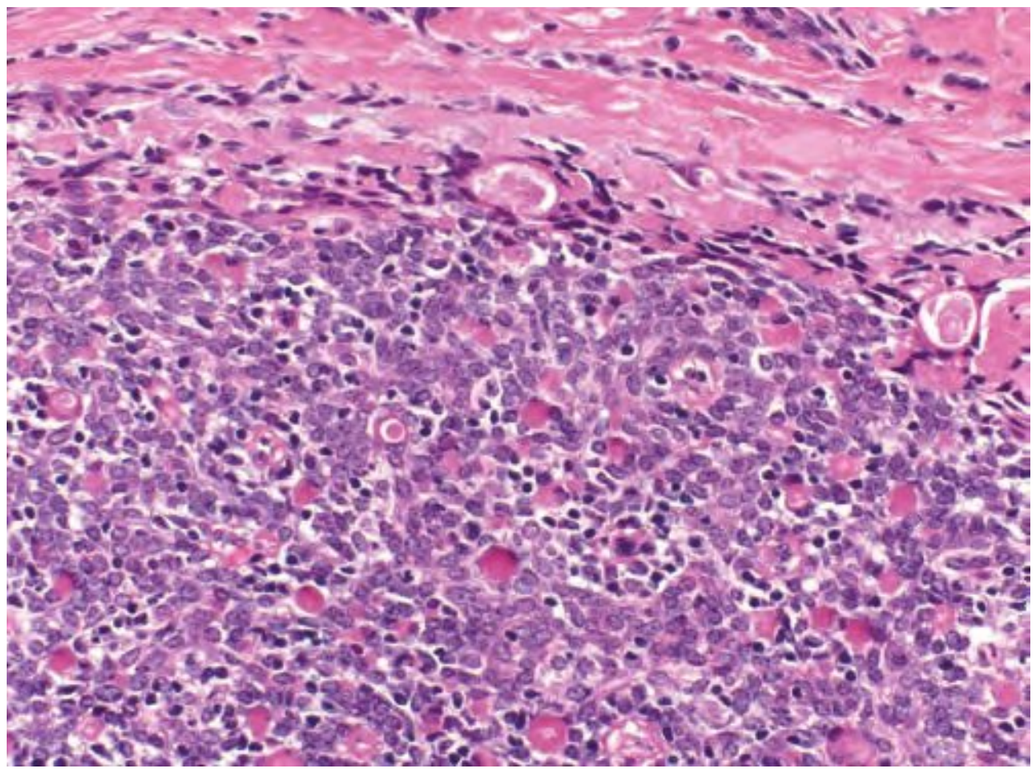


FIGURE 30-81. Eccrine spiradenoma. The epithelial cells are arranged in intertwining bands. Two types of cells can be seen. Cells with small, dark nuclei lie at the periphery of the bands; they represent undifferentiated cells. Cells with large, pale nuclei lie in the center of the bands and around small lumina. Collections of hyalinized material are seen.

are several lesions, and, rarely, there are numerous small nodules in a zosteriform pattern or large nodules, up to 5 cm, in a linear arrangement (510–513). In most instances, eccrine spiradenoma arises in early adulthood. Lesions can arise in a variety of locations, and the nodules are often tender and occasionally painful.

Histopathology. The tumor may consist of one large, sharply demarcated lobule, but more commonly there are several lobules located in the dermis without connections to the epidermis (Fig. 30-80). The lobules are evenly and sharply demarcated and may display a fibrous capsule (514). On low magnification, the tumor lobules often appear deeply basophilic because of the dense packing of nuclei.

On higher magnification, the epithelial cells within the tumor lobules are found to be arranged in intertwining cords (515,516). These cords may enclose small, irregularly shaped islands of edematous connective tissue (517). Two types of epithelial cells are present in the cords, both of which possess only scant amounts of cytoplasm (Fig. 30-81). The cells of the first type possess small, dark nuclei; they are generally located at the periphery of the cellular aggregates. The cells of the second type have large, pale nuclei; they are located in the center of the aggregates and may be arranged partially around small lumina observed in about half of the tumors (514). The lumina frequently contain small amounts of a granular, eosinophilic material that is PAS positive and diastase resistant (515). In the absence of lumina, the cells with pale nuclei may show a rosette arrangement. Glycogen is absent in the tumor cells or is present in insignificant amounts.

In some cases of eccrine spiradenoma, hyaline material is focally present in the stroma that surrounds the cords of tumor cells (Fig. 30-81). In addition, hyalin may be seen within some of the cords among the tumor cells as hyaline droplets (515). The stroma surrounding the tumor lobules occasionally shows lymphedema with dilated blood vessels or lymphatics (515). A heavy diffuse lymphocytic infiltrate, mainly of T cells, may be present (518). Malignant progression can occur but is rare.

Additional Studies. Enzyme histochemical staining has revealed a prevalence of eccrine enzymes in eccrine spiradenoma, but the reactions are not as strong as in syringoma or eccrine poroma (512,517,519).

Electron microscopic examination, similar to light microscopic examination, has shown two types of cells: undifferentiated basal cells with small, dark nuclei, and differentiating cells with large, pale nuclei. Most of the differentiating cells are immature ("indeterminate cells") and, in some tumors, may show no further differentiation (517). In most instances, however, there is some degree of differentiation toward intradermal eccrine ductal cells or toward eccrine secretory cells. Around the same lumen, some cells may show numerous microvilli and a well-developed periluminal zone of tonofilaments and thus resemble ductal cells, whereas other cells have only a few thin microvilli and thus resemble secretory cells (416,512). All secretory cells demonstrate features of serous cells (clear cells) (520). A few myoepithelial cells with typical myofilaments are present occasionally at the periphery of tubular structures (512).

Eccrine spiradenoma exhibits features of both the dermal duct and the secretory segment of the eccrine sweat gland. However, the weakness and inconsistency of the enzyme histochemical reactions, the presence largely of undifferentiated and indeterminate cells, and the absence of dark mucus cells indicate a rather mild degree of differentiation. Immunohistochemical studies for cytokeratins demonstrate that the large, pale epithelial cells expressed keratins similar to those of luminal cells in the transitional portions between the secretory portions and the coiled ducts (521). The small, dark cells expressed cytokeratins similar to the basal cells in the transitional portions of the eccrine gland.

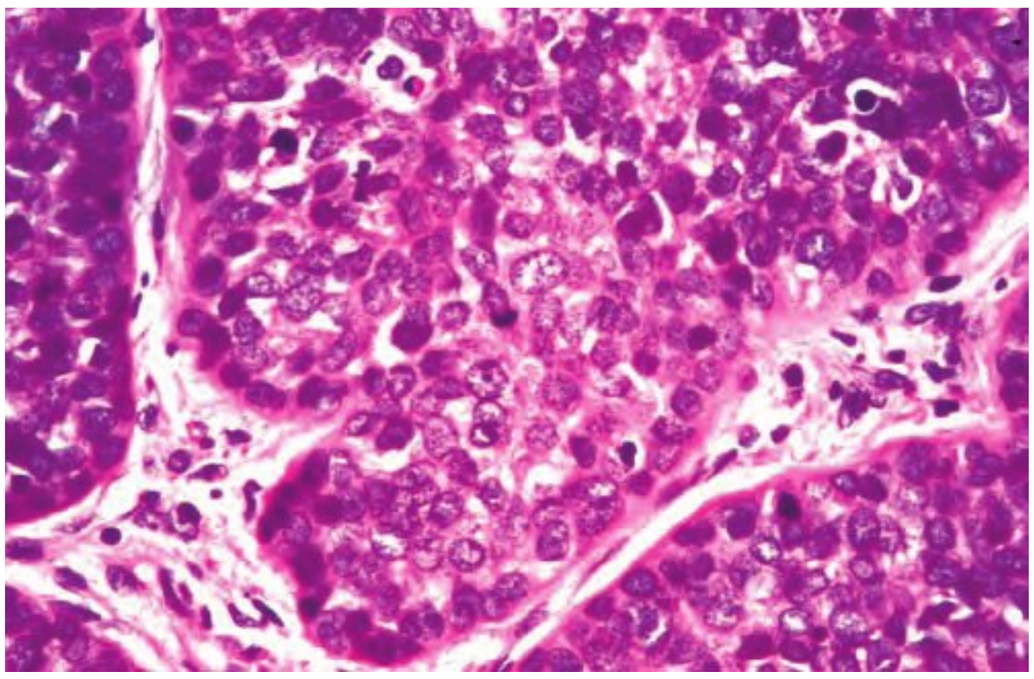


FIGURE 30-82. Malignant eccrine spiradenoma. Lesional cells demonstrate marked atypia with a predominance of larger atypical cells. Cellular necrosis and mitotic activity are seen.

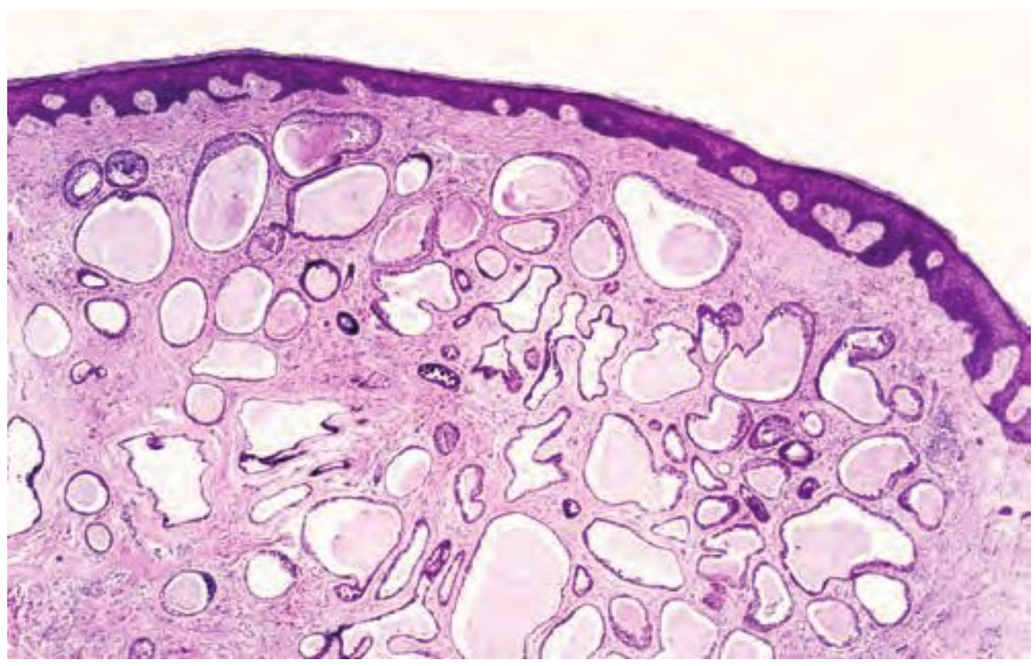


FIGURE 30-83. Papillary eccrine adenoma. The tumor is well circumscribed and symmetric and consists of dilated, occasionally branching tubular structures.

Malignant Eccrine Spiradenoma

Occasionally, malignant degeneration occurs in eccrine spiradenomas; usually such lesions have been present for years (429,522,523). However, malignant transformation of spiradenomas has been reported in lesions with a clinical history as short as 7 months (524). Metastases can occur; fortunately, few patients die of generalized metastases (523–525). Regional lymph node metastasis has been reported (524,526). Notable clinical features may include a history of enlargement in a previously stable lesion.

Histopathology: In malignant lesions, two distinct components typically are seen: benign eccrine spiradenoma and carcinomatous regions associated with areas of transitions (524,526). However, lesions consisting of well-demarcated zones of spiradenoma and spiradenocarcinoma have also been described (524). The carcinomatous lesion may display glandular formation, squamous differentiation, sarcomatous change, or no evidence of differentiation (524,526–530). Although mitoses may be seen in benign eccrine spiradenomas, malignant spiradenomas usually show a high mitotic rate (Fig. 30-82) (524,526). Other histologic features indicative of malignancy include the loss of two cell populations, increased nuclear-to-cytoplasmic ratio, and hyperchromasia (Fig. 30-82) (524). Because the malignant changes may be focal in a benign spiradenoma, the malignancy may be missed if the specimen is inadequately sampled (531).

Papillary Eccrine Adenoma

Papillary eccrine adenoma is a benign tumor that exhibits prominent eccrine differentiation and architectural features similar to tubular apocrine adenoma. First described in 1977, it occurs most commonly on the distal portions of the extremities as a small, solitary nodule (532).

Histopathology: As in tubular apocrine adenoma, the tumor comprises a well-circumscribed, symmetric collection of dilated, occasionally branching tubular structures lined by two layers of epithelial cells (Figs. 30-83 and 30-84). Papillary projections extend into the lumina (532). The ducts may contain amorphous eosinophilic material (Fig. 30-83) (533). However, evidence of decapitation secretion is lacking (387). Small microcysts representing dilated ducts may be present (387,534–537). The low-power impression may suggest a benign breast lesion, such as intraductal hyperplasia, especially when, as is characteristic, the tumor is located within the superficial and deep dermis and is not continuous with the overlying epidermis. Amorphous and granular eosinophilic secretions are present in many of the duct lumens, and occasionally there are small, keratin-filled cysts. Adenomatous regions present variably spaced ducts and glands lined by one to several layers of cuboidal epithelium. The presence of a dense fibrovascular stromal tissue distinguishes this lesion from dermal endometriosis, which has a more cellular stroma. The tumor may recur locally but does not metastasize systemically.

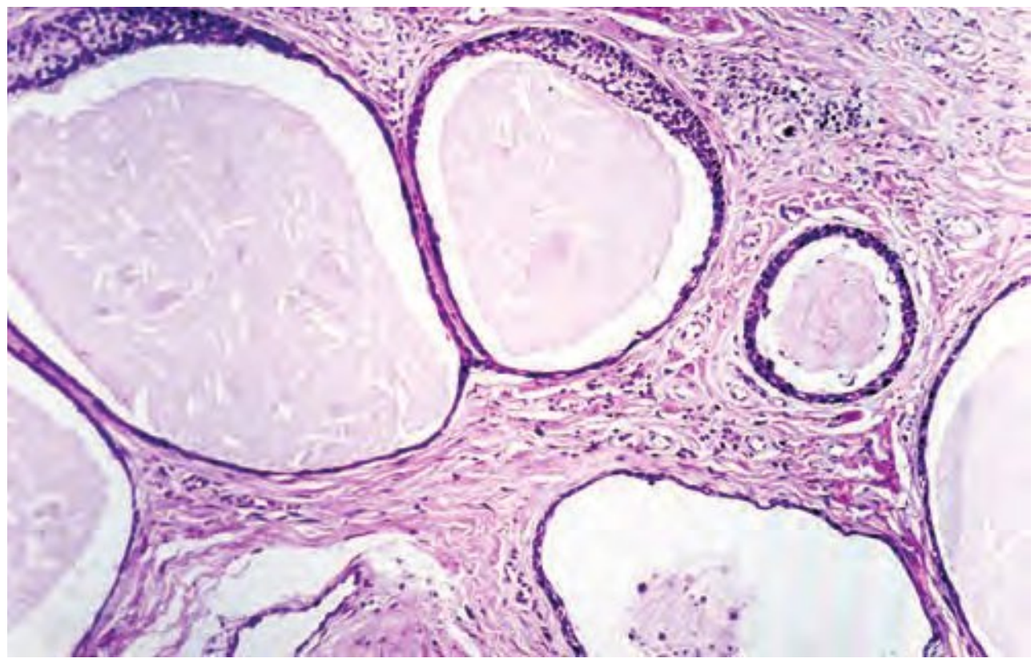


FIGURE 30-84. Papillary eccrine adenoma. The dilated tubular structures are lined by two layers of cells and contain amorphous eosinophilic material.

Additional Studies. The amylophosphorylase reaction indicates eccrine differentiation is prominent, but the reaction with acid phosphatase, an apocrine enzyme, shows practically no staining in the tumor (387). Immunoreactivity for S100 protein, CEA, and EMA is typically present, consistent with differentiation toward the secretory epithelium of sweat glands (533,536,537).

Nodular Hidradenoma

Nodular hidradenoma is a fairly common cutaneous neoplasm that has been referred to as *clear cell myoepithelioma*, *clear cell hidradenoma*, *eccrine sweat gland adenoma of the clear cell type*, *solid cystic hidradenoma*, and *eccrine acrospiroma* (519,538–543). Nodular hidradenoma can arise in a variety of anatomic sites.

Nodular hidradenoma exhibits eccrine differentiation based on its enzyme histochemical and electron microscopic features (544). The tumor is usually solitary; however, on rare occasions, multiple lesions have been reported (544). The tumors present as intradermal nodules and in most instances measure between 0.5 and 2.0 cm in diameter, although they may be larger. They are usually covered by intact skin, but some tumors show superficial ulceration and discharge serous material (542). Although clinically the tumor only rarely gives the impression of being cystic, gross examination of the specimen often reveals the presence of cysts (540,543).

Histopathology. The tumor is well circumscribed and may appear encapsulated. It is composed of epithelial lobules located in the dermis, which may extend into the subcutaneous fat. Within the lobulated masses, tubular lumina of various sizes are often present (Figs. 30-85 and 30-86). However, such lumina may be absent or few in number, so that step sectioning is needed to find them. The tubular lumina in some instances are branched. There are often cystic spaces, which may be of considerable size and contain a faintly eosinophilic, homogeneous material (Fig. 30-85) (542). The tubular lumina are lined by cuboidal ductal cells or by columnar secretory cells. Occasionally, the secretory cells show active secretion suggestive of decapitation secretion (540,544). The wide cystic spaces are only rarely lined by a single row of luminal cells; more frequently, they are bordered by tumor cells that show no particular orientation and occasionally show degenerative changes (540). This suggests that the cystic spaces may result from tumor cell degeneration.

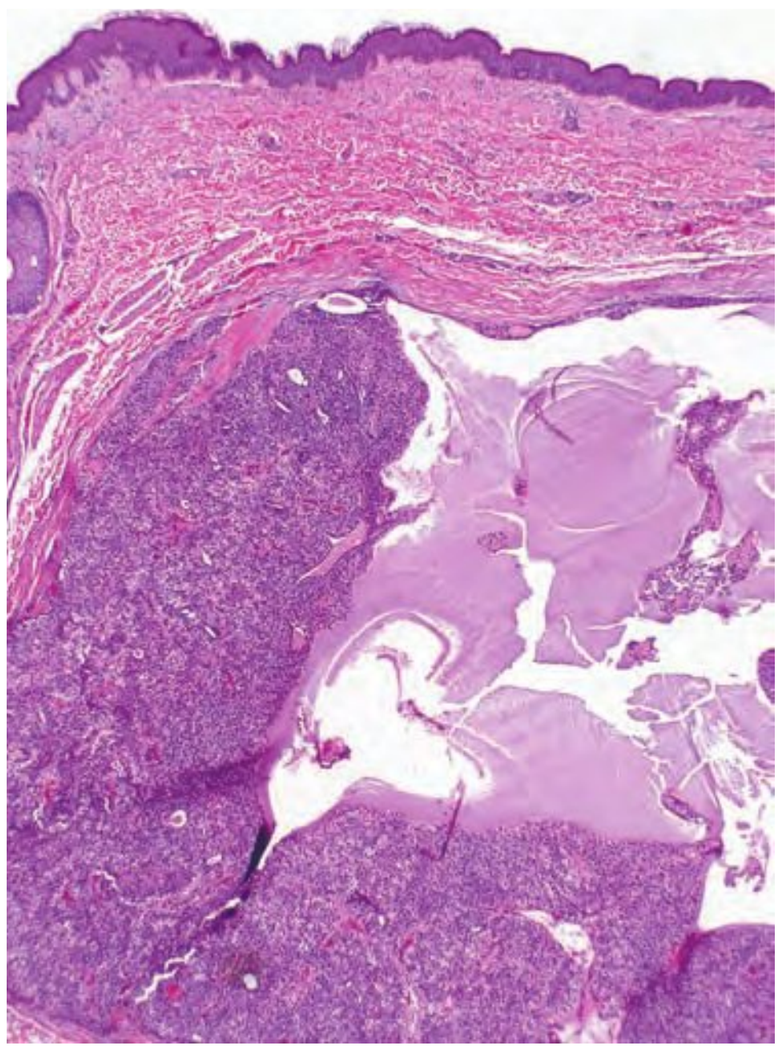


FIGURE 30-85. Nodular hidradenoma. Multiple lobules of lesional cells are present in the dermis. Focal cystic change is seen.

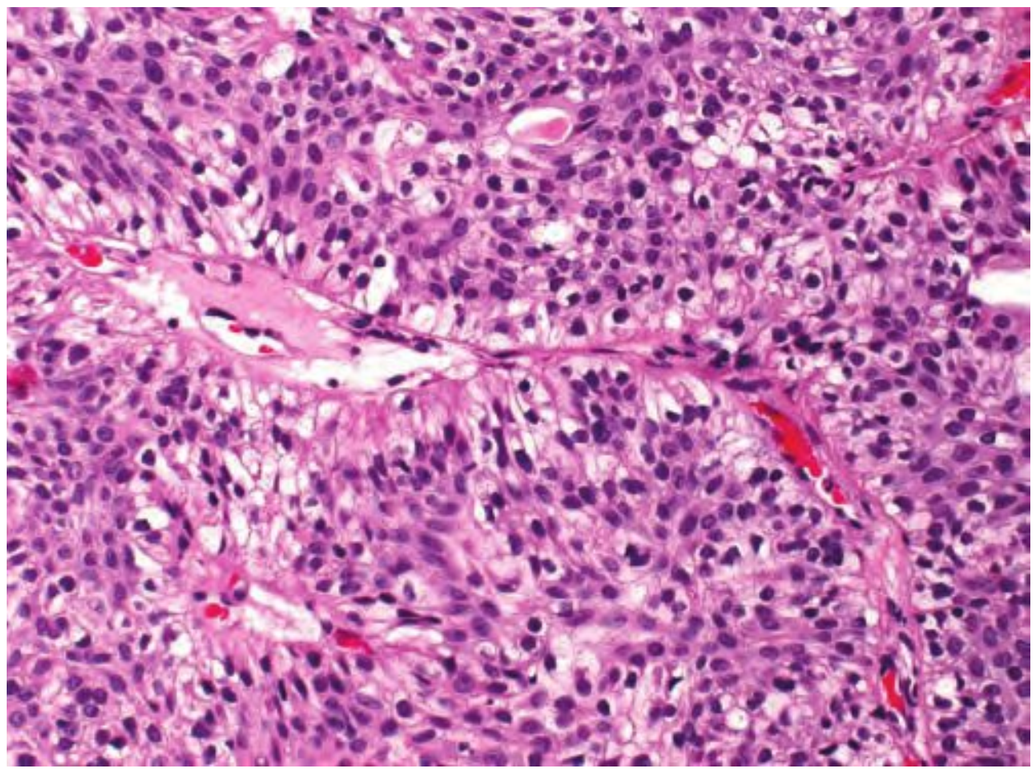


FIGURE 30-86. Nodular hidradenoma. The tumor comprises clear and polygonal cells, some of which appear fusiform. Foci of eosinophilic material and small ductal lumina are seen.

In solid portions of the tumor, two types of cells can be recognized (540,542,545,546). The proportion of these two types of cells varies considerably from tumor to tumor. One cell type is polyhedral with a rounded nucleus and slightly basophilic cytoplasm. These cells may appear fusiform and show an elongated nucleus (Fig. 30-85). Another cell type is usually round and contains very clear cytoplasm, so that the cell membrane is distinctly visible; the cell nucleus appears small and dark (Fig. 30-85). There also are cells with features of both varieties; these cells usually show a rather light, eosinophilic cytoplasm. The clear cells contain considerable amounts of glycogen, but they may show, in addition, significant amounts of PAS-positive, diastase-resistant material along their periphery (545). In some tumors, squamoid differentiation is seen, with the cells appearing large and polyhedral and showing eosinophilic cytoplasm (Fig. 30-86) (547). There even may be keratinizing cells with formation of horn pearls (Fig. 30-86) (540,541). In other tumors, groups of squamous cells are arranged around small lumina that are lined with a well-defined eosinophilic cuticle and thus resemble the intraepidermal portion of the eccrine duct (543,545).

In most cases, no connections of the tumor lobules with the surface epidermis are noted; however, in some instances, the

tumor replaces the epidermis centrally and merges with the acanthotic epidermis at the periphery of the tumor (540,541,543). The tumor nodules are frequently associated with foci of a characteristic eosinophilic hyalinized stroma (Fig. 30-86).

Additional Studies. The polyhedral and fusiform cells, because of their location peripheral to the luminal cells and because of their shape, were originally regarded as cells exhibiting myoepithelial differentiation (540,544). However, the absence of alkaline phosphatase and, ultrastructurally, of myofilaments has disproved their relationship to myoepithelial cells.

Enzyme histochemical staining has established the presence in nodular hidradenoma of high concentrations of eccrine enzymes, particularly phosphorylase and respiratory enzymes, including succinic dehydrogenase and diphosphopyridine nucleotide diaphorase (519,546). Immunohistochemical reactivity for keratin, EMA, CEA, S100 protein, and vimentin is characteristic (548).

Electron microscopy has demonstrated tonofilaments in the polyhedral and fusiform cells and an abundance of glycogen in the clear cells. These tumor cell types resemble those of eccrine poroma and those that compose the outer layers of the intraepidermal eccrine duct (546). In addition, four types of luminal cells can be recognized: a secretory type, dermal-ductal and epidermal-ductal types, and an immature type (546). It can be concluded that nodular hidradenoma shows differentiation toward intraepidermal and intradermal eccrine structures ranging from the poral epithelium to the secretory segment (538,546). Thus, ultrastructurally, nodular hidradenoma seems to be intermediate between eccrine poroma, with its largely intraepidermal ductal differentiation, and eccrine spiradenoma, with its dermal-ductal and secretory differentiation. From this point of view, the clear cells represent immature poral epithelial cells, and the horn-pearl formation can be regarded as the keratinization of poral epithelial cells.

Differential Diagnosis. Nodular hidradenoma shares with trichilemmoma the presence of clear cells rich in glycogen. Foci of keratinization may also be found in both. However, only nodular hidradenoma usually shows the presence of large cystic spaces and of tubular lumina, and only trichilemmoma shows peripheral palisading of its tumor cells.

Although tumor nuclei may be hyperchromatic and there may be coarsely clumped chromatin, marked pleomorphism and frequent or atypical mitoses are not observed. If such changes are present, the tumor should be considered to have a potential for aggressive behavior. Zonal or diffuse patterns of necrosis also suggest malignancy, but the most important indicator of malignancy is an infiltrative, poorly circumscribed, and asymmetric perimeter.

Nodular hidradenomas may occasionally reform after local excision. Associated distortion and fibrosis may impede the diagnostic interpretation when the histology of the primary lesion is unknown or unavailable. Lesions that have frequent mitoses or nuclear atypia but lack clear evidence of asymmetric invasive growth may be termed atypical, and a reexcision to ensure their complete removal may be contemplated.

Malignant Nodular Hidradenoma

Malignant nodular hidradenomas, also known as hidradenocarcinomas, are rare and usually malignant from their inception; however, malignant lesions may arise from benign nodular hidradenomas (549,550). Malignant nodular hidradenomas usually present as a solitary nodule on the head, trunk, or distal extremity. Most reported cases are in patients older than 50 years of age, though they may occur at any age. These lesions tend to metastasize, and they may cause death. Although there is insufficient evidence in the literature, the recurrence rate may be estimated at about 50%, and the metastasis rate is about 60%, including metastases to regional nodes, bone, viscera, and skin (550–554).

Histopathology. Whereas nodular hidradenomas are typically well demarcated, malignant nodular hidradenomas are usually larger, asymmetric, and show invasion into the surrounding tissue (Fig. 30-87). In addition, there may be angiolymphatic invasion (555). Mitoses are usually easily detected, and some may be atypical. Tumor necrosis, areas of high cellularity, and focal or diffuse areas of marked cytologic atypia in which differentiated elements are unrecognizable are present in some examples (Fig. 30-88). In these, the diagnosis of malignancy may be evident, but the recognition of adnexal origin and the precise subclassification may be problematic. In some cases of malignant nodular hidradenomas, nuclear anaplasia may be only slight to moderate or even absent in both the primary tumor and the metastases (556). Nuclear anaplasia, if present, may be limited to the clear cells or found in both the polyhedral and the clear cells.

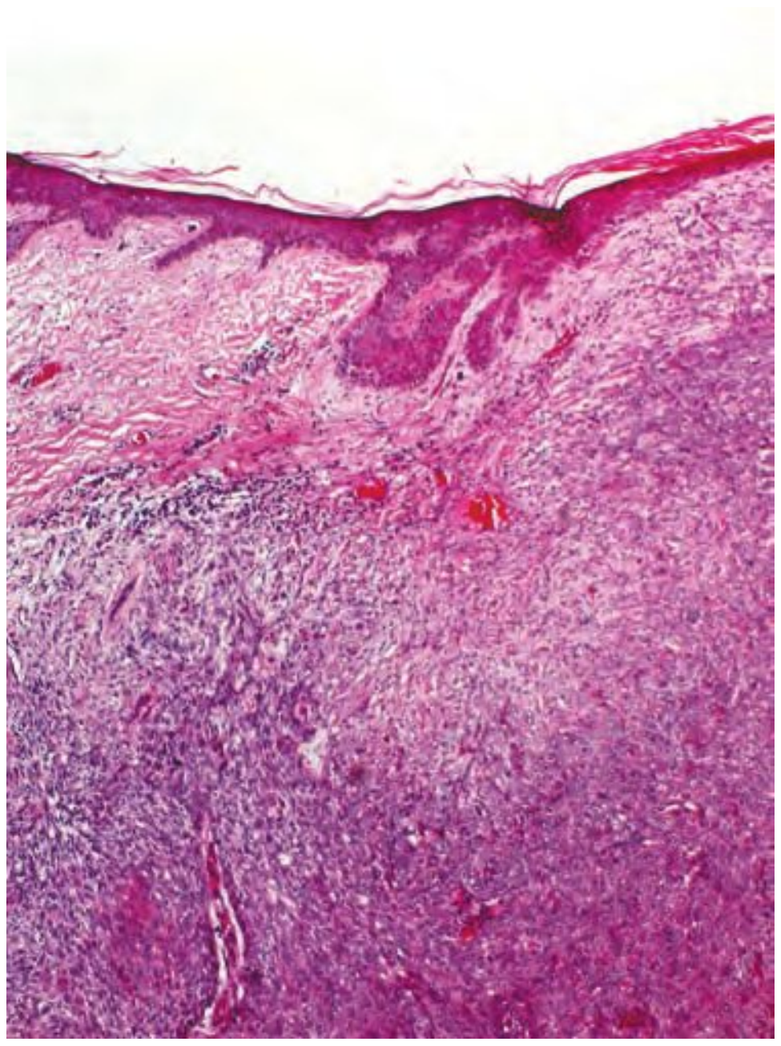


FIGURE 30-87. Malignant nodular hidradenoma. A large, cellular tumor with infiltrative borders is seen.

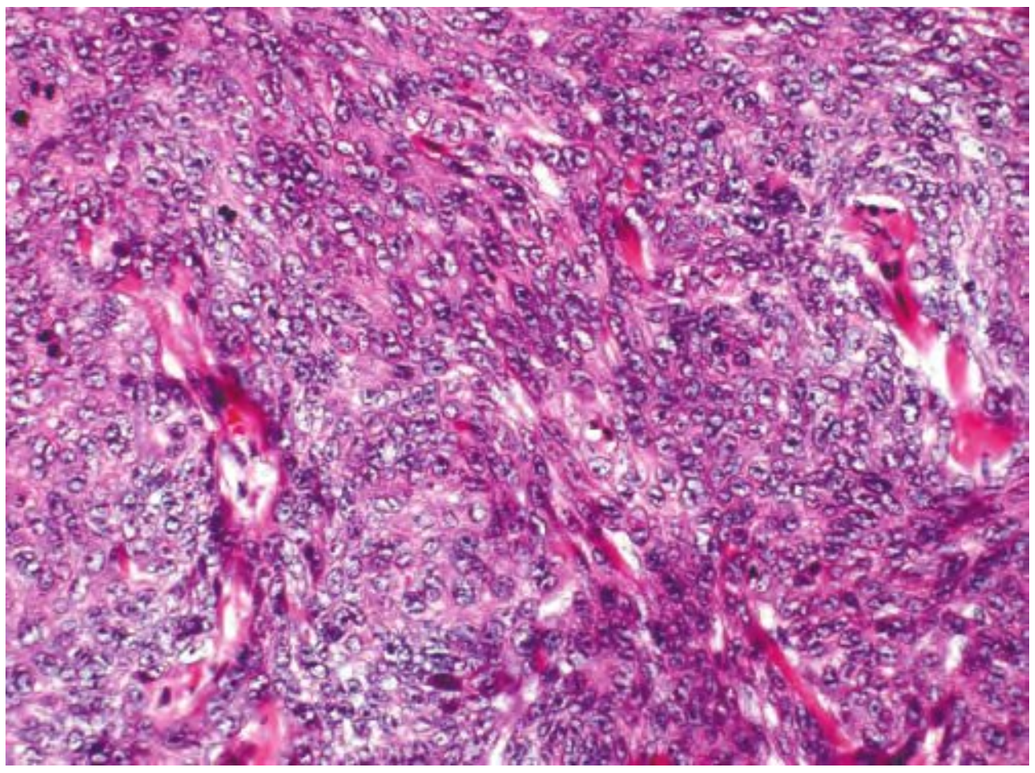


FIGURE 30-88. Malignant nodular hidradenoma. Sheets of atypical epithelial cells exhibit mitotic activity.

Chondroid Syringoma (Mixed Tumor of the Skin)

The condition known by the term *chondroid syringoma*, introduced in 1961, is also known as *mixed tumor of the skin* because the tumor is epithelial, with associated mesenchymal changes (557,558). Chondroid syringomas are firm intradermal or subcutaneous nodules. Although the overlying skin may be attached to the tumor, it otherwise appears normal. Mixed tumors occur most commonly on the head and neck (557,558). Their usual size is between 0.5 and 3.0 cm.

Histopathology. Histologically, two types of chondroid syringomas can be recognized: one with tubular, cystic, partially branching lumina, and the other with small, tubular lumina (558). The former type is much more common than the latter.

Chondroid syringoma with tubular, branching lumina shows marked variation in the size and shape of the tubular lumina; it also shows cystic dilation and branching (Figs. 30-89 and 30-90). Embedded in an abundant stroma, the tubular lumina are lined by two layers of epithelial cells: a luminal layer of cuboidal cells, and a peripheral layer of flattened cells (Fig. 30-90). Furthermore, there are large and small aggregates of epithelial cells without lumina, as well as single epithelial cells widely scattered through the stroma. It appears that cells from the peripheral cell layer of the tubular structures and from the solid aggregates proliferate into the stroma (557). In most instances, the tubular lumina contain small amounts of amorphous, eosinophilic material that is PAS positive and resistant to digestion with diastase. In general, the tubular structures are suggestive of eccrine differentiation (557). Occasionally, the luminal cells show an apocrine type of decapitation secretion, at least in some areas (558–562).

The abundant stroma in many areas has a mucoid, faintly basophilic appearance. As a result of shrinkage of the mucoid substance, the fibroblasts and epithelial cells that are scattered through it are surrounded by a halo, so that they resemble the cells of cartilage (Fig. 30-90). The mucoid stroma stains with Alcian blue, mucicarmine, and aldehyde-fuchsin. The Alcian blue material is not appreciably decreased by predigestion with hyaluronidase (557). Furthermore, on staining with toluidine blue or the Giemsa stain, there is distinct metachromasia (559). Therefore, it can be concluded that the mucin consists largely of sulfated acid mucopolysaccharides or chondroitin sulfate. The stroma is histochemically similar to normal cartilage (557). In a few areas, the

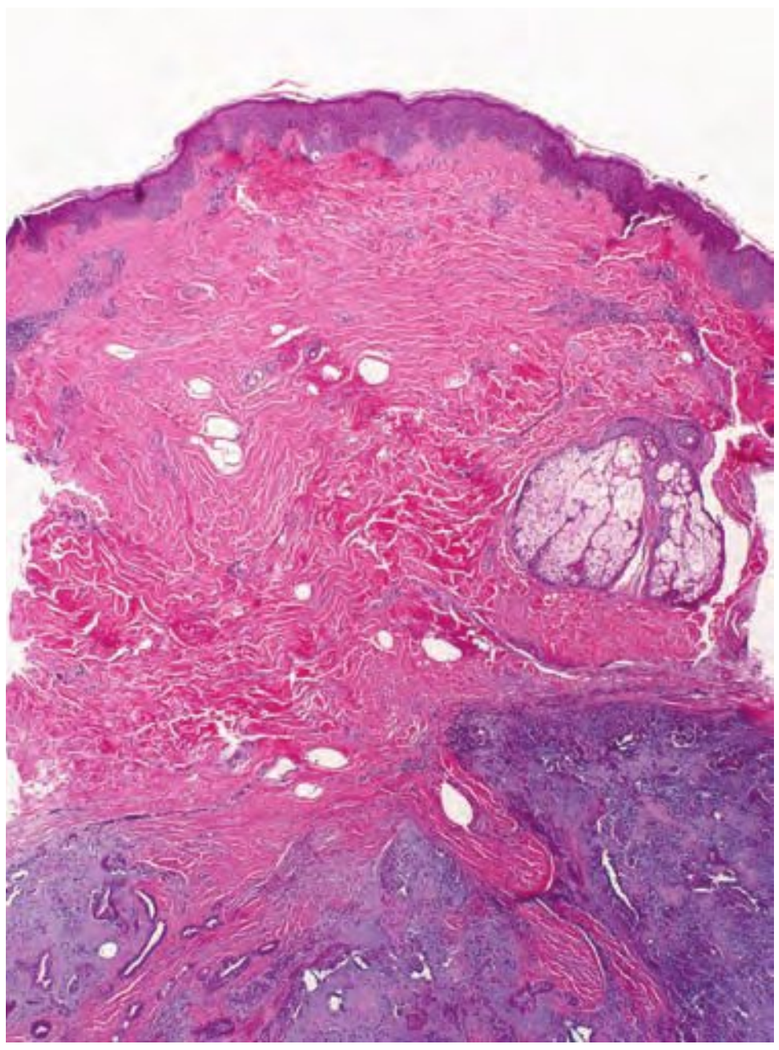


FIGURE 30-89. Chondroid syringoma. In the dermis, there is a nodular tumor comprised of branching tubular epithelial elements embedded in a basophilic stroma.

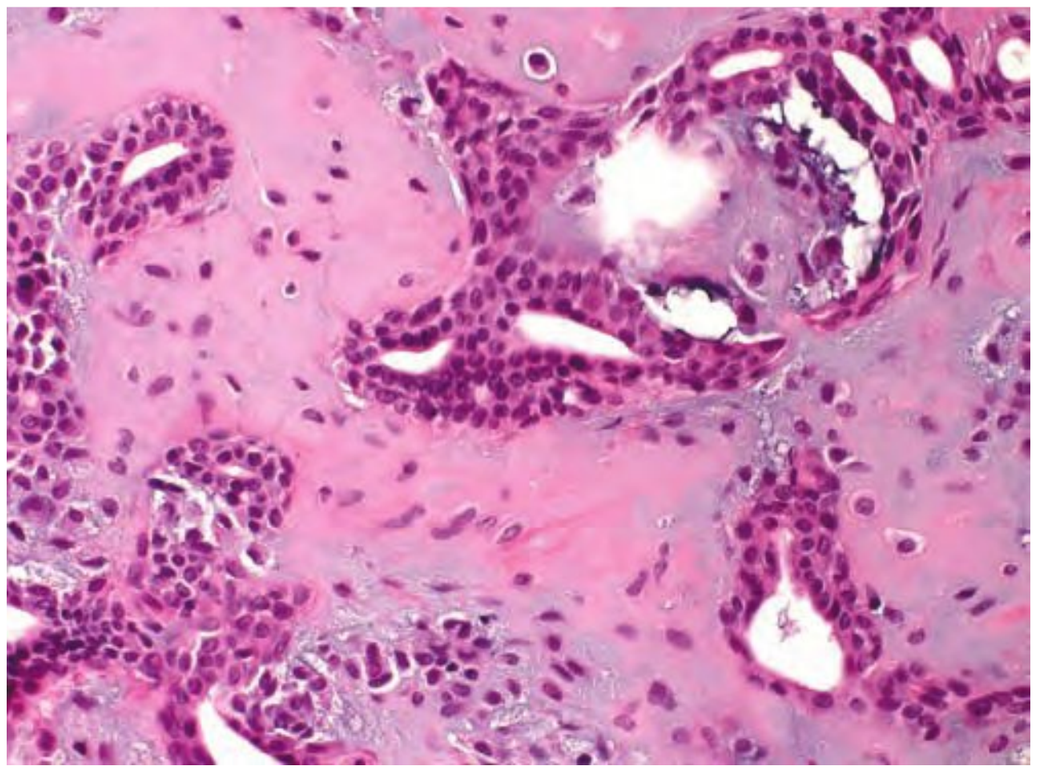


FIGURE 30-90. Chondroid syringoma. The tubular lumina are lined by two layers of cells: a luminal layer of cuboidal cells and a peripheral layer of flattened cells. Cells in the mucoid stroma have the appearance of chondrocytes.

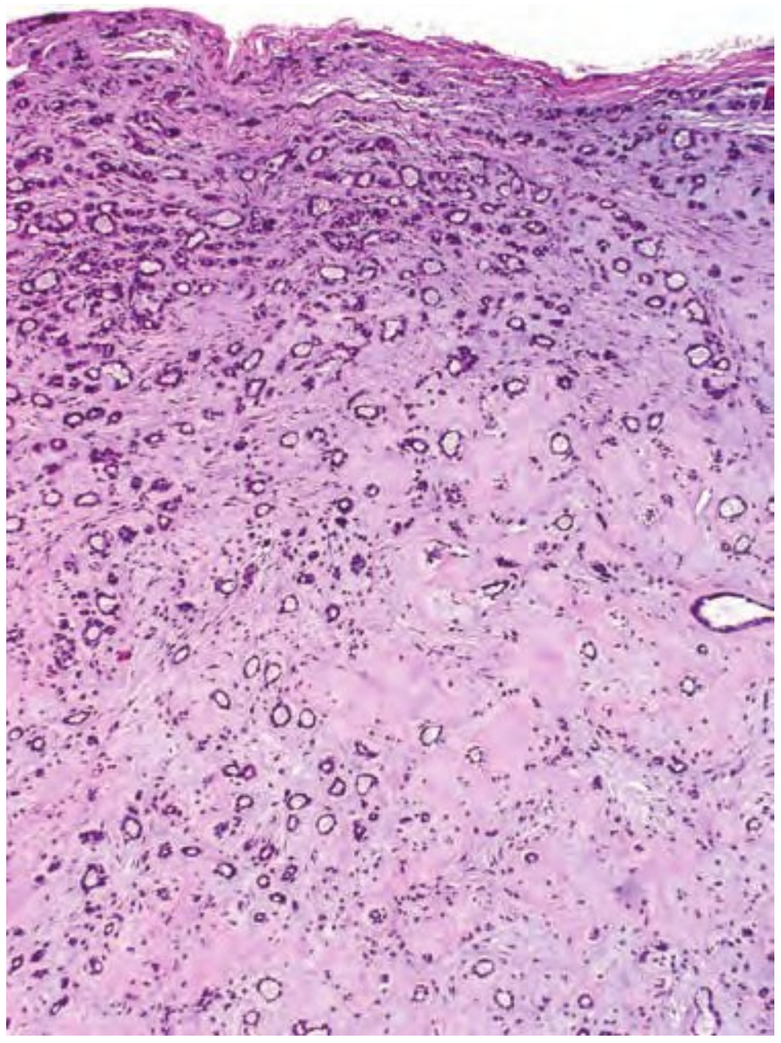


FIGURE 30-91. Chondroid syringoma, small tubular variant. In the dermis, there is a tumor comprised of nonbranching tubular epithelial elements embedded in an abundant stroma.

stroma may appear homogeneous and eosinophilic, like hyalin, and is then PAS positive and diastase resistant (557,561).

Chondroid syringoma with small, tubular lumina shows numerous small ducts, as well as small groups of epithelial cells and solitary epithelial cells scattered through a mucoid stroma (Fig. 30-91). The tubular lumina usually are lined by a single layer of flat epithelial cells, from which small, comma-like proliferations often extend into the stroma, resembling a syringoma (Fig. 30-92) (558). The mucoid stroma contains

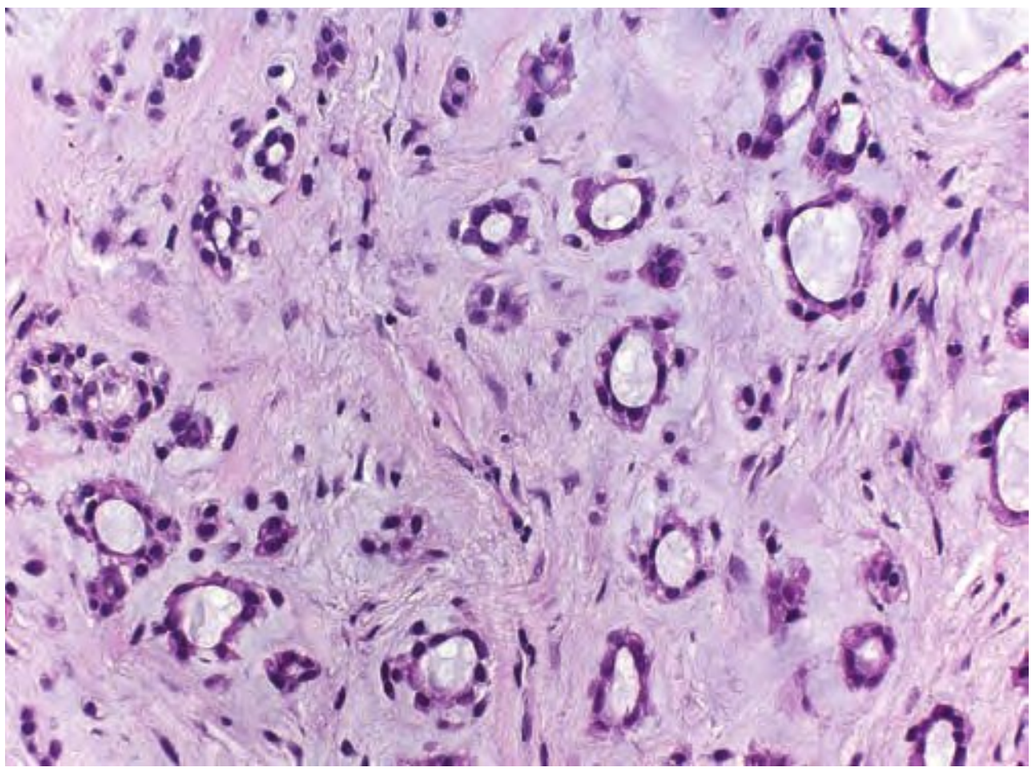


FIGURE 30-92. Chondroid syringoma, small tubular variant. The tubular lumina are lined by one or two layers of cells and are dispersed in the basophilic stroma.

acid mucopolysaccharides that stain metachromatically with toluidine blue.

Additional Studies. By immunohistochemistry, the inner-layer cells express cytokeratin, CEA, and EMA. The outer cell layer, when discernible, is positive for vimentin, S100 protein, neuron-specific enolase, and, occasionally, glial fibrillary acidic protein (563–566). The tumor can show either eccrine or apocrine differentiation. In three cases examined by electron microscopy, eccrine differentiation was noted (561,567). On the other hand, immunohistochemical examination with gross cystic disease fluid protein indicated apocrine differentiation in both cases tested (377). The stroma appears to evolve. Initially, delicate stellate, fibroblast-like cells possibly related to ductal myoepithelial cells are suspended in the Alcian blue–positive, hyaluronidase-resistant myxoid stroma. Stromal cells may acquire cytoplasmic lipid, resulting in a scattering of mature signet ring fat cells within the myxoid background. In some lesions, there is complete synthesis and secretion of solid hyaline cartilage populated by cells in lacunae showing ultrastructural features of true chondrocytes and S100 positivity.

Electron microscopy demonstrates that both ductal and secretory lumina are present, with the secretory lumina lined by clear and dark cells as in eccrine secretory lumina (567). The cells of the outer layer of the tubuloalveolar and ductal structures, like myoepithelial cells, contain numerous filaments and extend into the chondroid matrix, which they apparently produce (561). No chondrocytes were seen in the chondroid matrix in one study (561). In another study, the stroma showed epithelial cells and fibroblasts embedded in a fibrocollagenous matrix and islands of cartilaginous tissue containing chondrocytes with ultrastructural features similar to those of mature cartilage (567). In this case, foci of ossification were also observed, indicating that metaplasia into cartilage and bone had taken place.

Differential Diagnosis. Although most mixed tumors do not recur after surgical excision, seeding and regrowth of stromal and epithelial elements may occur, especially after an incomplete curettage. Lack of symmetry and an infiltrative pattern of growth are important features in distinguishing between benign mixed tumors and the rarely encountered malignant variant (see text following) (568).

Malignant Chondroid Syringoma

In most cases of malignant chondroid syringoma, anaplastic changes are present from the beginning (569). Rarely, a chondroid syringoma of many years' duration suddenly undergoes malignant changes with widespread metastases (570,571). The degree of aggressive behavior varies with malignant chondroid syringomas. For example, there may be only a local recurrence, but some cases have shown regional lymph node metastases or an osseous metastasis (569,572,573). In several cases, fatal visceral metastases have occurred (570,574–576). When this tumor metastasizes, it generally does so as an adenocarcinoma, often losing the tendency to form chondroid stroma.

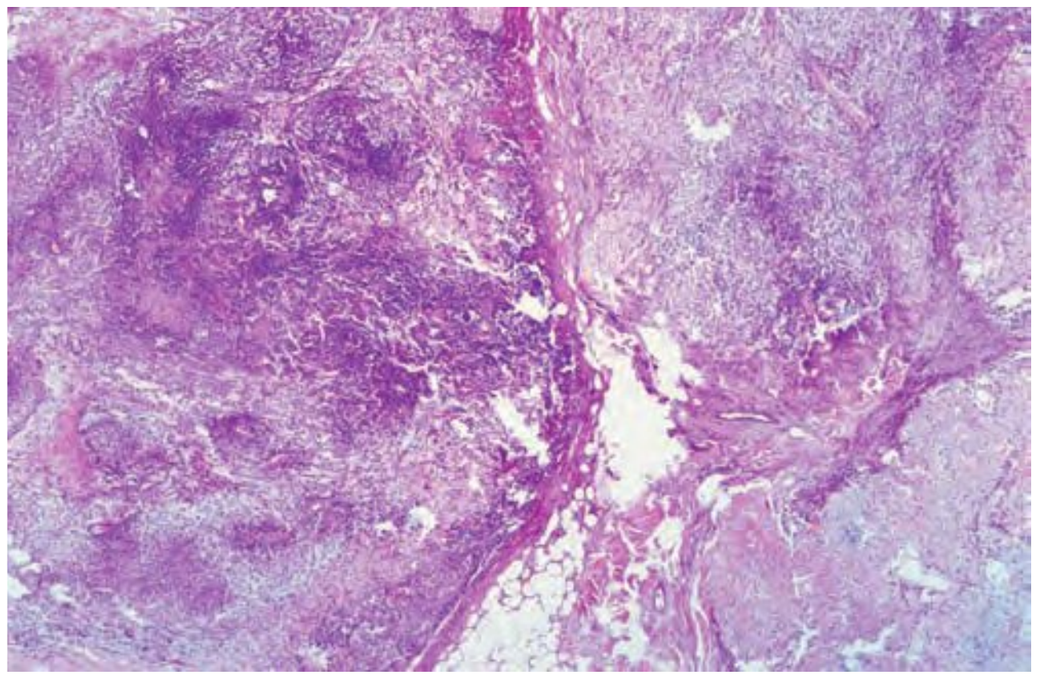


FIGURE 30-93. Malignant chondroid syringoma. An asymmetric cellular tumor is seen in the dermis.

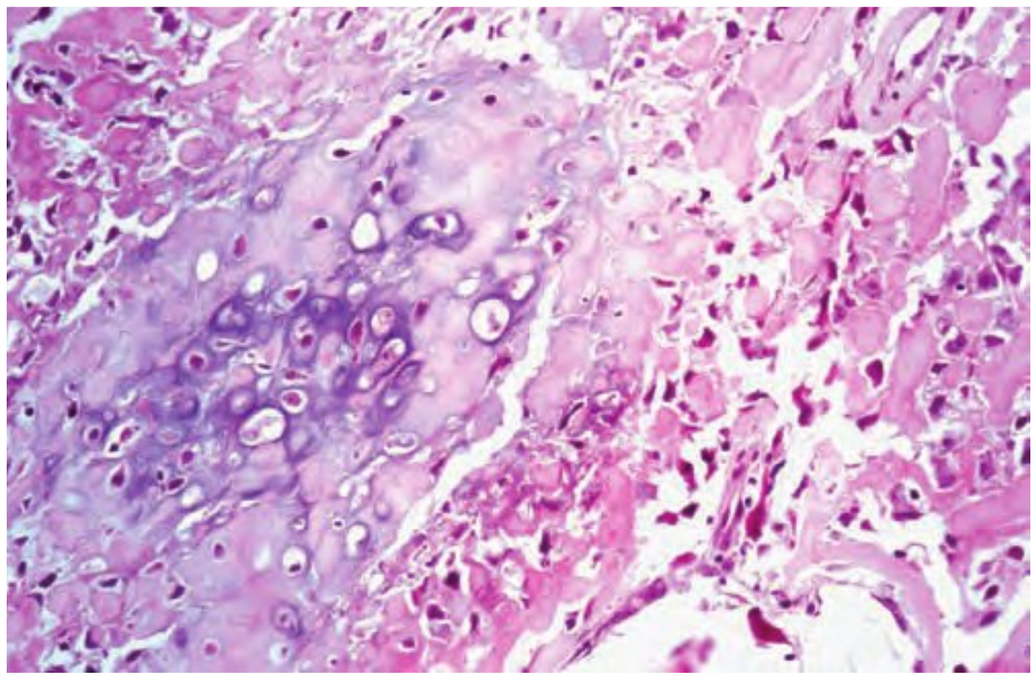


FIGURE 30-95. Malignant chondroid syringoma. Focally, cells embedded in a mucoid stroma reminiscent of chondroid syringoma are seen.

Histopathology. Histologically, malignant chondroid syringoma is composed of epithelial structures with glandular differentiation and carcinomatous features embedded in a mucinous stroma with spindle mesenchymal cells and areas of chondroid differentiation (Figs. 30.93 to 30-95). Sheets of atypical cells with increased mitotic activity can also be seen (Fig. 30-94). Unlike biphasic synovial sarcoma, in which both components express cytokeratins, only the epithelial structures of malignant chondroid syringoma are cytokeratin positive. The malignant tumor and its metastases are recognizable as chondroid syringoma through their chondroid stroma and tubular structures (Fig. 30-95). However, tubular differentiation is much less evident than in benign lesions (574). Most of the epithelial cells in the malignant tumor are arranged in irregular cords or sheets (Fig. 30-94) (572). The tumor cells appear atypical and hyperchromatic (573). In addition, an increased mitotic rate, vascular invasion, infiltration into the surrounding tissue, and necrosis have been noted (569).

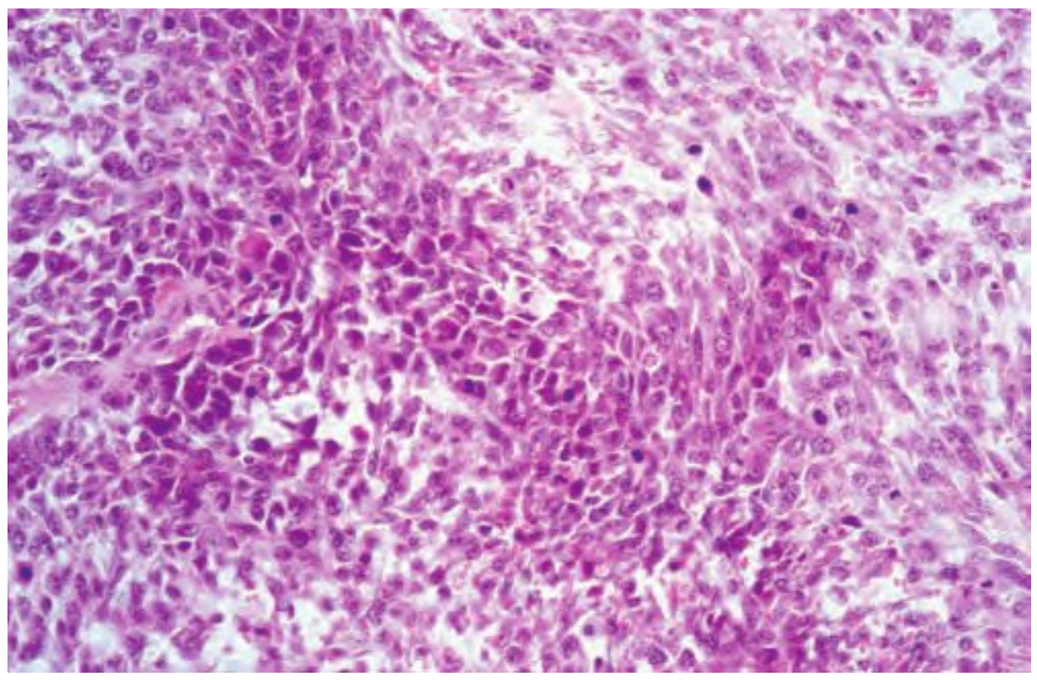


FIGURE 30-94. Malignant chondroid syringoma. Sheets of anaplastic cells are present.

CARCINOMAS OF APOCRINE AND ECCRINE GLANDS

Carcinomas exhibiting apocrine and eccrine differentiation can be classified in several different ways. One logical classification scheme distinguishes lesions based on whether the carcinoma may frequently evolve from a benign lesion. In reality, this group of tumors may derive either from a benign precursor through tumor progression or *de novo* as a malignant lesion. In this group are malignant cylindroma, malignant eccrine poroma, malignant eccrine spiradenoma, malignant nodular hidradenoma, and malignant chondroid syringoma, lesions that have already been discussed. The second group comprises apocrine and eccrine carcinomas that appear to have no benign precursor. In this group are carcinoma of apocrine glands, eccrine adenocarcinoma, syringoid eccrine carcinoma, microcystic adnexal carcinoma, mucinous (adenocystic) carcinoma, adenoid cystic carcinoma, and aggressive digital papillary adenocarcinoma.

CARCINOMAS OF APOCRINE GLANDS

Carcinomas of apocrine glands are rare tumors (390,577–581). These lesions occur primarily in the axillae and in other anatomic regions endowed with apocrine glands, including the anogenital region (390,578). Lesions can occur elsewhere on the skin (577,579). Apocrine carcinomas can also occur in the external auditory meatus, where ceruminous glands, which represent modified apocrine glands, are located (582,583). These tumors may involve the ear and preauricular skin (584).

Some cases of carcinoma of apocrine glands exhibit only local invasiveness, but other lesions metastasize to regional lymph nodes (390,578,579). In fact, some patients have died from widespread metastases (577,579).

Histopathology. The histologic picture is that of an adenocarcinoma that may be well, moderately, or poorly differentiated (590).

In well-differentiated apocrine gland carcinomas, nuclear atypicality and invasiveness are limited. Well-developed

glandular lumina are present; these lumina may be cystic and show branching (390). The cytoplasm of the tumor cells is strongly eosinophilic. Evidence of decapitation secretion, typical of apocrine glands, is present, at least in some areas. In addition, the cytoplasm of the tumor cells contains PAS-positive, diastase-resistant granules and often contains iron-positive granules (390). Myoepithelial cells are seen rarely (579).

In moderately or poorly differentiated apocrine gland carcinomas, recognition of apocrine histopathologic features may be difficult to assess, although even poorly differentiated tumors often demonstrate regions with prominent apocrine differentiation (390).

Additional Studies. Enzyme histochemical determinations are of value in establishing an apocrine genesis. Apocrine gland carcinomas show strong activity for apocrine enzymes, such as acid phosphatase, β-glucuronidase, and indoxyl acetate esterase, and low activity or absence of eccrine enzymes, such as phosphorylase and succinic dehydrogenase (577,579).

Differential Diagnosis. Apocrine gland carcinoma of the axilla must be differentiated from a carcinoma arising in ectopic breast tissue. Features that favor the diagnosis of a carcinoma of apocrine glands are the presence of neoplastic glands high in the dermis, apocrine glands near the tumor, and intracytoplasmic granules of iron (390).

Classic Type of Eccrine Adenocarcinoma

Only few lesions of primary eccrine carcinoma possess a clinical appearance suggesting an eccrine malignancy. Although they may arise on the palms or on the soles, they more commonly arise elsewhere, particularly in the head and neck region (13,585–587).

The classic type of eccrine gland adenocarcinoma has a high incidence of metastases. Of 68 patients followed for 5 years or more, 29 had regional lymph node metastases, and visceral metastases were present in 26 (588).

Histopathology. The histologic configuration in the classic type of eccrine gland adenocarcinoma varies from areas of fairly well differentiated tubular structures to anaplastic cells in other areas, not recognizable by themselves as eccrine sweat gland structures (586). The tubular structures usually show only small lumina that are lined by either a single layer or a double layer of cells (586). In some areas, the lumina are lined by secretory cells, which appear large and vacuolated because of the presence of glycogen and which also often contain PAS-positive, diastase-resistant granules (15,589).

Additional Studies. Immunohistochemical techniques have been of little help in characterizing these lesions (585). So-called eccrine enzymes, such as amylophosphorylase and succinic dehydrogenase, may be present in moderate amounts, but their role in identifying the tumors as eccrine rather than as metastatic has not been well defined (13,590).

Differential Diagnosis. It is often difficult to differentiate the classic type of eccrine sweat gland carcinoma from a metastatic adenocarcinoma. Therefore, the diagnosis of metastatic adenocarcinoma should always be given serious consideration before a diagnosis of eccrine sweat gland carcinoma is decided on.

Syringoid Eccrine Carcinoma

This tumor was originally referred to in 1969 as *basal cell tumor with eccrine differentiation* (591) and subsequently as *eccrine epithelioma* (592); the term *syringoid eccrine carcinoma* is preferable because the tumor differs from basal cell carcinoma in its cytologic and enzymatic patterns. It represents a relatively well differentiated form of eccrine carcinoma (593). Although first reported as a deeply invasive and destructive tumor of the scalp (591), it also occurs in other locations, and metastases rarely occur (593).

Histopathology. Syringoid eccrine carcinoma resembles syringoma by showing ductal, cystic, and comma-like epithelial components and by containing eccrine enzymes such as phosphorylase and succinic dehydrogenase (Figs. 30-96 and 30-97) (591). It differs from syringoma by its cellularity, anaplasia, and deep infiltrative growth (Fig. 30-96). This uncommonly diagnosed tumor is probably related to the microcystic adnexal carcinoma. A clear cell variant of syringoid eccrine carcinoma has been described (594,595).

Additional Studies. Immunohistochemical analysis revealed that most tumor cells expressed simple epithelial cytokeratins (cytokeratins 7, 8, 18, 19), consistent with sweat gland secretory differentiation (596).

Microcystic Adnexal Carcinoma

Microcystic adnexal carcinoma, or sclerosing sweat duct carcinoma, may best be considered as a sclerosing variant of ductal eccrine carcinoma (597,598). This tumor is most commonly seen on the skin of the upper lip, but occasionally also on the chin, nasolabial fold, or cheek (598,599). Rare cases of multiple primary microcystic adnexal carcinomas have been reported (600). Microcystic adnexal carcinoma is an aggressive neoplasm that invades deeply. Local recurrence is common; however, metastases have not been reported.

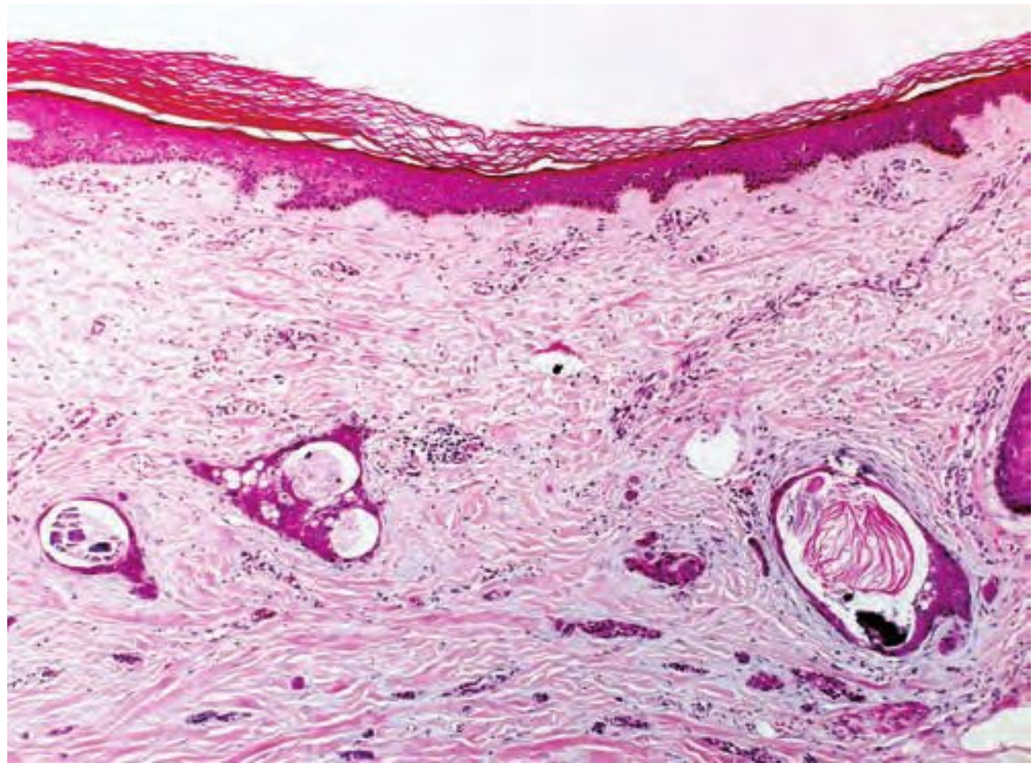


FIGURE 30-96. Syringoid eccrine carcinoma. An infiltrative tumor exhibiting ductal differentiation is identified.

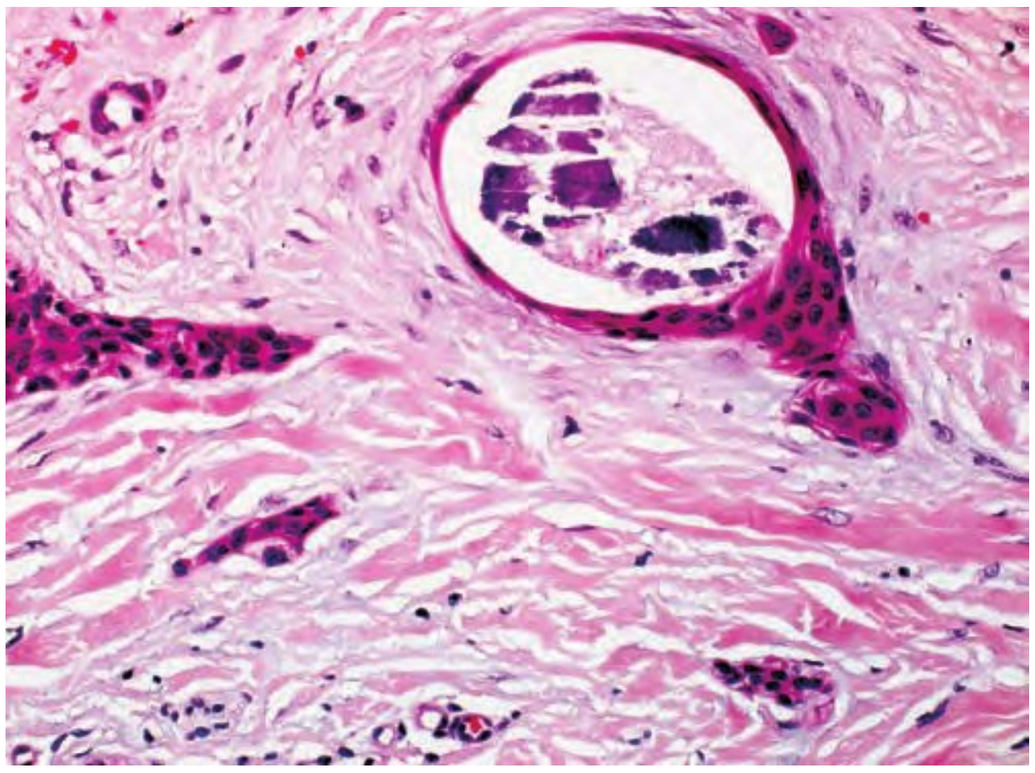


FIGURE 30-97. Syringoid eccrine carcinoma. Infiltrative epithelial elements resembling a syringoma are seen.

Histopathology. Microcystic adnexal carcinoma is a poorly circumscribed dermal tumor that may extend into the subcutis and skeletal muscle (Fig. 30-98). Continuity with the epidermis or follicular epithelium may be seen. Two components within a desmoplastic stroma may be evident. In some areas, basaloid keratinocytes are seen, some of which contain horn cysts and abortive hair follicles; in other areas, ducts and glandlike structures lined by a two-cell layer predominate (Figs. 30-99 and 30-100) (599). The tumor islands typically reduce in size as the tumor extends deeper into the dermis. Cells with clear cytoplasm may be present, and sebaceous differentiation has been reported (601). Cytologically, the cells are bland without significant atypia; mitoses are rare or absent. Perineural invasion may be seen, a feature that may account for the high recurrence rate.

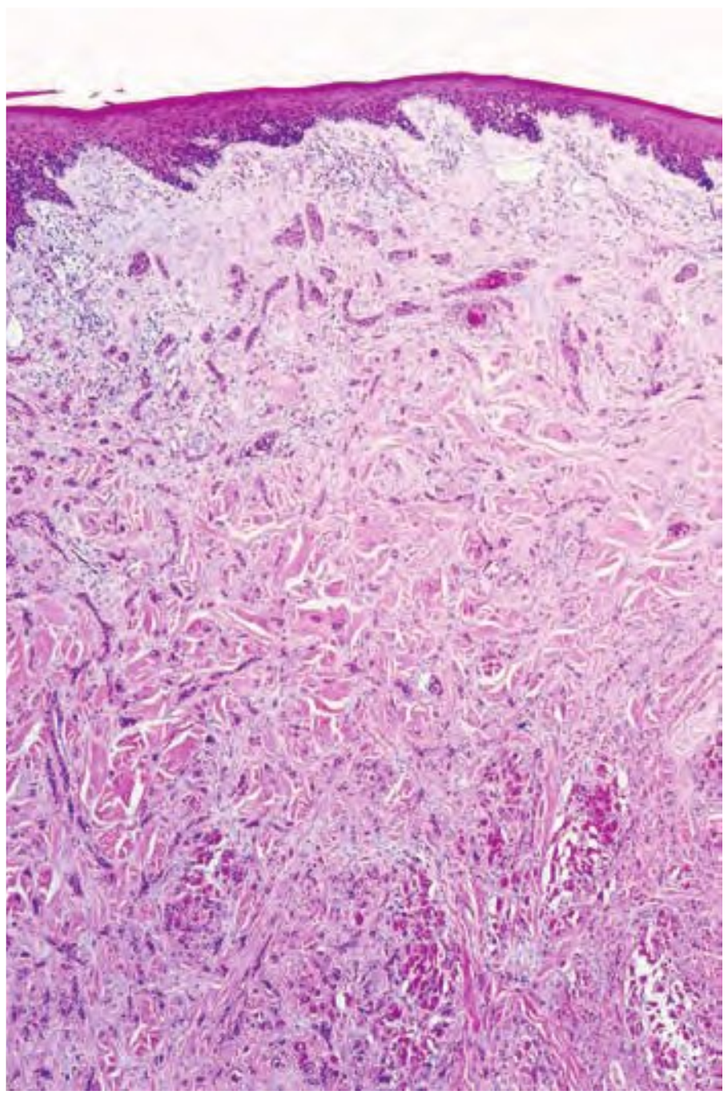


FIGURE 30-98. Microcystic adnexal carcinoma. There is a large, poorly circumscribed tumor comprised of epithelial cords that invades deeply into the dermis.

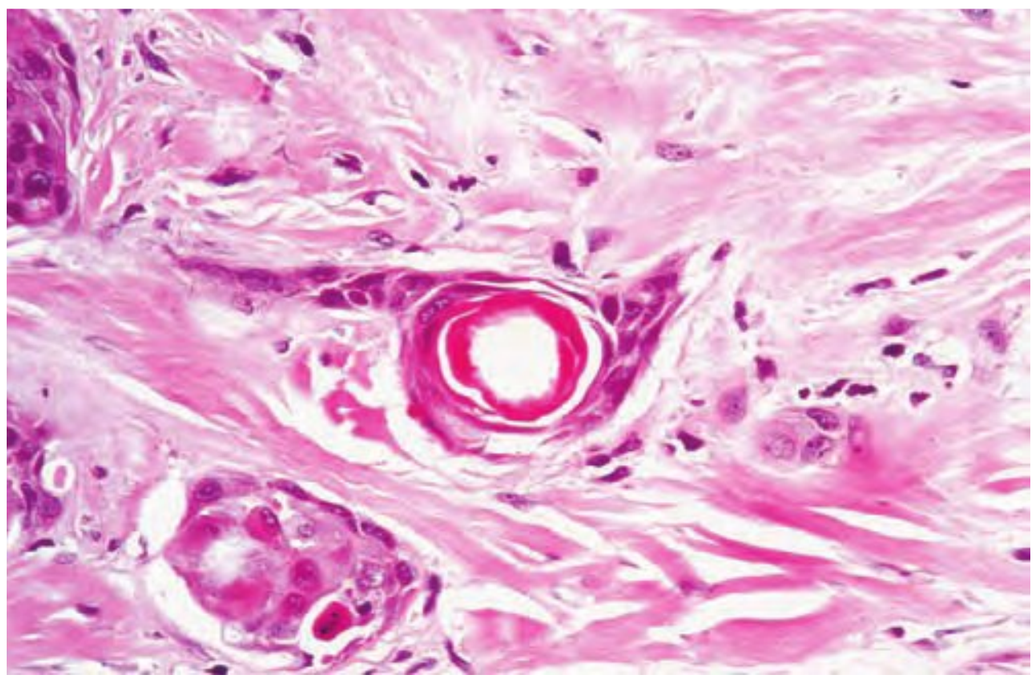


FIGURE 30-99. Microcystic adnexal carcinoma. Superficially, keratin-filled cystic glands are present and may be mistaken for the cysts of a trichoepithelioma, but the lesion invades deeply into the dermis.

Additional Studies. Immunoperoxidase staining for carcinoembryonic antigen stains the glandular structures but not the pilar structures (598). The presence of both pilar and eccrine structures allows differentiation from desmoplastic trichoepithelioma and syringoma. Lack of circumscription, deep dermal involvement, and perineural involvement all aid in diagnosis because the cytology mimics benign adnexal neoplasms. This diagnosis should always be considered and complete excision contemplated when a syringomatous or trichoepithelioma-like proliferation extends to the base of a biopsy, especially in an elderly patient. Immunohistochemical studies have shown that CD23 can help to distinguish microcystic adnexal carcinoma from desmoplastic trichoepithelioma (602).

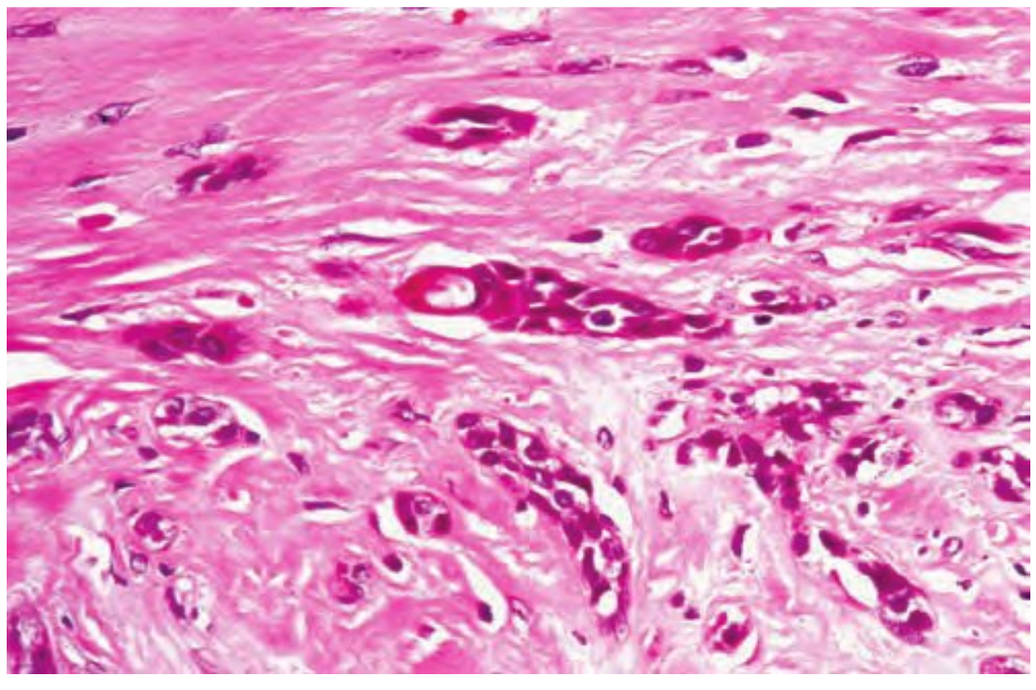


FIGURE 30-100. Microcystic adnexal carcinoma. In the deep dermis, cords of bland epithelial cells demonstrate focal ductal differentiation. A marked desmoplastic response is noted.

Mucinous Eccrine Carcinoma

First described in 1971, mucinous eccrine carcinoma is a rather uncommon tumor that metastasizes to regional lymph nodes occasionally (603,604). Widespread metastases have been described only very rarely (605).

Histopathology. The histologic appearance of mucinous eccrine carcinoma is highly characteristic (606). The tumor is divided into numerous compartments by strands of fibrous tissue. In each compartment, abundant amounts of pale-staining mucin surround nests or cords of moderately anaplastic epithelial cells, some of which show a tubular lumen (Figs. 30-101 and 30-102) (603,607). The mucin shows strongly positive reactions with both PAS and colloidal iron. The mucinous material is resistant to diastase and hyaluronidase but is sensitive to digestion with sialidase. The reaction with Alcian blue is positive at pH 2.5 but negative at pH 1.0 and pH 0.4, which indicates that the mucin is nonsulfated (608). It can be concluded that the mucin represents sialomucin, an epithelial mucin (603,607).

Additional Studies. Enzyme histochemical studies have revealed a prevalence of eccrine enzymes in these tumors (607). Electron microscopy has revealed two types of secretory cells in the tumor—dark and light—analogous to the two types normally encountered in eccrine coils. The sialomucin is secreted by the dark cells (609). Immunohistochemical results also suggest differentiation toward eccrine secretory coil (610).

It is important to differentiate this tumor from a metastatic mucinous adenocarcinoma, in which the primary lesion most commonly is located in the large intestines (603). In both primary and metastatic mucinous adenocarcinoma, islands of tumor cells appear to be floating in lakes of mucin, but the tumor cells are more atypical in the metastatic type, and the atypical cells invade between collagen bundles at the margin of the nodule (611). Exclusion of primary visceral carcinomas is often impossible by histology alone.

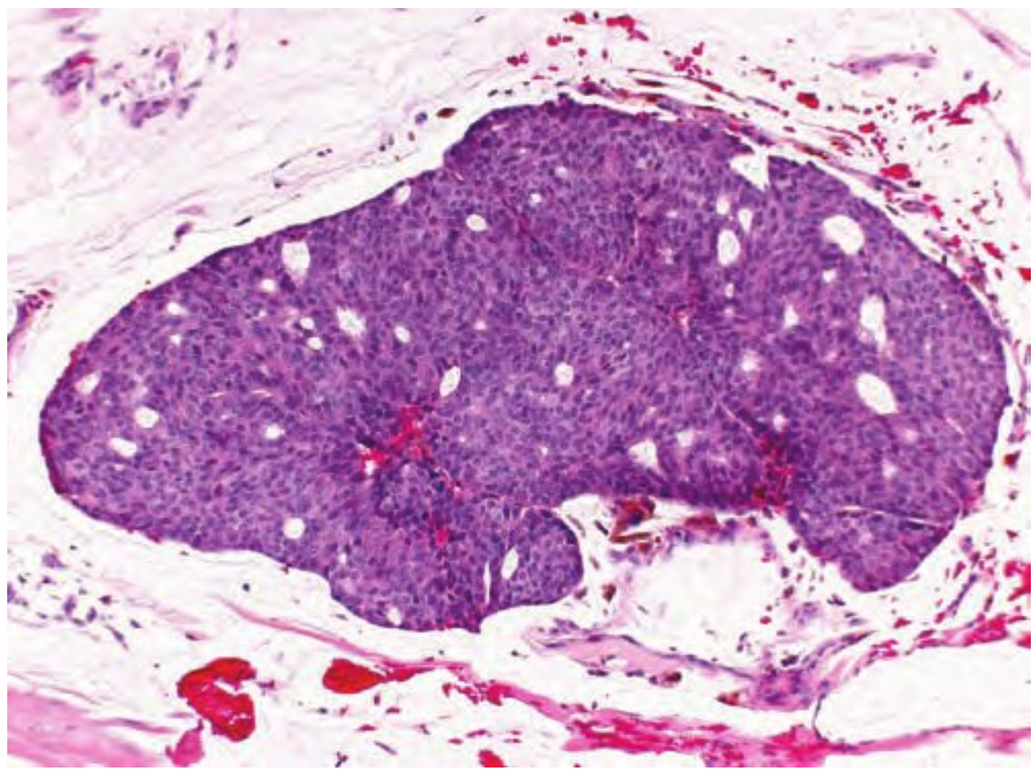


FIGURE 30-102. Mucinous eccrine adenocarcinoma. The islands of tumor cells show mild cytologic atypia and focal duct formation.

Mucoepidermoid (Low-Grade Adenosquamous) Carcinoma

This tumor, which combines well-differentiated squamous and glandular epithelium, is histologically identical to that of sali-

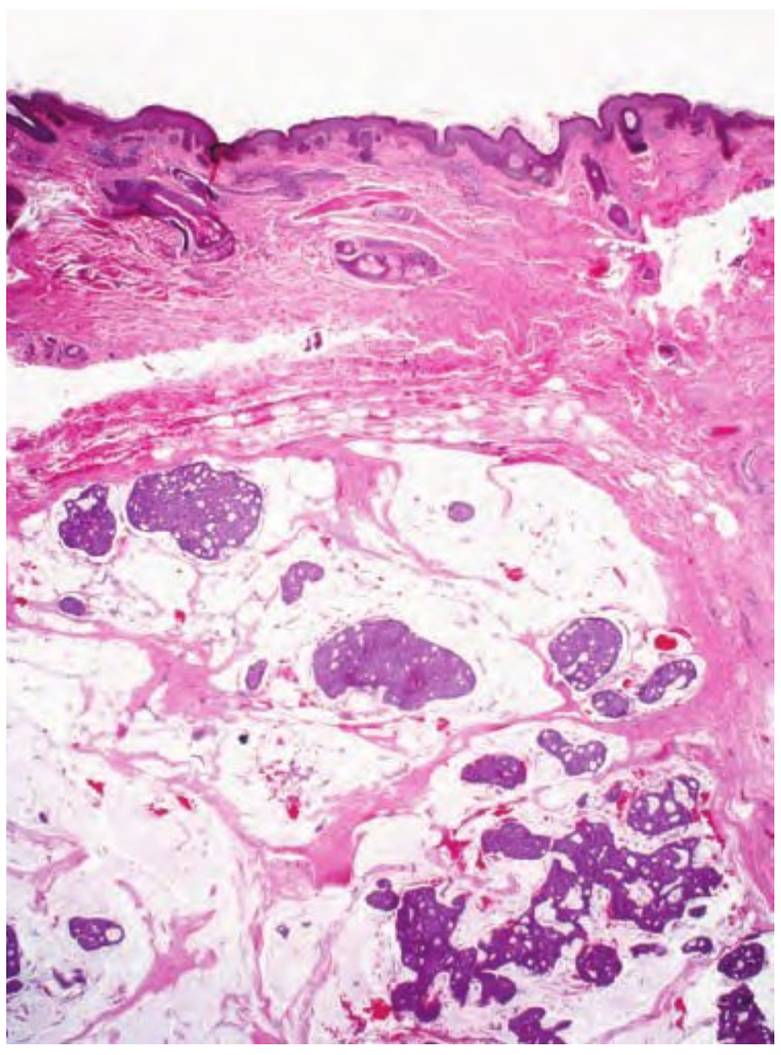


FIGURE 30-101. Mucinous eccrine adenocarcinoma. The tumor is divided into numerous compartments. In each compartment, abundant amounts of mucin surround small islets of tumor cells.

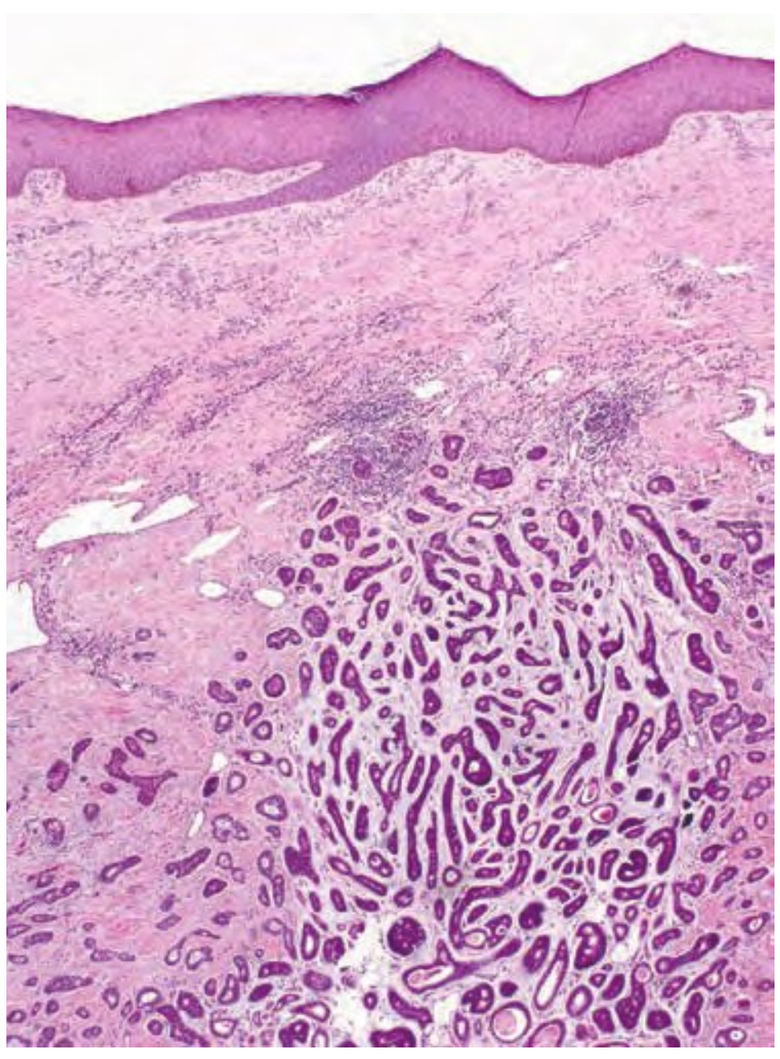


FIGURE 30-103. Adenoid cystic carcinoma of eccrine glands. A large cell mass shows an adenoid or cribriform pattern. In addition, many small, solid epithelial islands are present.

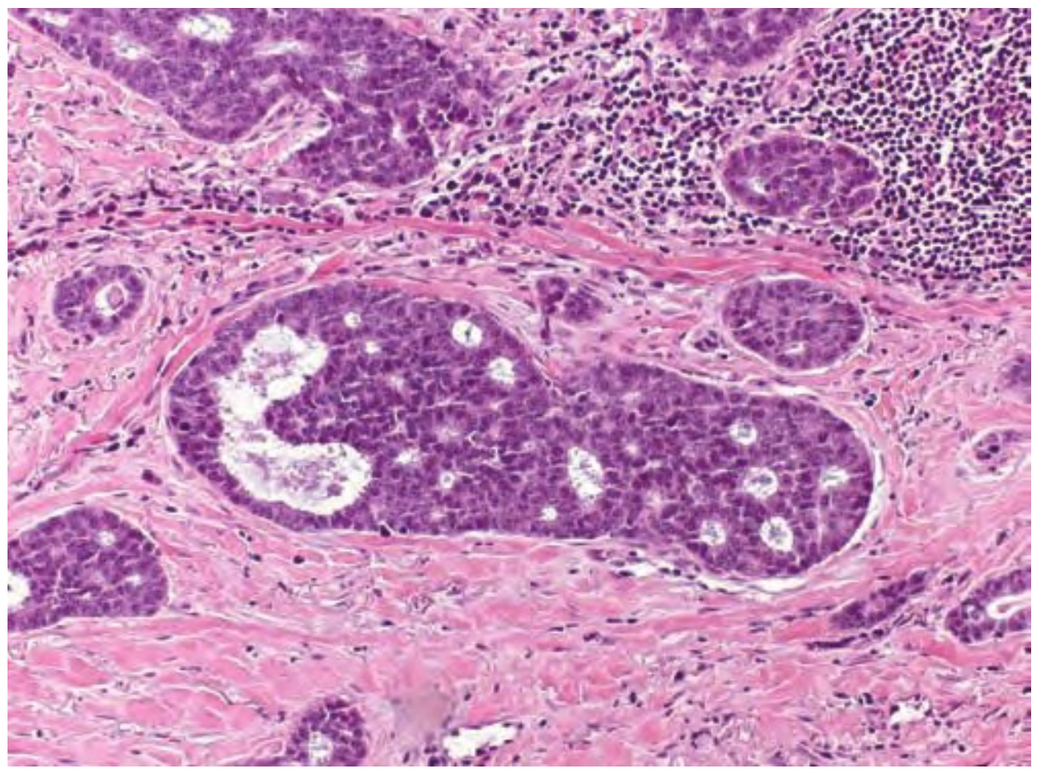


FIGURE 30-104. Adenoid cystic carcinoma of eccrine glands. Some epithelial islands demonstrate a cribriform pattern.

vary glands and may occur as a primary cutaneous malignancy (612–614).

Adenoid Cystic Carcinoma

One of the rarest types of eccrine carcinomas is the adenoid cystic carcinoma, first described in 1975 (615). Metastases have been reported but are uncommon (616). This indolent tumor, like its more aggressive counterpart in salivary glands, spreads in perineural spaces and, therefore, recurs in 20% of cases (616,617).

Histopathology. Microscopic examination reveals lesions exhibiting an adenoid or cribriform pattern comprised of many small, epithelial islands (Fig. 30-103). Round spaces formed by malignant epithelial cells and containing amphophilic basement membrane–like material occur in the cribriform type and tubular variants (Fig. 30-104) (618). Through the accumulation of mucin, the adenoid spaces may be transformed into multiple cystic spaces lined by a flattened cuboidal epithelium. The adenoid and cystic spaces contain pale-staining mucin that in some cases is hyaluronidase sensitive but in others was resistant to hyaluronidase digestion and reacted with the Alcian blue stain at pH 2.5 and pH 0.5 (619,620). In several instances, there has been extension along perineural spaces.

Additional Studies. Adenoid cystic carcinoma is immunoreactive for carcinoembryonic antigen, amylase, and S100 protein (620).

Adenoid cystic carcinoma of eccrine glands must be distinguished from the adenoid type of basal cell carcinoma, from which it differs by lack of continuity with the epidermis or hair sheath and by the absence of peripheral palisading (619). In addition, the adenoid type of basal cell carcinoma shows negative reactions to carcinoembryonic antigen, amylase, and S100 protein (620). Cutaneous extension from a parotid tumor or scar recurrence should be ruled out in adjacent body sites.

Aggressive Digital Papillary Adenocarcinoma

These tumors, originally described in 1987, occur on the fingers, toes, and adjacent skin of the palms and soles, especially in adult males, as a single, often cystic mass that rarely ulcerates but often invades soft tissue (621).

Histopathology. Aggressive digital papillary adenocarcinoma shares some histologic features with papillary eccrine adenoma. These tumors are usually cellular, dermal nodules with cystic cavities (Fig. 30-105). Characteristic histologic findings of this lesion include tubuloalveolar and ductal structures associated with papillary projections protruding into cystically dilated lumina (Figs. 30-106 and 30-107) (621). Macropapillae lined by atypical epithelial cells project into microcysts. These areas may merge with more cellular regions of moderately differentiated adenocarcinoma. Mitotic activity and cytologic atypia are

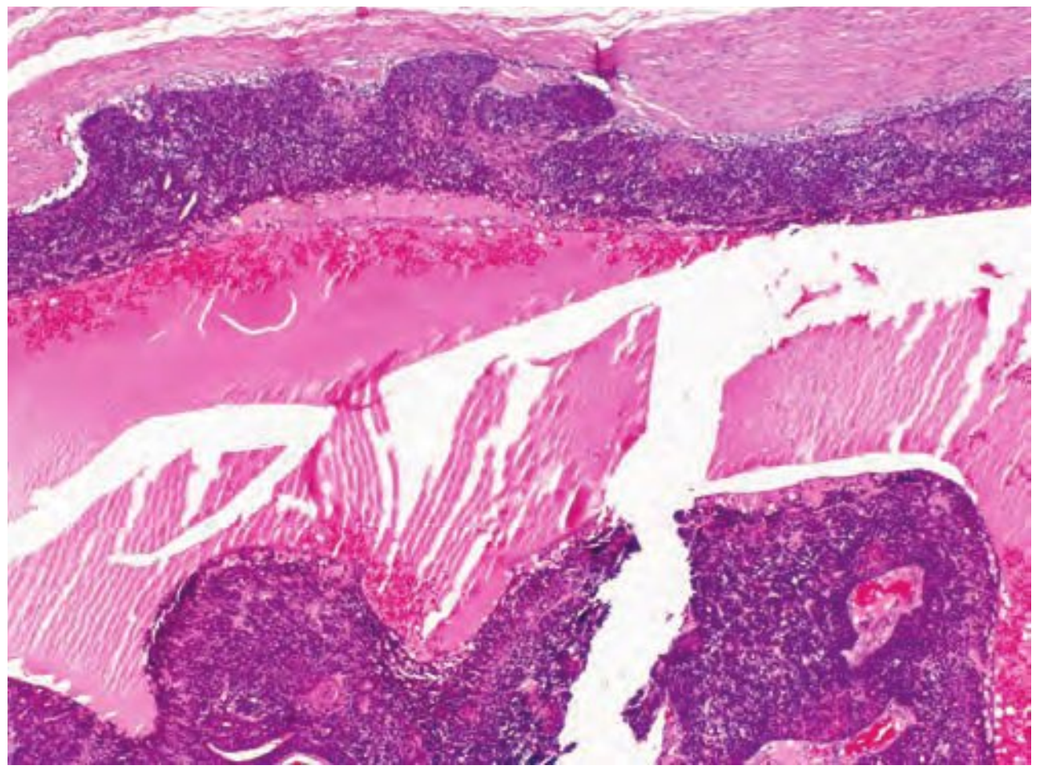


FIGURE 30-105. Aggressive digital papillary adenocarcinoma. A large, lobulated dermal tumor with focal cystic change is seen in the dermis of acral skin.

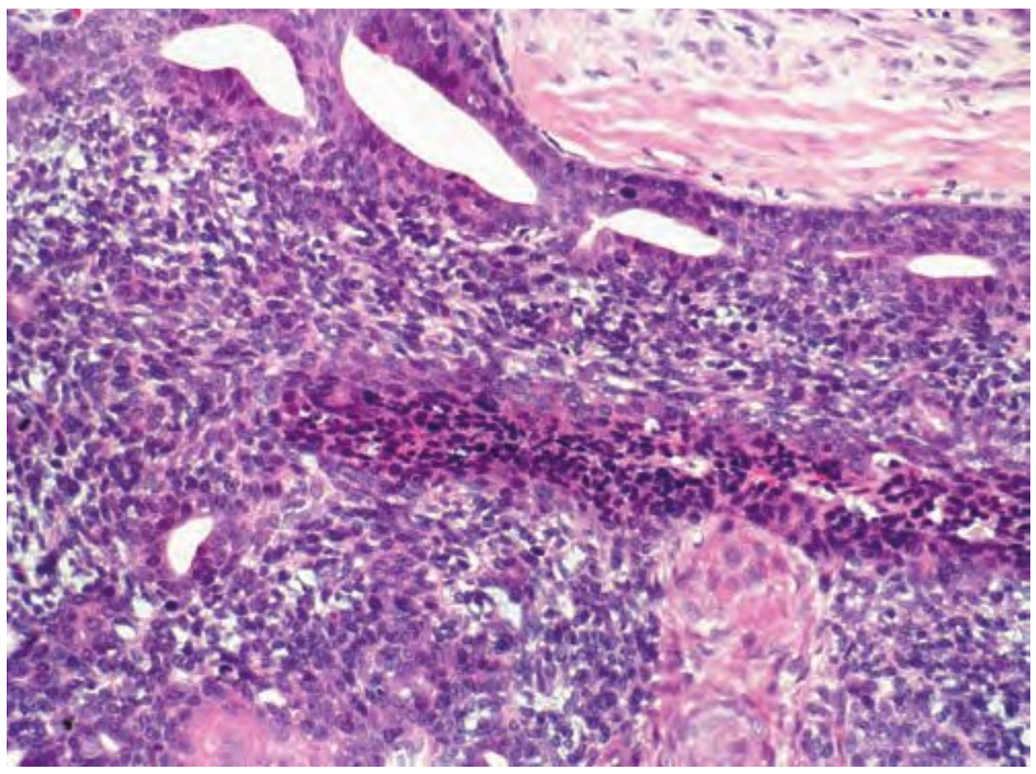


FIGURE 30-106. Aggressive digital papillary adenocarcinoma. Gland formation and focal squamoid differentiation are seen.

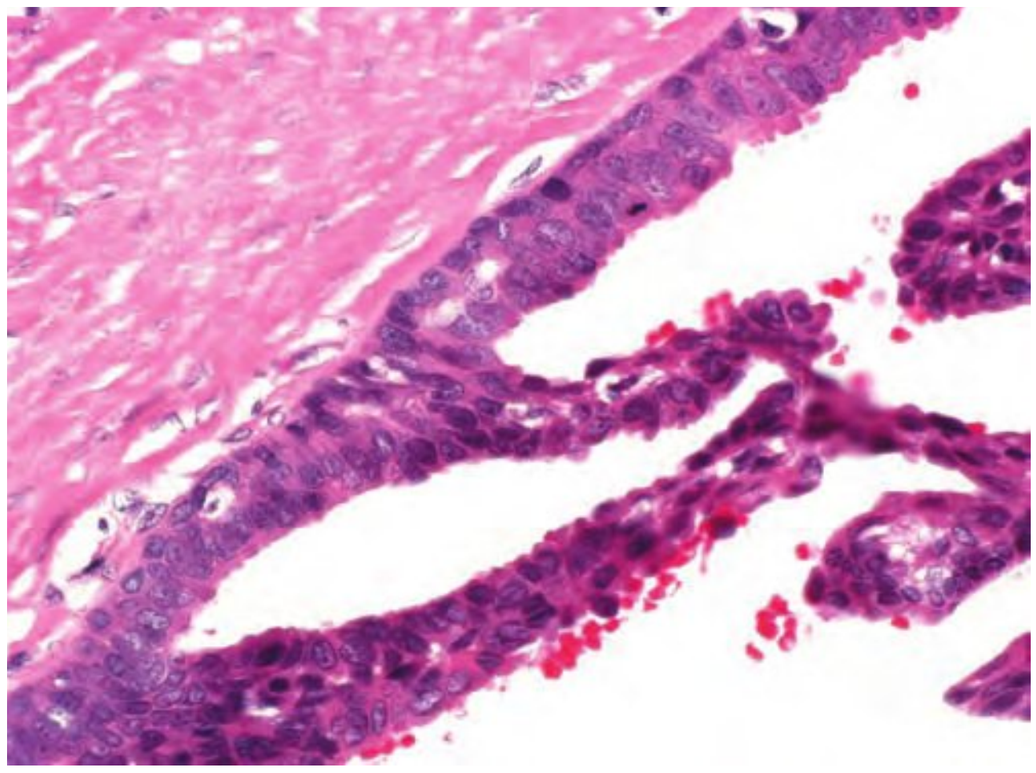


FIGURE 30-107. Aggressive digital papillary adenocarcinoma. Micropapillary structures are seen and mitotic activity is present.

often present (Fig. 30-107). Metastatic papillary carcinoma from breast, lung, thyroid, and ovary are in the histologic differential. Initially, a low-grade variant—"aggressive digital papillary adenoma"—was described that differed from adenocarcinoma based on degree of pleomorphism, mitotic rate, and necrosis (621). However, recent studies suggest that histologic features alone cannot reliably predict clinical behavior, and, therefore, all lesions should be considered aggressive digital papillary adenocarcinomas (622,623). When metastases develop, they often involve the lung.

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CHAPTER 31

Mei-Yu Hsu
George F. Murphy

Cutaneous Lymphomas and Leukemias

The subject of cutaneous lymphoma and leukemia has long been one of conceptual confusion and diagnostic challenge. Aside from the inherent difficulties in differentiating hyperplastic from neoplastic hematopoietic cells in skin, the recent evolution in classification schemas for lymphoma and leukemia have contributed significantly to this dilemma. Moreover, some traditional didactic treatments of this issue too often provide information so abundant as to confound the overview necessary for a practical, confident, and accurate diagnostic approach to potential lymphoproliferative disorders of skin.

The classification system adapted to skin and used in this chapter is that of the 2005 World Health Organization (WHO)/European Organization for Research and Treatment of Cancer (EORTC) Consensus Classification of cutaneous lymphomas (1). This recent and seminal contribution reflects the understanding that primary cutaneous lymphomas have a distinctive clinical behavior and prognosis from histologically similar nodal diseases and require different management and treatment regimens. The new classification pays special attention to recognizing only those diseases that represent distinct clinicopathologic entities and offers pathologists, dermatologists, oncologists, and geneticists a universal system for lymphoma/leukemia classification. In this regard, a synthesis of clinical, histopathologic, immunohistochemical, molecular, and cytogenetic features are often required to define individual disease entities.

The treatment of lymphoproliferative disorders detailed in this chapter is in no small part indebted to the outstanding foundations that have been developed in previous editions of this text. In particular, the classification, images, and related commentary provided by LeBoit and McCalmont (2) as well as Murphy and Schwarting (3) were integral to the development of the present material and represent a major advance in the textural treatment of this difficult and rapidly evolving topic.

Lymphoproliferative disorders of the skin fall into two major categories: primary cutaneous neoplasms (those where lymphoma presents in the skin without extracutaneous involvement at the time of diagnosis) and extracutaneous neoplasms that may secondarily involve the skin. Furthermore, most cutaneous lymphomas have putative histogenetic origin from the distinct cell types of the immune system (4). The specific diseases that follow will thus be grouped according to the following schema in order to include the vast majority of conditions recognized by the current WHO/EORTC classification that have specific relevance to the skin (Table 31-1).

CUTANEOUS HEMATOPOIETIC INFILTRATES: OVERVIEW AND GENERAL CONCEPTS

Hematopoietic Cell Lineage: Relevance to Cutaneous Immune Surveillance and Lineage Differentiation

One of the major functions of skin is protection against environmental hazards, including infectious organisms. Evolution has allowed the development of a highly effective two-tiered defense mechanism composed of a rapid "innate" and a sustained "adaptive" response. The innate immunity is mediated by macrophages, leukocytes, natural killer (NK) cells, γ/δ T cells, and dendritic cells, which detect nonspecific epitopes commonly shared by different pathogens (such as glycolipids, lipoproteins, peptidoglycans, and double-stranded RNA) and mount immediate responses. In contrast, the adaptive arm of the cutaneous immune system targets specific protein antigens in a major histocompatibility–restricted manner through effectors like α/β T and B cells. Most cutaneous lymphomas have putative lineage derivation from and perhaps biologic behavior attributed to the distinct cell populations of the immune system and their evolutionary stages of maturation (4). Malignant T cells and myeloid cells tend to recapitulate morphologic and antigenic features of cells undergoing intrathymic/postthymic and intraosseous maturation, respectively. Malignant B cells also have definite developmental relationships to normal B-cell ontogeny within bone marrow and lymphoid organs. Because B-cell malignancies compose a clinically and morphologically diverse group of diseases, it is helpful conceptually to relate specific disorders to developmental stages of normal B-cell maturation. Figure 31-1 is an adaptation of the current classification schema that attempt to achieve this end.

T- and B-cell Infiltration Patterns

While numerous exceptions exist, there are fundamental and often reproducible trends in the patterns produced when lymphocytes infiltrate the skin (5). This is based in part on differences in adhesive ligands between B and T cells, resulting in

TABLE 31-1 Classification of Cutaneous Lymphoproliferative Disorders

Primary Cutaneous Lymphoproliferative Disorders
Mature B-cell lineage
- B-cell lymphomatoid hyperplasia
- Cutaneous follicle center lymphoma
- Cutaneous marginal zone B-cell lymphoma (MALT type)
- Cutaneous diffuse large B-cell lymphoma, leg type
- Cutaneous diffuse large B-cell lymphoma, other
  - Extraosseous plasmacytoma

Mature T-/NK-cell lineage
- T-cell lymphomatoid hyperplasia
- Mycosis fungoides
- Variants of mycosis fungoides
  - Localized pagetoid reticulosis
    - Follicular, syringotropic, granulomatous variants
  - Subtype of mycosis fungoides
    - Granulomatous slack skin
  - Sézary syndrome
- Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous large T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Primary extranodal NK-/T-cell lymphoma, nasal type
- Primary cutaneous peripheral T-cell lymphoma, unspecified
- Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma (provisional)
- Cutaneous γ/δ T-cell lymphoma (provisional)
- Primary cutaneous $CD4^+$ small-/medium-sized pleomorphic T-cell lymphoma (provisional)

Myeloid lineage
- Extramedullary hematopoiesis
- Myeloid sarcoma (aleukemic leukemia)

Precursor plasmacytoid dendritic cell lineage
- $CD4^+/CD56^+$ hematodermic neoplasm (blastic NK-cell lymphoma)

Secondary Lymphoproliferative Disorders Affecting Skin
B-cell lineage
- Precursor B-lymphoblastic leukemia/lymphoma
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- Follicular lymphoma, nodal type
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma, nodal type
- Intravascular large B-cell lymphoma
- Lymphomatoid granulomatosis
- Hodgkin's lymphoma

T-/NK-cell lineage
- Secondary extranodal NK-/T-cell lymphoma, nasal type
- Adult T-cell leukemia/lymphoma
- Peripheral T-cell lymphoma/angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma
- Precursor T-lymphoblastic leukemia/lymphoblastic lymphoma
- T-cell prolymphocytic leukemia

Myeloid lineage
- Acute myeloid leukemia
- Chronic myeloid leukemia

Precursor plasmacytoid dendritic cell lineage
- Plasmacytoid dendritic cell leukemia/lymphoma

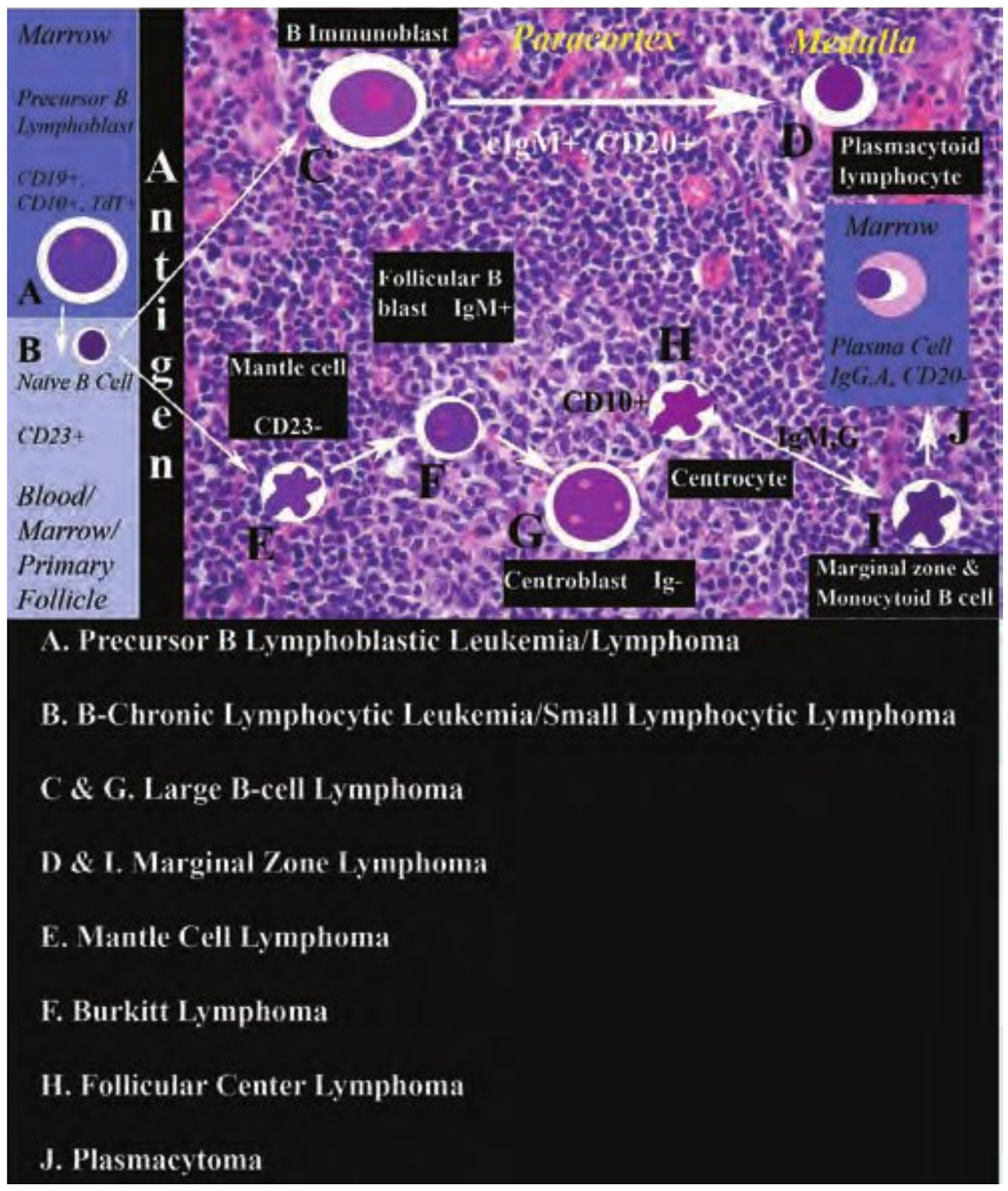


FIGURE 31-1. Schematic diagram of B-cell differentiation in relationship to sites of nodal maturation, relevant markers, and corresponding lymphomas that may develop.

differential affinity for various compartments within the skin. Moreover, chemokinetic and chemotactic signals may influence the migration of various classes of lymphoid cells in different ways. The best example of this is the tendency for both benign and malignant T cells, but not B cells, to migrate into epithelial structures, including the epidermis and its adnexae. This results in the phenomena of "epidermotropism" and "folliculotropism," accounting for the tendency to identify T cells within the epidermal layer and often as a band of cells within the underlying papillary dermis (Fig. 31-2A). Occasionally, as is the case in epidermotropic phases of mycosis fungoides (MF), T cells may align along the basement membrane zone of the dermal–epidermal junction, a finding that may have a basis in expression by these cells of integrin receptors for the specific membrane components (6). This "T-cell pattern" of infiltration is not invariable among T-cell malignancies, however, and epidermotropism may be blunted as tumors evolve and progress to more aggressive and poorly differentiated states. B cells, on the other hand, do not demonstrate the same affinity for the epidermis and adnexae, and seldom are these cells detected in significant numbers within the epidermis or papillary dermis. The sparing of the latter produces the characteristic "grenz zone" seen in B-cell pattern infiltrates of the skin. Moreover, perhaps because of the innate proclivity of B cells to aggregate into follicular structures, B-cell infiltrates in the skin often (but not invariably) show a nodular architecture (Fig. 31-2B).

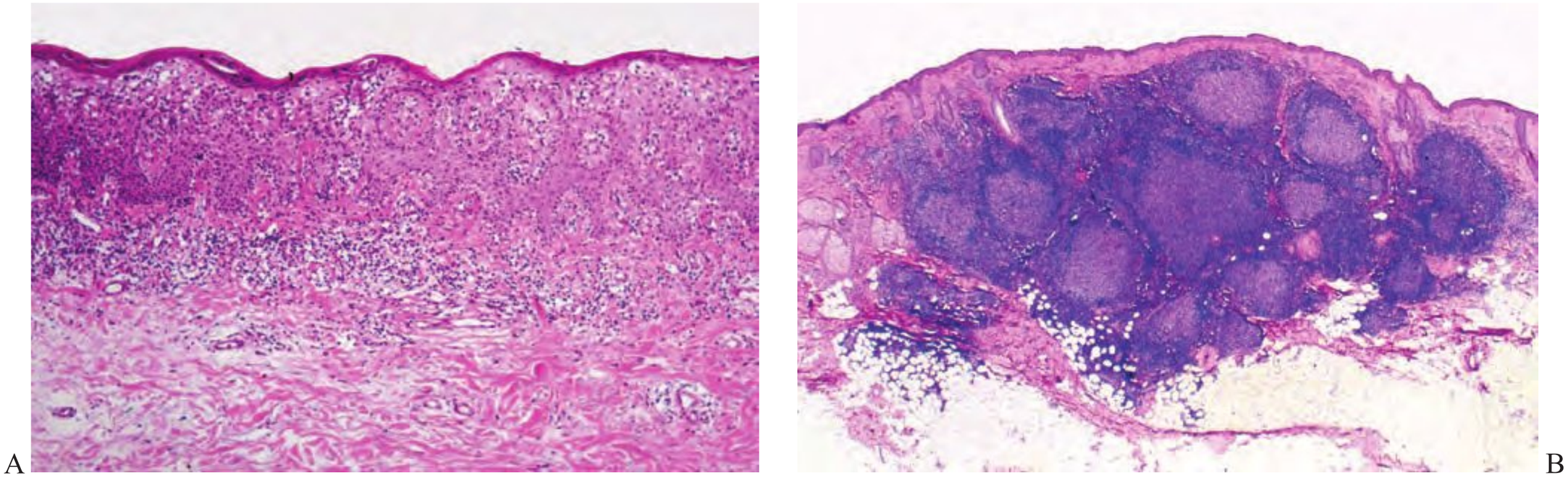


FIGURE 31-2. Patterns of T- and B-cell infiltration. A: T-cell pattern. B: B-cell pattern with grenz zone and germinal center formation.

T- and B-cell patterns are potentially helpful in presumptive assignment of cell lineage, but they are not invariable, cannot be used as a reliable surrogate for immunohistochemical detection of lineage-related antigens, and do not permit separation of reactive from dysplastic and malignant (Table 31-2). Although this latter distinction frequently depends on cytology, immunophenotype, and genotype, the architecture or "trafficking patterns" of hematopoietic cells in the skin may also provide insight into the biologic potential for aggressive behavior.

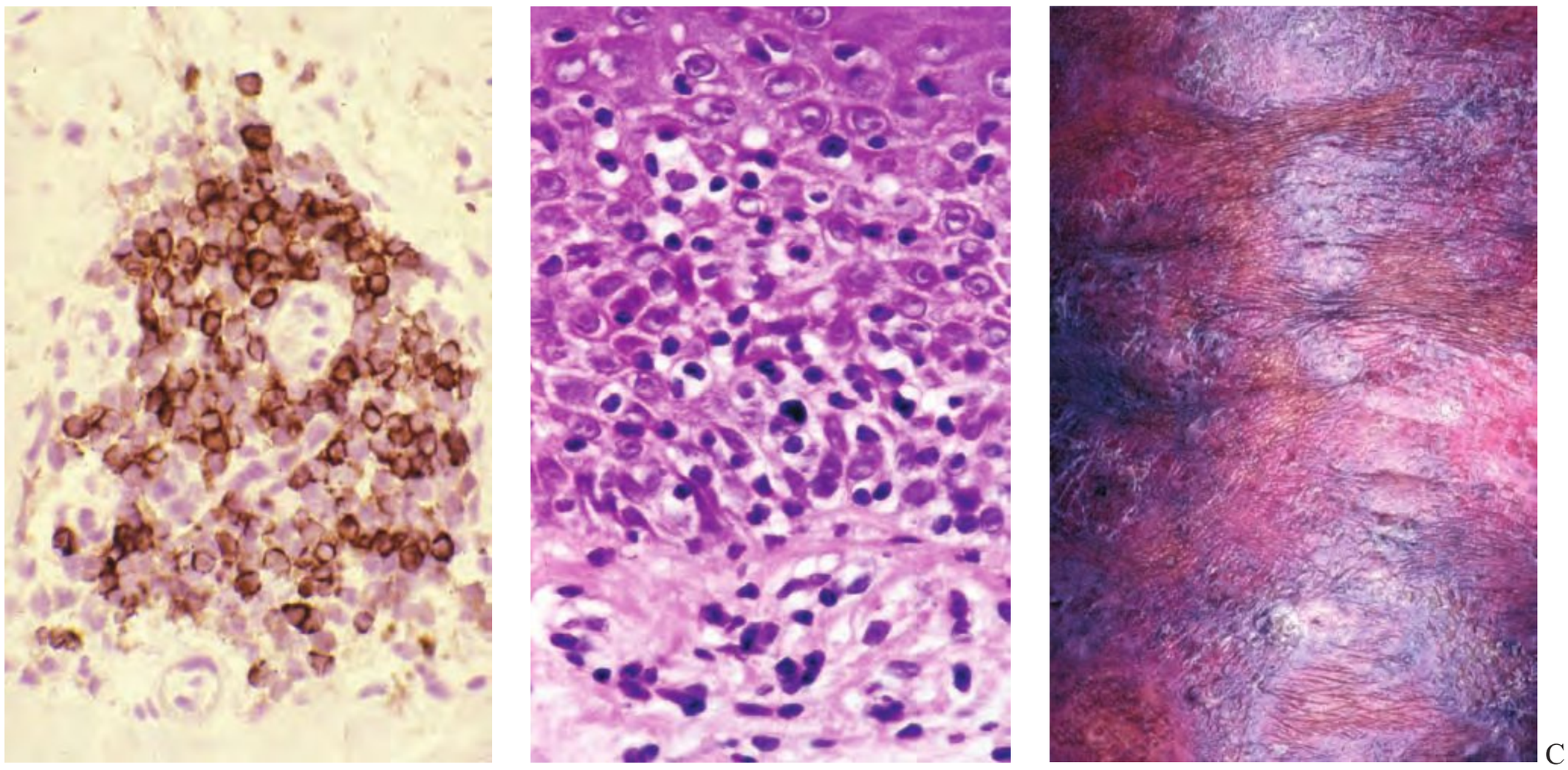
Abnormal Trafficking: Distinction from Inflammation

Skin is a lymphoid organ, and both the epidermal and dermal layers represent interactive immune systems that contribute to and partially regulate inflammatory cell trafficking (7,8). In both T- and B-cell responses in skin, circulating lymphocytes initially adhere to activated endothelium lining dermal postcapillary venules. Migration across the vessel wall results in perivascular or angiocentric dermatitis (Fig. 31-3A). If further migration is stunted, this exclusive angiocentric localization may produce a pattern that may lead to a specified number of differential diagnostic considerations based on correlation with clinical parameters (e.g., as in erythema chronicum migrans). Migration away from the vessel wall is presumably swift enough that in the case of T cells, papillary dermal accumulation and epidermotropism, in addition to a persistent angiocentric pattern, may result. However, activated T cells on an immunologic mission, as in the case of contact hypersensitivity, psoriasis, or cytotoxic dermatitis, generally alter the epidermis as they enter it by way of the cytokines and growth factors that they produce. Thus, reactive T-cell exocytosis is often accompanied by epithelial spongiosis, acanthosis, or apoptosis. In the case of malignant epidermotropic T-cell infiltration, in contrast, the epidermis tends to be "passive," with T-cell infiltration resulting in permissive aggregation of variably atypical lymphocytes within the epidermis (Fig. 31-3B) and sometimes also or exclusively in adnexal epithelium. This infiltration is not generally associated with reactive epithelial alteration in the form of spongiosis or apoptosis but rather may be associated with epithelial injury in the form of localized mucinous degeneration, a potential contributing factor to the development of Pautrier microabscesses and follicular mucinosis that may accompany MF (9). Moreover, as the epidermis becomes more extensively infiltrated, impaired maturation often manifests as clinical abnormalities in scale production. Hence, many T-cell lymphoproliferative disorders will show surface hyperkeratosis that in early stages may mimic dermatitis clinically (Fig. 31-3C).

Infiltration of the skin by reactive B cells often results in a perivascular accumulation of cells usually without significant epidermotropism or papillary dermal/interstitial involvement (i.e., producing a grenz zone of papillary dermal sparing). With persistence of antigenic stimulus, as may occur in the setting of some insect bite reactions, nodular aggregates of B cells may form in order to variably recapitulate the formation of germinal centers within the dermis (Fig. 31-4A). These patterns of infiltration contrast sharply with those of malignant B cells. Although malignant B cells may also form nodules vaguely reminiscent of germinal centers, or even induce the formation of associated reactive B-cell infiltrates, the former tends to show a destructive relationship to preexisting structures (Fig. 31-4B). Accordingly, malignant B cells will frequently infiltrate in an interstitial pattern (versus perivascular), resulting in splaying apart of collagen bundles and mesenchymal cells (e.g., smooth muscle cells forming arrector pili muscles) within the reticular dermis. Moreover, nodular

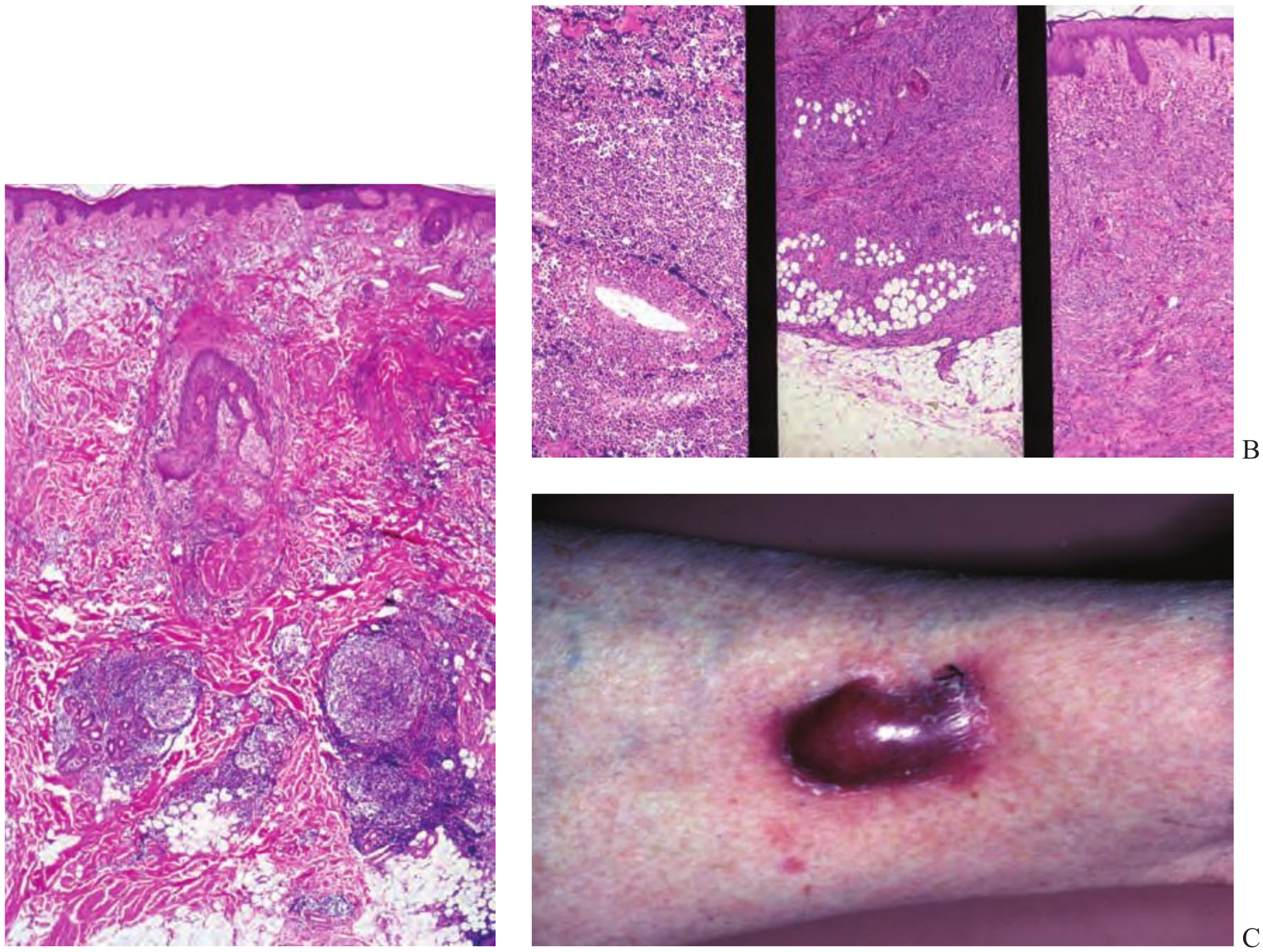
TABLE 31-2 T-Versus B-cell "Trafficking" Pattern

	T cell	B cell
Overall architecture	Band-like	Nodular
Pattern of the infiltrate	Perivascular	Perivascular and interstitial
Epidermal involvement (exocytosis/ epidermotropism/ folliculotropism)	Present	Absent
Grenz zone	Absent	Present



A, B C

FIGURE 31-3. Normal and abnormal trafficking patterns. A: T-cell immunohistochemistry of angiocentric pattern. B: Abnormal epidermotropism into a "passive" epidermis. C: Scaling patches and plaques as a consequence of altered epidermal maturation associated with T-cell epidermotropism (MF).



A B C

FIGURE 31-4. Normal and abnormal trafficking patterns. A: B-cell pattern showing nondestructive infiltration of superficial and deep dermis. B: B-cell lymphomas showing vascular invasion (left), replacement of subcutis (middle), and diffuse interstitial pattern (right). C: Plum-colored nodule covered by thinned, glistening epidermis due to B-cell dermal infiltration.

aggregation of malignant B cells tends to displace adnexal epithelium, resulting in their distortion and occasionally in their ischemic destruction in the process.

Circulating leukemic cells, like inflammatory cells, may show a perivascular pattern of infiltration on initial infiltration of skin. However, unlike reactive and malignant T cells, they will avoid epithelial infiltration, and like other malignant cells, they will soon infiltrate in an interstitial pattern within the dermis. This interstitial architecture, albeit suggestive of abnormal trafficking inherent to malignancy, does not invariably correlate with a malignant phenotype. In this regard, it should be recalled that histiocytes in the setting of certain evolutionary stages of palisaded granulomatous dermatitis, lymphocytes in early inflammatory lesions of morphea, and immature myeloid cells in the setting of extramedullary hematopoiesis may also show similar interstitial patterns.

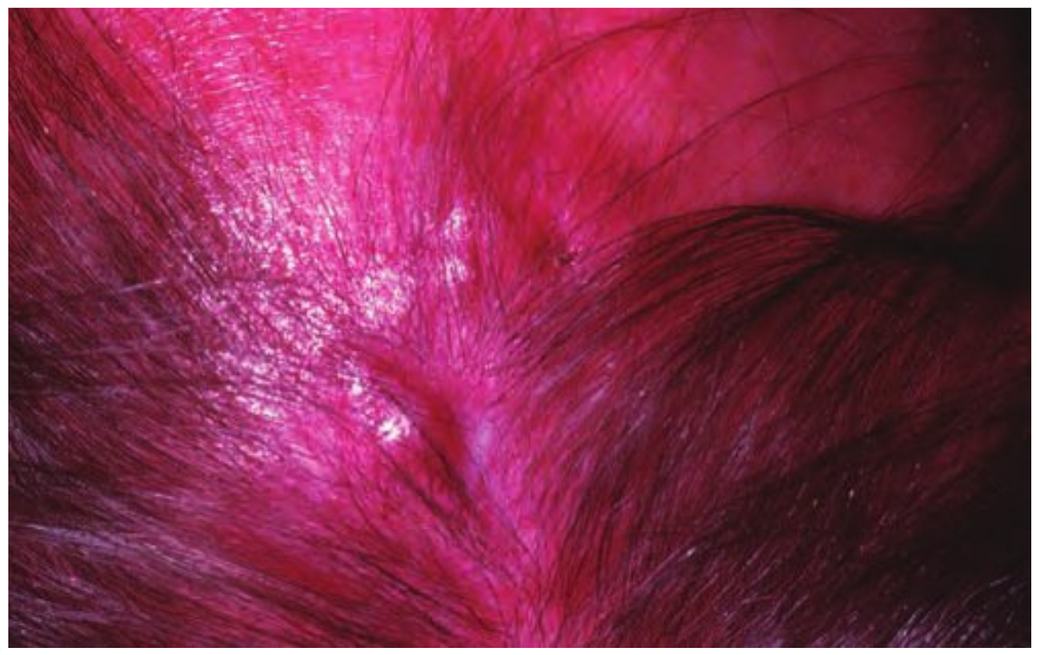
The tendency for progressive dermal infiltration with relative sparing of the epidermal layer in both B-cell and many leukemic malignancies results in clinical lesions that are red to plum colored and covered by thin, shiny (nonkeratotic) epidermal surfaces (Fig. 31-4C).

PRIMARY CUTANEOUS B-CELL LYMPHOPROLIFERATIVE DISORDERS

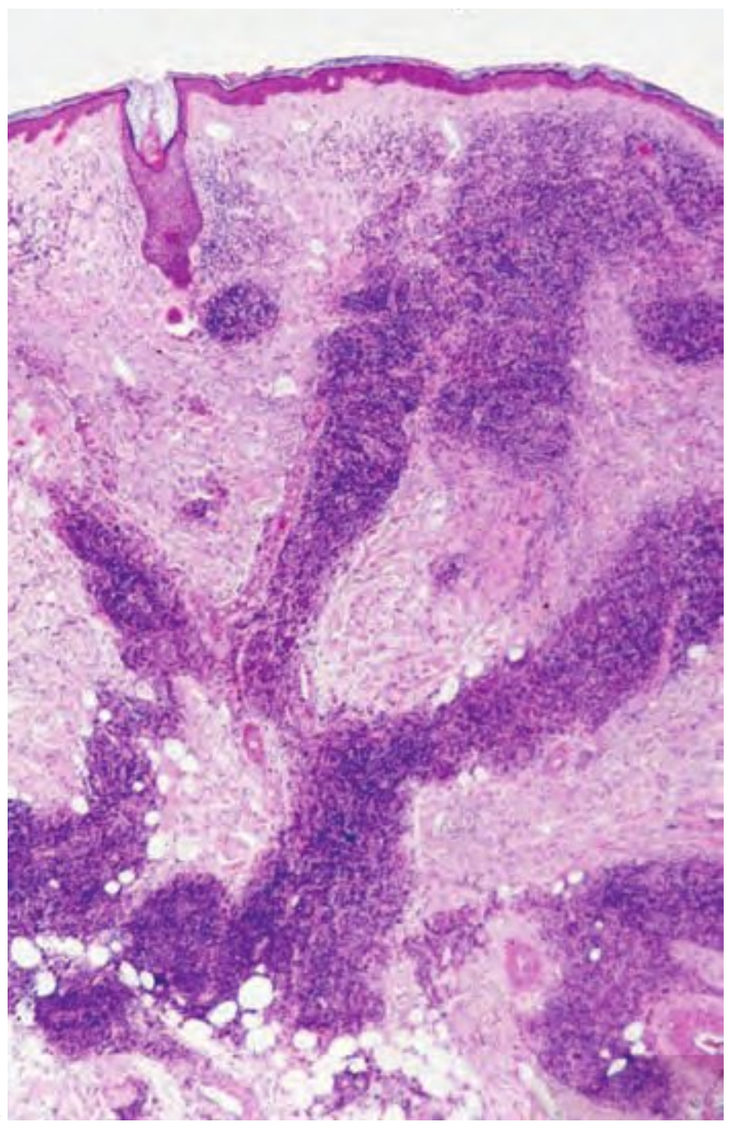
B-cell Lymphomatoid Hyperplasia

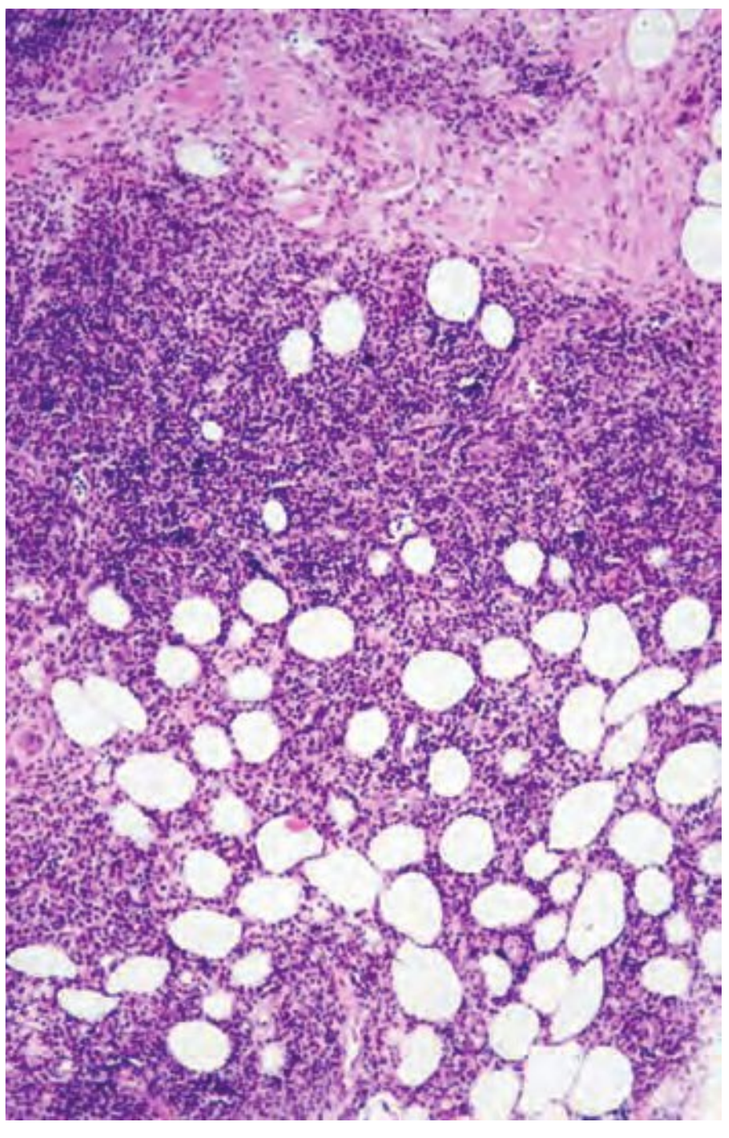
Critical to consideration of B-cell malignancies of the skin is understanding of the patterns and compositions inherent to forms of cutaneous lymphoid hyperplasia where B-cells predominate. Because such lesions have been confused with true lymphomatous infiltrates, the unfortunate term *pseudolymphoma* has been coined, and its use is discouraged for obvious semantic reasons.

Clinical Features. Typically, B-cell lymphomatoid hyperplasia (B-CLH) develops as one or several clustered nodular lesions without evidence of epidermal involvement (e.g., scaling). The head, neck, and trunk are most frequently involved, although any site is potentially vulnerable. The color is often red to



A





B, C

FIGURE 31-5. Clinical and histologic features of B-cell lymphomatoid hyperplasia. A: Clinical lesions. B: Scanning magnification of dermal infiltrate. C: Involvement of deep dermis and subcutis.

purple, and thus the clinical appearance may overlap with that of true B-cell lymphoma (Fig. 31-5A). Lesions may persist for many months before resolution occurs, and on occasion, evolution to lymphoma has been documented.

Histopathology. Infiltrates may show a nodular or diffuse architecture, and although many lesions will be most concentrated in the more superficial dermal layers, equal or preferential involvement of the deeper dermis and subcutis may be seen (Fig. 31-5B, C). This "bottom heavy" pattern of infiltration that by convention has been associated with B-cell malignancies does not reliably permit exclusion of B-CLH. Unlike true B-cell lymphoma, however, hyperplastic B-cell infiltrates generally do not exhibit a pattern of infiltration that destroys preexisting structures (e.g., vessels, adnexae). While hair follicles may be distorted and hyperplastic in certain cases where primary follicular pathology presumably incites the B-cell proliferative response (so-called pseudolymphomatous folliculitis), this is distinct from secondary follicular injury that may be seen in the setting of true lymphoma.

The hallmark of B-CLH is the formation of true lymphoid follicles (Fig. 31-6A). These follicles contain a cytologic continuum of B-cell maturation, and this exhibits lymphocytes with small and large, cleaved and uncleaved nuclear contours (Fig. 31-6B, C), immunoblasts, and tingible-body macrophages (macrophages containing particulate basophilic debris within their cytoplasm), the so-called starry-sky pattern. Mitotic figures and apoptotic cells may be numerous in follicles showing florid evidence of immune activation (Fig. 31-6D). Reactive follicles may show expanded mantle zones, whereas follicle-like structures formed in certain B-cell lymphomas tend to show thinned or absent mantle zones. Because reactive follicles are generally polyclonal, both kappa and lambda light chains are expressed by immunohistochemistry. Moreover, immunoglobulin gene rearrangements are usually not present, although clonal proliferation within B-CLH has been described (10), and this feature alone should not be used to separate reactive from malignant infiltrates of B cells.

Histogenesis. The cause is often unknown, although persistent localized immune responses to injected or extruded antigens, as may occur with arthropod bite assaults or even in the context of follicular cyst rupture, have been implicated. Certain drugs may also result in B-cell as well as T-cell pattern cutaneous infiltrates that may mimic lymphoma both clinically and histologically (11,12).

Differential Diagnosis. B-CLH must be differentiated from follicle center lymphoma, which is a lesion that generally shows a follicular pattern of dermal infiltration. Immunohistochemical and molecular analyses generally permit differential in difficult cases where cytologic features that separate reactive from neoplastic lymphoid follicles are not present (see below). It is noteworthy that establishing the presence of reactive germinal centers in a skin infiltrate does not definitively exclude lymphoma, because some forms of B-cell lymphoma are typically associated with admixed reactive follicles (e.g., extranodal marginal cell lymphoma). Moreover, as has been mentioned, patients with established B-CLH must be monitored over time in recognition of the fact that on occasion, this presentation will be a harbinger of eventual development of a clonal B-cell malignancy. Numerous eosinophils may be observed in association with some forms of B-cell cutaneous lymphoid hyperplasia, including lesions of angiolymphoid hyperplasia with eosinophilia and its localized variants.

Table 31-3 summarizes distinguishing characteristics that may be useful in differential diagnosis of benign vs. malignant B-cell lymphoproliferative disorders in the skin.

TABLE 31-3 Salient Differential Features of Reactive and Neoplastic Cutaneous B-cell Proliferations

	B-cell lymphomatoid hyperplasia	B-cell lymphomas
Distribution of infiltrate	Often top heavy	Often bottom heavy
Pattern of infiltrate	Nodular/Diffuse	Nodular/Diffuse/Interstitial
Destructive growth	Absent (adenexae spared)	Present (destructive growth affecting adnexae)
Composition of infiltrate	Mixed	Monomorphous with atypia
	Polyclonal	Clonal
	Light chain unrestricted	Light chain restricted
Follicle formation	Benign polarized follicles with expanded mantle zone	Loss of follicular polarization with thinned/absent mantle zone
Mitotic activity	Only in germinal centers	Both within and outside germinal centers
Prominent vasculature	Present	Absent

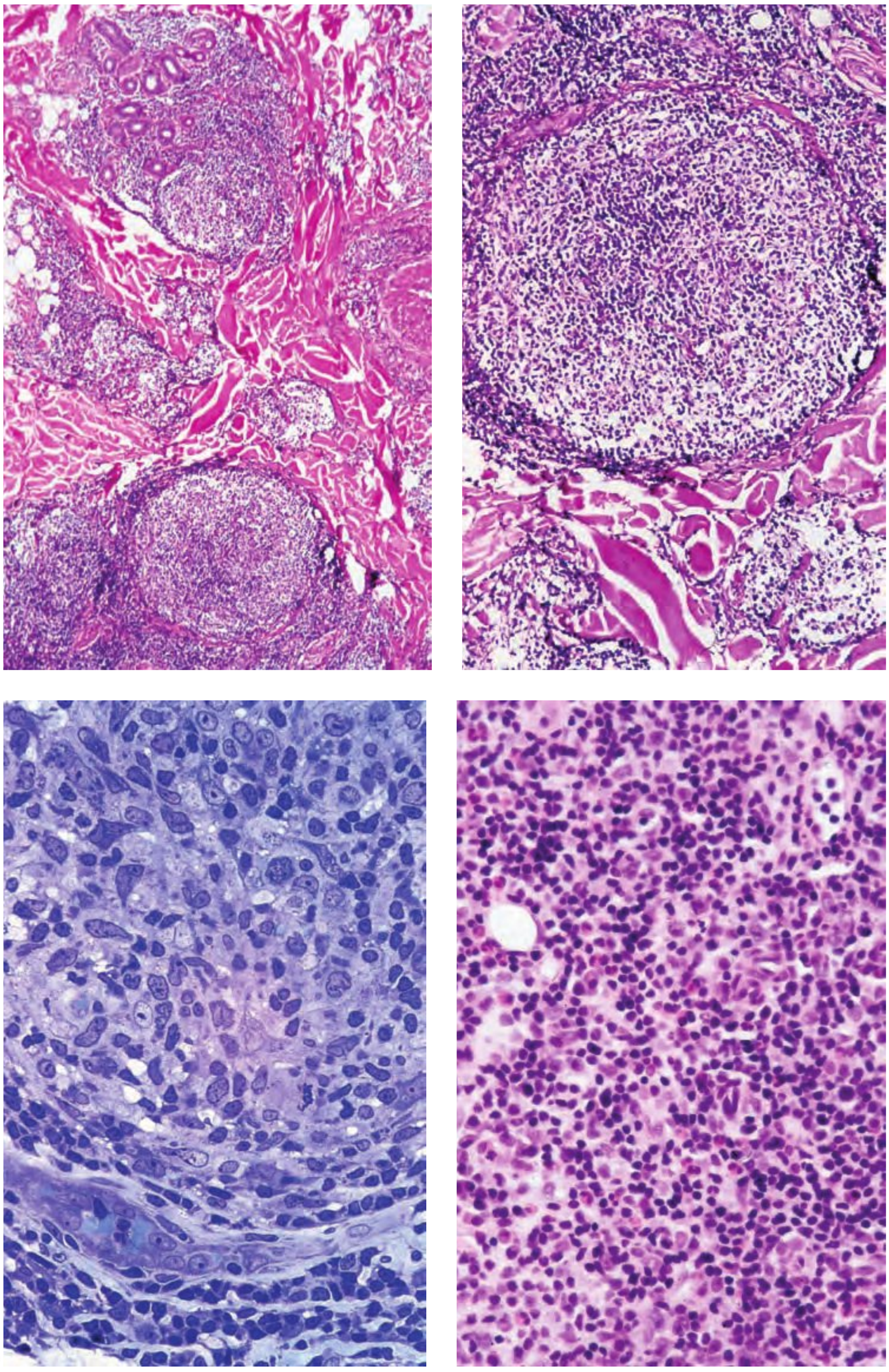


FIGURE 31-6. Cutaneous lymphoid hyperplasia, B-cell type. A: Nodular dermal infiltration by lymphoid cells with formation of germinal centers. B: Higher magnification of germinal center. C: One-micron, toluidine blue– stained section of germinal center composed of admixture of lymphocytes in various stages of maturation. D: Reactive germinal center characterized by mitotically active follicular center lymphocytes.

Primary Cutaneous Follicle Center Lymphoma

Primary cutaneous follicle center lymphoma (PCFCL), one of the most common types of primary B-cell lymphoma of the skin (comprising approximately 11% of cutaneous lymphoma [1,13]), is a neoplasm derived from follicular center B cells (centrocytes/cleaved follicular center cells [FCCs]) and centroblasts/noncleaved FCCs.

Clinical Features. PCFCL occurs primarily as one to several red- to plum-colored nodules (Fig. 31-7A) often on the head and trunk of the elderly without sex predilection and, unlike overt nodal follicular lymphoma, tends to remain localized in the skin where local therapy may be effective (14). Lesions with exclusive skin involvement tend to show a more favorable prognosis (5-year survival >95%) than is the case when skin is

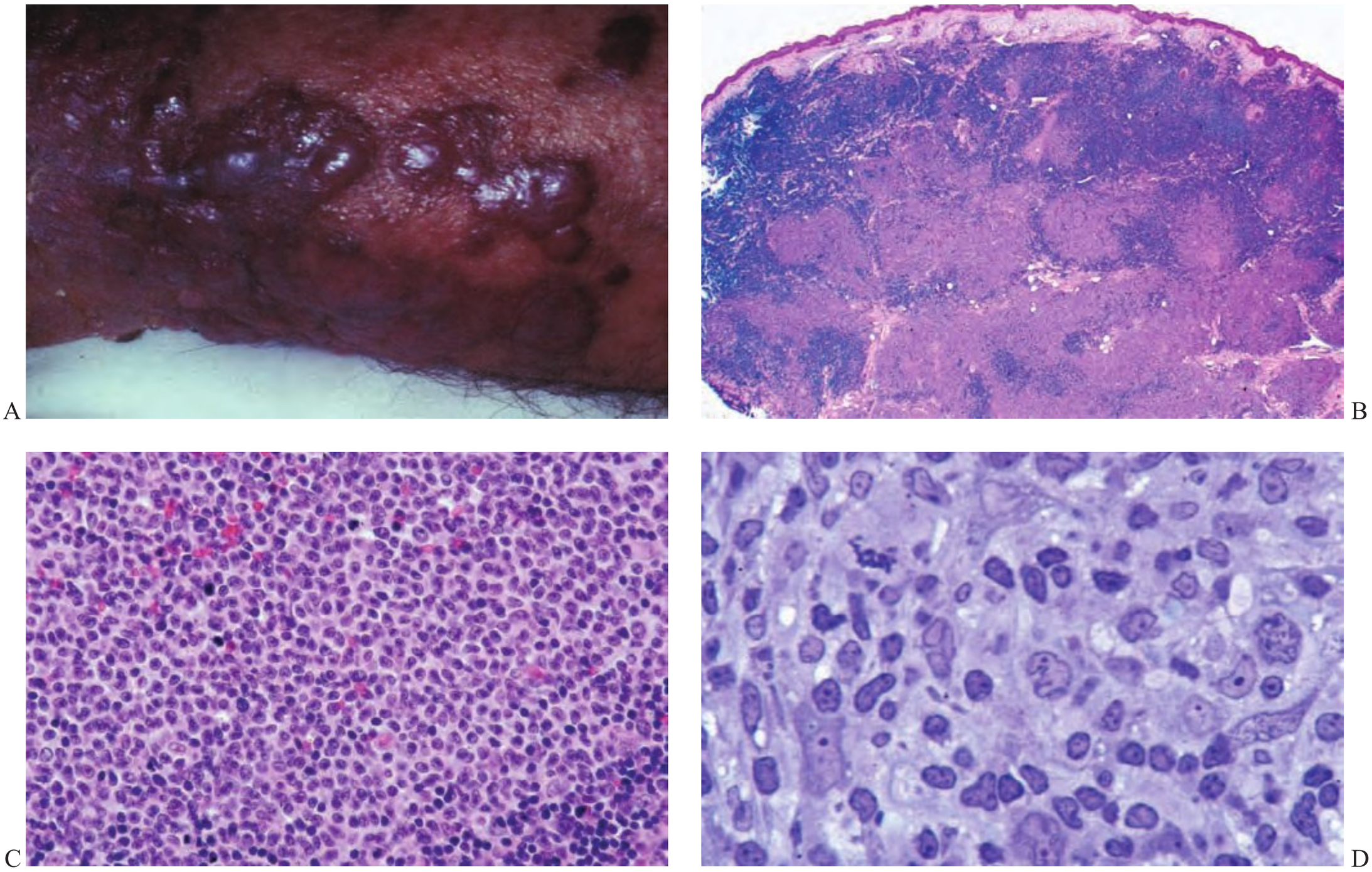


FIGURE 31-7. Primary cutaneous follicle center cell lymphoma. A: Clustered plum-colored nodules covered by thinned, glistening epidermal layer. B: Scanning magnification showing coalescent nodules forming follicle-like architecture. C: Higher magnification of malignant centrocytes and centroblasts. D: One-micron, toluidine blue–stained section showing cytologic features of centrocytes and centroblasts.

infiltrated secondary to nodal disease (15,16). Although recurrences are often observed, the overall prognosis is good (5-year survival of 95%), with spread beyond the skin being exceedingly rare.

Histopathology. Primary skin involvement (17,18) presents as nodular dermal infiltrates that may often extend to the subcutis (19). The dermal nodules initially may resemble germinal centers (17) but are composed of monomorphic neoplastic cells devoid of mantle zones (17). The neoplastic follicles are depolarized and do not show a prominent starry-sky pattern, and other regions may be characterized by a more diffuse pattern with associated sclerosis. Based on these architectural features (Fig. 31-7B), lesions may be classified as follicular (>75% follicular architecture), follicular and diffuse (25% to 75% follicular architecture), and minimally follicular (<25% follicular). Rarely, exclusively diffuse growth pattern may also be seen, where the diagnosis must be based on cellular composition. Cytologically, two types of neoplastic lymphocytes are observed in follicular lymphoma (Fig. 31-7C, D). The predominant cell is the centrocyte, or cleaved FCC, a small- to medium-sized lymphocyte with scant cytoplasm and with angulated, infolded, or twisted nuclear contours and inconspicuous nucleoli. Similar but often smaller centrocytes may also be present in the interfollicular regions. Centroblasts, or noncleaved FCCs, are larger transformed lymphocytes with round to oval nuclei with vesicular chromatin and several visible nucleoli. On occasion, an even admixture of centrocytes and centroblasts, or even a predominance of centroblasts, may be encountered. Unlike nodal follicular lymphoma, histologic grading of PCFCL is not advised by the WHO/EORTC, as the growth pattern and number of blast cells do not appear to have prognostic relevance (20–22).

Histogenesis. Germinal center B cells are believed to represent the cell of origin of follicle center lymphoma. Tumor cells tend to express surface immunoglobulins on frozen sections (immunoglobulin IgM, IgD, IgG, and rarely IgA); BCL6; CD10; and the B-cell associated markers CD20, CD19, CD22, and CD79a. Most cases are negative for CD5 (in

contrast to chronic lymphocytic leukemia [CLL]/small lymphocytic lymphoma [SLL]). Although BCL2 expression is useful in differentiating neoplastic follicles in extracutaneous sites from normally negative hyperplastic germinal centers, it should be noted that in PCFCL, BCL2 is frequently negative. The finding of BCL2 positivity in a follicular lymphoma at a cutaneous site should raise the strong suspicion of secondary cutaneous involvement of nodal follicular lymphoma. The t(14;18)(q32,q21) rearrangement of the BCL2 gene typical of nodal follicular lymphomas is not frequently detected in PCFCL, suggesting that these two entities may be separate diseases (23,24). Rearrangement of immunoglobulin heavy and light chain genes is the rule (Fig. 31-8), and cytogenetic abnormalities affecting the immunoglobulin heavy chain locus are identified (25).

Differential Diagnosis. PCFCL must be differentiated from nodal follicular lymphoma with secondary cutaneous involvement, cutaneous lymphoid hyperplasia of the B-cell type (B-CLH) (26,27), and other conditions associated with the formation of reactive follicles (e.g., primary cutaneous marginal zone lymphoma [PCMZL] and mantle cell lymphoma [MCL]) (Table 31-4). As mentioned previously, in contrast to nodal follicular lymphoma, PCFCL frequently lacks BCL2 immunoreactivity and t(14;18)(q32;q21). B-CLH often is clinically manifested by one or more erythematous to plum-colored plaques and nodules. Any site may be affected, but there is a predilection for skin of the face and scalp. The underlying cause is often unknown, although speculated etiologies include reactions to topical agents or to injected antigens, as may occur in insect bites, or localized infection

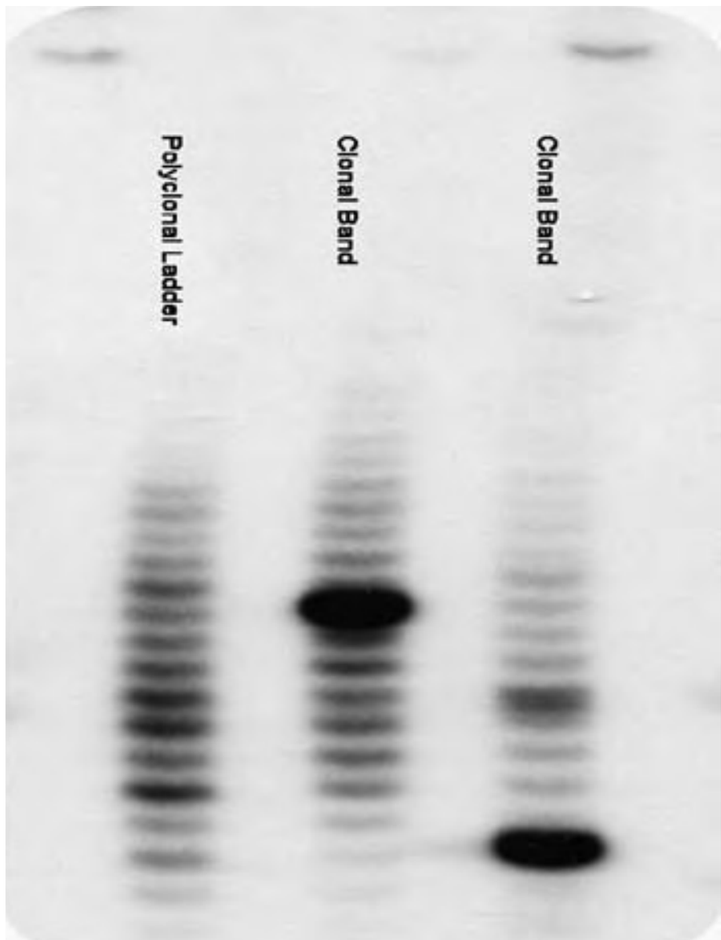


FIGURE 31-8. PCR analysis for clonal IgH gene rearrangements. The left lane shows a polyclonal ladder with no evidence of gene rearrangement, whereas the middle and right lanes show dominant bands in a background polyclonal ladder, indicating clonal IgH gene rearrangement in two cases of B-cell lymphoma.

with the spirochete *Borrelia burgdorferi* (28–30). Histologically, there may be a nodular to diffuse interstitial infiltrate that often involves the deep dermis and occasionally the subcutis. Germinal center formation may be variably pronounced, but occasionally these structures are indistinguishable from those

TABLE 31-4 Morphologic and Immunohistochemical Differential Diagnosis of Cutaneous B-cell Lymphoproliferative Disorders With a Follicular Growth Pattern

	Follicular growth pattern		Immunohistochemical markers					
Entities	Cellular composition	Follicular architecture	BCL2	BCL6	CD10	CD5	Cyclin D1	CD23
B-CLH	Benign, polymorphous, polyclonal	Variable size and circumscription	−	+	+	−	−	−
PCFCL	Neoplastic, monomorphous, clonal	Variable size and circumscription	−	+	+	−	−	+/−
Nodal follicular lymphoma	Neoplastic, monomorphous, clonal	Variable size and circumscription	+	+	+	−	−	−
PCMZL	Benign, polymorphous, polyclonal	Variable, irregular (when colonized with neoplastic cells)	+	−	−	−	−	−
MCL	Benign, polymorphous, polyclonal	Small, round, and circumscribed	+	−	−	+	+	−
B-CLL/SLL	Proliferation centers/ Prolymphocytes and paraimmunoblasts	Evenly dispersed uniform pale zones	+	−	−	+	−	+

B-CLH, B-cell lymphomatoid hyperplasia; PCFCL, primary cutaneous follicle center lymphoma; PCMZL, primary cutaneous marginal zone lymphoma; MCL, mantle cell lymphoma; B-CLL/SLL, B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma.

TABLE 31-5 Morphologic and Immunophenotypical Differential Diagnosis of Cutaneous B-cell Lymphoproliferative Disorders With a Diffuse/Nodular Growth Pattern

Entity	Cytomorphology	Immunohistochemical profile
PCFCL, diffuse pattern	Centroblast-like cells (large with round nuclei, vesicular chromatin, and several nucleoli) admixed with centrocyte-like cells (small to medium sized with scant cytoplasm, angulated nuclei, and inconspicuous nucleoli)	BCL2^{-}, BCL6^{+}, CD10$^{+/-}$*, MUM1/IRF4−
PCDLBCL, leg type	Predominance of centroblast-/immunoblast-like cells (medium sized to large with round to oval nuclei and prominent nucleoli)	BCL2^{+}, BCL6^{+}, CD10^{-}, MUM1/IRF4+
PCDLBCL, other	Predominance of centroblast-/immunoblast-like cells (medium sized to large with round to oval nuclei and prominent nucleoli)	BCL2^{-}, BCL6^{+}, CD10^{-}, MUM1/IRF4$^{+/-}$
Nodal DLBCL	Monomorphous, large centroblast-like cells with scant cytoplasm and large nuclei with vesicular chromatin and prominent nucleoli	CD19^{+}, CD20^{+}, CD22^{+}, CD79a^{+}, BCL6^{+}, cyclin D1^{-}; variable CD30, CD5, and BCL2
LYG	Polymorphous with cleaved atypical lymphocytes, immunoblasts, plasma cells, histiocytes, and reactive T cells with an angiodestructive growth pattern	EVB^{+}, CD20^{+}, CD15^{-}, variable CD30
B-LBL	Mitotically active lymphoblasts with sparse cytoplasm, convoluted nuclei, finely stippled chromatin, and inconspicuous nucleoli	TdT^{+}, CD19^{+}, CD79a^{+}, CD10^{+}, CD24^{+}, CD179a/b^{+}; variable CD20 and CD22
B-CLL/SLL	Uniform small lymphocytes with round hyperchromatic nuclei and inconspicuous nucleoli	BCL2^{+}, BCL6^{-}, CD10^{-}, CD5^{+}, CD23^{+}, cyclin D1^{-}

PCFCL, primary cutaneous follicle center lymphoma; PCDLBCL, primary cutaneous diffuse large B-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; LYG, lymphomatoid granulomatosis; B-LBL, B-cell lymphoblastic leukemia/lymphoma; B-CLL/SLL, B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma.
*Lesions with a diffuse growth pattern may lose CD10 expression.

encountered in reactive lymph nodes. Specifically, in addition to smaller lymphocytes with cleaved nuclei (centrocytes) and larger lymphocytes with noncleaved nuclei (centroblasts), they will contain an admixture of immunoblasts, antigen-presenting follicular dendritic cells, and macrophages containing phagocytized cellular debris (tingible body macrophages). Moreover, there tends to be aggregation of centroblasts and tingible body macrophages at one pole of the hyperplastic follicle and of centrocytes at the opposite pole, producing darker and lighter-staining regions, respectively. Immunohistochemistry will reveal both kappa and lambda immunoglobulin light chain expression in B-CLH, as opposed to monotypic expression in follicular lymphoma. Genotypic analysis may also be of assistance in establishing a diagnosis of B-CLH when it fails to reveal clonal immunoglobulin gene rearrangements. However, it must be noted that on occasion, cases of B-CLH appear to evolve over time into more aggressive clonal processes or may harbor a malignant clone in the midst of otherwise reactive histologic and immunophenotypic changes (31). While PCFCL displays a BCL2^{-}/CD5^{-}/CD10^{+}/BCL6^{+} phenotype, PCMZL cells are BCL2^{+}/CD5^{-}/CD10^{-}/BCL6^{-}. MCL expresses CD5 and cyclin D1. Morphologic distinction between PCFCL with a purely diffuse pattern from diffuse large B-cell lymphoma, leg type (PCDLBCL, leg type) is difficult, especially in cases where centroblasts predominate in the infiltrate. Immunohistochemical profiling is most useful in this scenario. Although both entities express BCL6, CD10 is often negative in the latter. In addition, PCFCL lacks BCL2 and multiple myeloma-1/interferon regulatory factor-4 (MUM-1/IRF-4) expression, both of which are strongly positive in PCDLBCL, leg type (32) (Table 31-5).

Primary Cutaneous Marginal Zone B-cell Lymphoma

PCMZL belongs to a group of extranodal marginal zone B-cell lymphomas, referred to as *mucosa-associated lymphoid tissue* (MALT) lymphoma, in which these neoplasms were first recognized (33) and includes cases with high numbers of plasmacytoid cells previously designated as primary cutaneous immunocytoma. PCMZL comprises approximately 7% of all cutaneous lymphoma cases (1).

Clinical Features. MALT lymphoma is responsible for <10% of all B-cell lymphomas, and the gastrointestinal tract is the primary site of involvement in 50% of cases (33). Other sites may be affected, with skin infiltration noted in 11% of cases (32). The male-to-female ratio is 1.0:1.2, and the median age of occurrence is 61 (34). Chronic lymphoid hyperplasia caused by antigenic stimulation may be a predisposing feature, with *Helicobacter pylori*–associated

chronic gastritis (35,36), Hashimoto thyroiditis (37–39), and autoimmune sialadenitis (40,41) representing important examples. Other examples of MALT lymphoma being associated with an infectious agent are orbital lymphoma (*Chlamydia psittaci*) and cutaneous MALT lymphoma (*B. burgdorferi*) (42–45). Patients with hepatitis C have a higher incidence of splenic marginal zone lymphoma (46). Conceptually, MALT lymphomas are divided into a "native" type that arises in extranodal anatomic compartments where lymphoid tissue is normally present and an "acquired" type that emanates from tissue that normally lacks lymphoid tissue. In general, MALT lymphoma is an indolent form of lymphoma (with a 5-year survival close to 100%) that responds well to a variety of therapeutic modalities, including eradication of chronic antigenic stimulus in cases where infectious agents are implicated.

Histopathology. A characteristic feature of PCMZL is the tendency of the neoplastic cells to infiltrate around reactive B-cell follicles. This infiltration is in a marginal zone distribution (external to the mantle zone), and expansion of these areas may result in confluent zones that displace and separate the reactive follicles (47,48). Marginal zone B cells have small- to medium-sized nuclei with slightly irregular contours and inconspicuous nuclei and thus resemble centrocytes (Fig. 31-9). The cytoplasm is variably visible and pale, with cells showing less cytoplasm resembling small lymphocytes and those with more ample cytoplasm acquiring a monocytoid appearance. Variable plasmacytic differentiation may also be present. A minority population of centroblasts and immunoblasts may also be observed. Colonization of the reactive germinal centers by neoplastic cells may occasionally produce a picture that initially resembles follicular lymphoma.Transformation to diffuse large B-cell lymphoma (DLBCL) (see below), although rare, has been described.

Histogenesis. The cell of origin is speculated to be a post-germinal center marginal zone B cell. Tumor cells express immunoglobulins (most often IgM) and show light chain restriction. The typical immunophenotype is $CD20^+$, $CD79^+$, $CD21^+$, $BCL2^+$, $BCL6^-$, $CD5^-$, $CD10^-$, and $CD23^-$, although a marker entirely specific for MALT lymphoma does not presently exist. It is worth noticing that abnormal BCL10 expression common to MALT lymphomas is absent in PCMZL (49). Immunoglobulin genes are rearranged. More recently, understanding of the underlying genetic abnormalities in MALT lymphoma has increased (43,45,50,51). In contrast to gastric MALT lymphomas, t(11;18)(q21;q21), in which the apoptosis inhibitor gene API2 on chromosome 11 partners with the MALT1 gene on chromosome 18, has not been observed in PCMZL (25,52,53). Instead, a novel t(14;18)(q32;q21) recurrent translocation involving IgH and MALT1 was documented in about one third of cases of PCMZL (25).

Differential Diagnosis. The differential diagnosis includes other small B-cell lymphomas as well as B-CLH. Absence of CD5 and cyclin D1 are useful in separating PCMZL from MCL, absence of CD5 alone in excluding B-CLL/SLL, and absence of CD10 and BCL6 in ruling out follicular lymphoma. Presence of expanded interfollicular zones by B cells with cytologic and immunophenotypic features of PCMZL should distinguish this entity from most cases of B-CLH where interfollicular regions, if expanded, should contain a predominant population of T cells (Table 31-4).

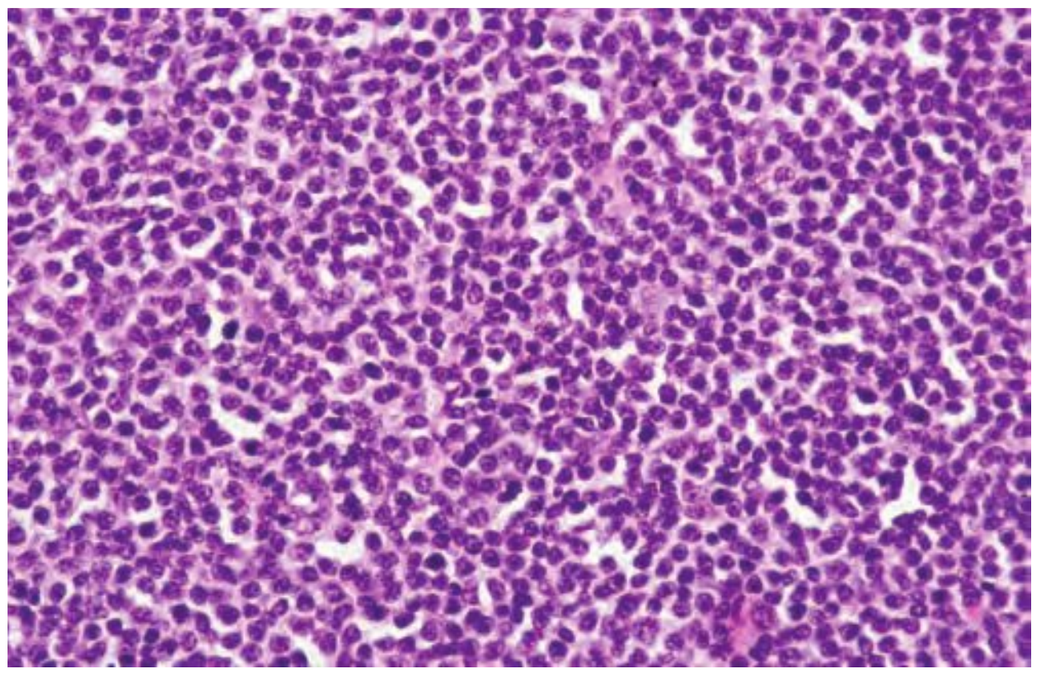


FIGURE 31-9. Extranodal marginal B-cell lymphoma (MALT lymphoma). The interfollicular confluent infiltrate is composed of B cells that resemble centrocytes.

Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg Type

Previously, PCLBCL, leg type was not recognized by the WHO classification as an entity, and cases were incorporated into the general group of DLBCL. The WHO/EORTC consensus classification now defines PCLBCL, leg type as a primary cutaneous large B-cell lymphoma with a predominance of centroblasts and immunoblasts.

Clinical Features. Although the disease typically presents on the leg of elderly women, lesions with a similar morphology and phenotype can arise at any cutaneous site. The overall prognosis is poor, with a 5-year survival of 55% and a tendency to disseminate to extracutaneous sites. Ulceration, primary manifestation on the leg, or multiple lesions at presentation are associated with adverse prognosis (54,55).

Histopathology. Histopathologically, PCLBCL, leg type exhibits a dense monotonous dermal infiltrate of predominantly medium-sized to large cells with round (noncleaved) nuclei, prominent nucleoli, and frequent mitoses resembling centroblasts and/or immunoblasts obliterating the adnexae. Focal epidermotropism with Pautrier-like microabscesses may be seen (56) and should be distinguished from cutaneous T-cell lymphoma (CTCL). Extension into the subcutis may be observed.

Histogenesis. PCLBCL, leg type has a B-cell differentiation profile of post-germinal center (activated) B cells (57).

Consistent with this, the neoplastic cells strongly express MUM-1/IRF-4 and BCL2 but not CD10. Most cases also express BCL6, a marker for B-cell germinal center differentiation. Cytogenetic studies have demonstrated frequent translocations, similar to those in systemic DLBCL, involving IgH, myc, and bcl-6 loci (58).

Differential Diagnosis. Differential diagnosis includes PCFCL, diffuse type and PCLBCL, other (Table 31-5). Cytomorphology may provide clues to differential diagnosis (cleaved small- to medium-sized centrocytes with inconspicuous nucleoli in PCFCL vs. large, round centroblasts with prominent nucleoli in PCLBCL). Occasionally, cases of PCFCL may exhibit an admixture of centrocytes and centroblasts or even predominance of centroblasts. In the latter scenarios, immunohistochemical profiling is paramount for diagnosis. In contrast to PCDLBCL, leg type, which strongly expresses BCL2 and MUM-1/IRF-4, PCFCL, diffuse type is negative for both markers. Cases with a prominent centroblast component but lacking BCL2 expression are currently classified as DLBCL, other under the new WHO/EORTC consensus classification (24).

Primary Cutaneous Diffuse Large B-cell Lymphoma, Other

Primary cutaneous diffuse large B-cell lymphoma, other refers to rare cases of PCLBCL that do not fit the diagnostic criteria for PCFCL and PCLBCL, leg type (i.e., BCL2-negative PCDLBCL with centroblastic round-cell morphology). These include rare cases of T-cell/histiocyte-rich DLBCL, where Reed-Sternberg–like large B cells with clear cytoplasm and multilobular nuclei scatter within a background of small reactive T cells and epithelioid histiocytes (59,60). The large neoplastic cells express B-cell markers CD19, CD22, and CD79a, and display light chain restriction. In contrast to Hodgkin's lymphoma (HL), the Reed-Sternberg–like cells are negative for CD15 and CD30 (61). The IgH gene rearrangement may be difficult to demonstrate due to the small number of neoplastic cells as well as admixed reactive B cells. Despite that the WHO/EORTC classification defines PCLBCL, other as a separate entity, it is unclear whether these represent a BCL2-negative variant of PCDLBCL, leg type or a large cell variant of PCFCL, diffuse type (62). Further follow-up studies are required to clarify whether these cases indeed show distinct clinicopathologic features that warrant distinction as a disease entity (62).

Extraosseous Plasmacytoma

Extraosseous plasmacytoma is a neoplasm of plasma cells that occurs at primary sites other than bone marrow and as such represents only a small percentage of all plasma cell neoplasms (63).

Clinical Features. The majority of affected individuals are middle-aged adult males (male-to-female ratio is 2:1). Although lesions may present in skin, most such tumors occur in tissues of the oropharynx, nasopharynx, and nasal sinuses as well as the larynx (64). Approximately 15% to 20% of patients will have a monoclonal gammopathy, but neoplastic cells, by definition, spare the bone marrow and peripheral blood. Prognosis seems to be related primarily to the presence of solitary versus multiple lesions, with the former responding well to either surgical excision or radiotherapy and the latter associated with a significant rate of mortality.

Histopathology. There is diffuse to nodular dermal infiltration by mature and occasionally less differentiated (plasmablastic) plasma cells (Fig. 31-10A). Occasional cells may have polylobated nuclear contours, nucleoli, and/or binucleation (Fig. 31-10B). It is of note that nuclear immaturity and pleomorphism tend not to occur in the setting of reactive plasma cell infiltrates. The cytoplasm of the neoplastic plasma cells may contain a variety of inclusions usually related to abnormal accumulation of immunoglobulin, including round eosinophilic (Russell) bodies. However, such cytoplasmic changes are not specific for neoplastic plasma cells. In cases where systemic dissemination occurs or when primary myeloma involves skin secondarily, abnormal plasma cells may be detected in bone marrow aspirates (Fig. 31-10C).

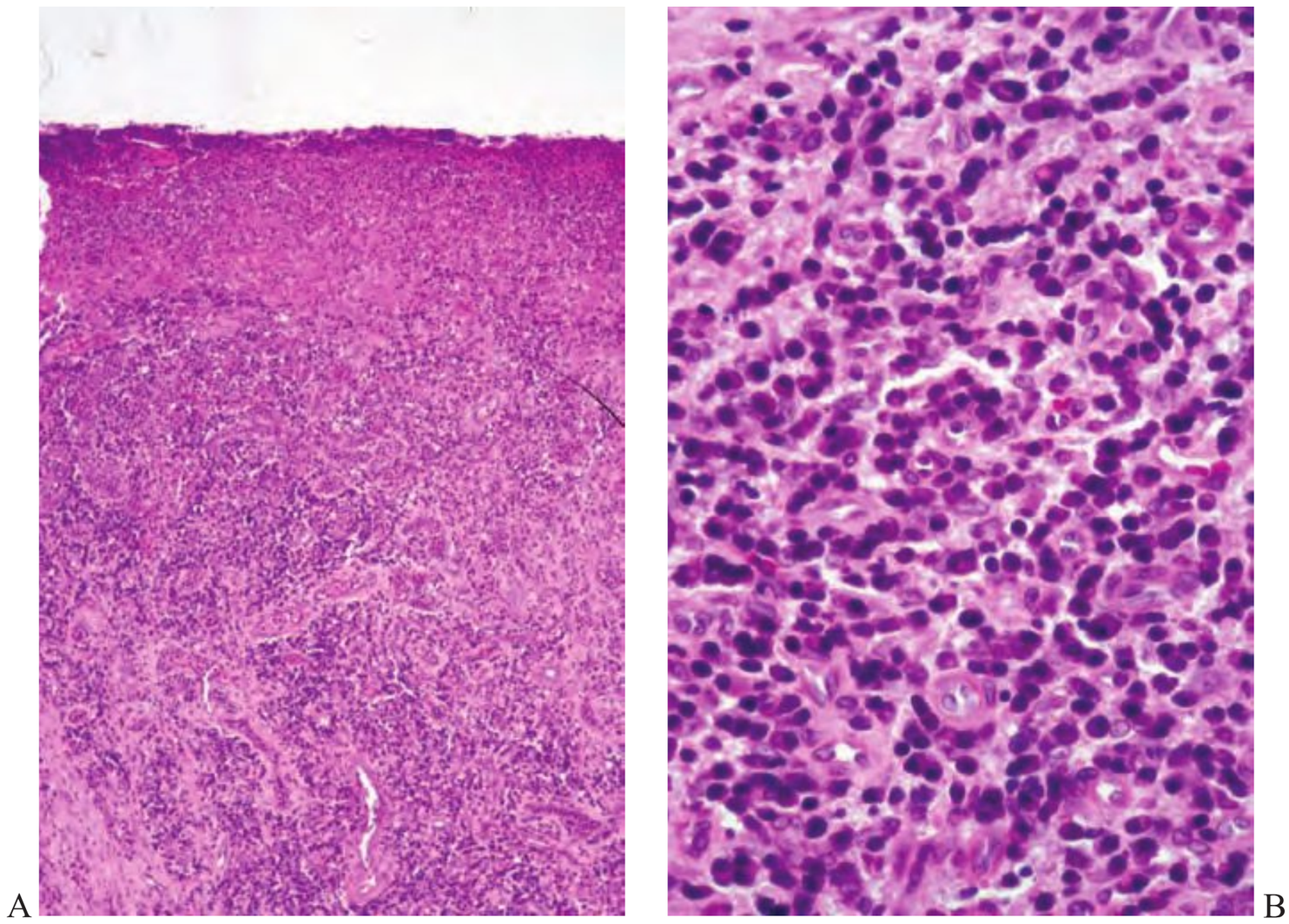
Histogenesis. Clonal transformation of a peripheral plasma cell is the most likely cell of origin. A key feature, therefore, is the expression of monotypic cytoplasmic immunoglobulin and light chain restriction that, unlike cell surface-associated monotypic immunoglobulin in B-cell lymphomas, is generally demonstrable in formalin-fixed, paraffin-embedded material (Fig. 10D, E), CD38 and CD79a are usually expressed, although most but not all plasma cells lack pan-B-cell antigens, CD19 and CD20. Molecular studies generally reveal rearrangement of immunoglobulin genes.

Differential Diagnosis. The differential diagnosis includes extranodal, marginal zone B-cell lymphoma (MALT type, see above) with marked plasmacytic differentiation and reactive, plasma cell-rich, immune responses.

SECONDARY B-CELL LYMPHOPROLIFERATIVE DISORDERS AFFECTING SKIN

Precursor B-cell Lymphoblastic Lymphoma

Precursor B-cell lymphoblastic lymphoma (B-LBL) is a relatively rare neoplasm of B lymphoblasts (accounting for only 5% of all non-HL) with a tendency for skin, lymph node, and bone marrow involvement. It may also present primarily in a leukemic



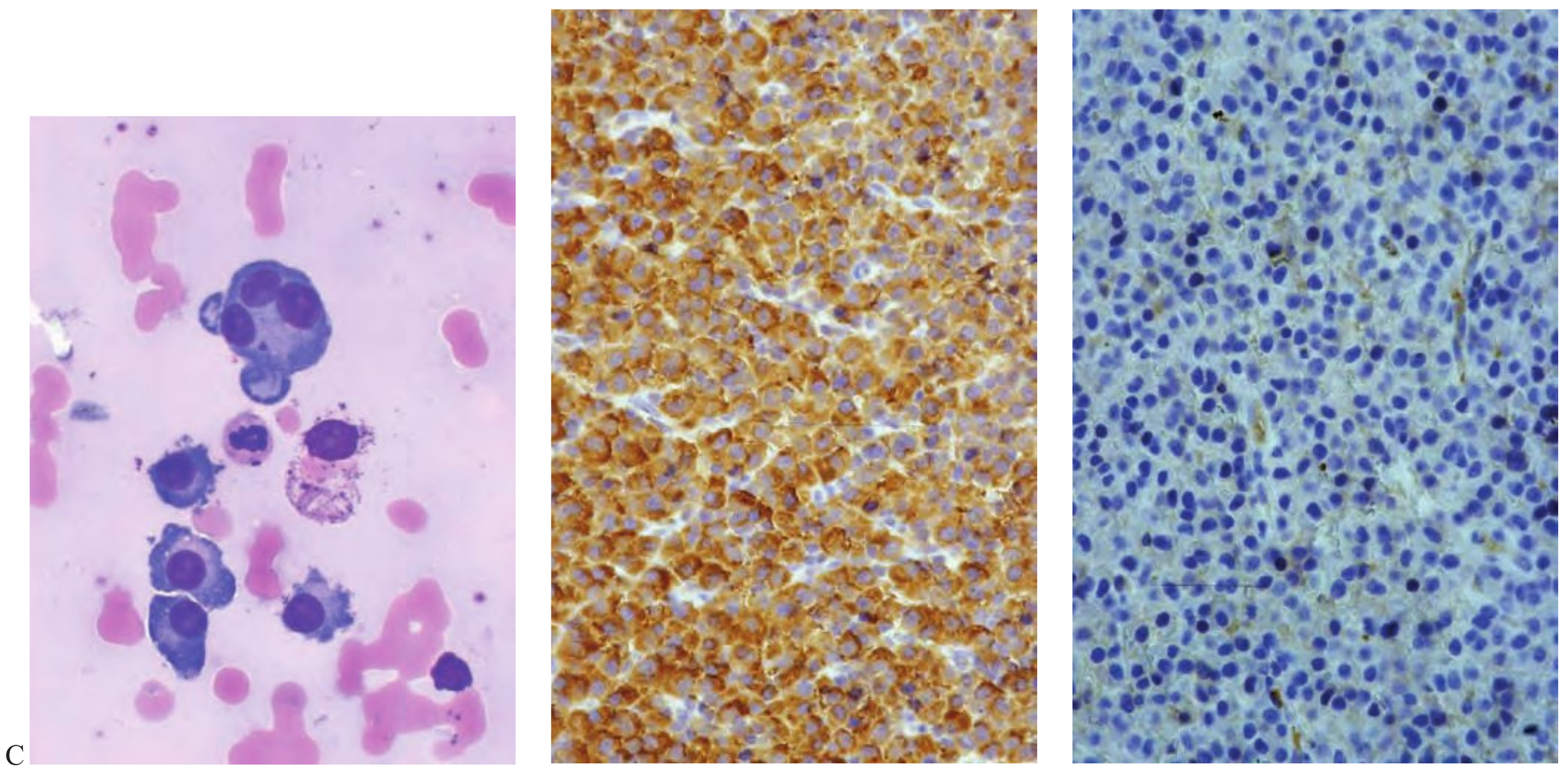
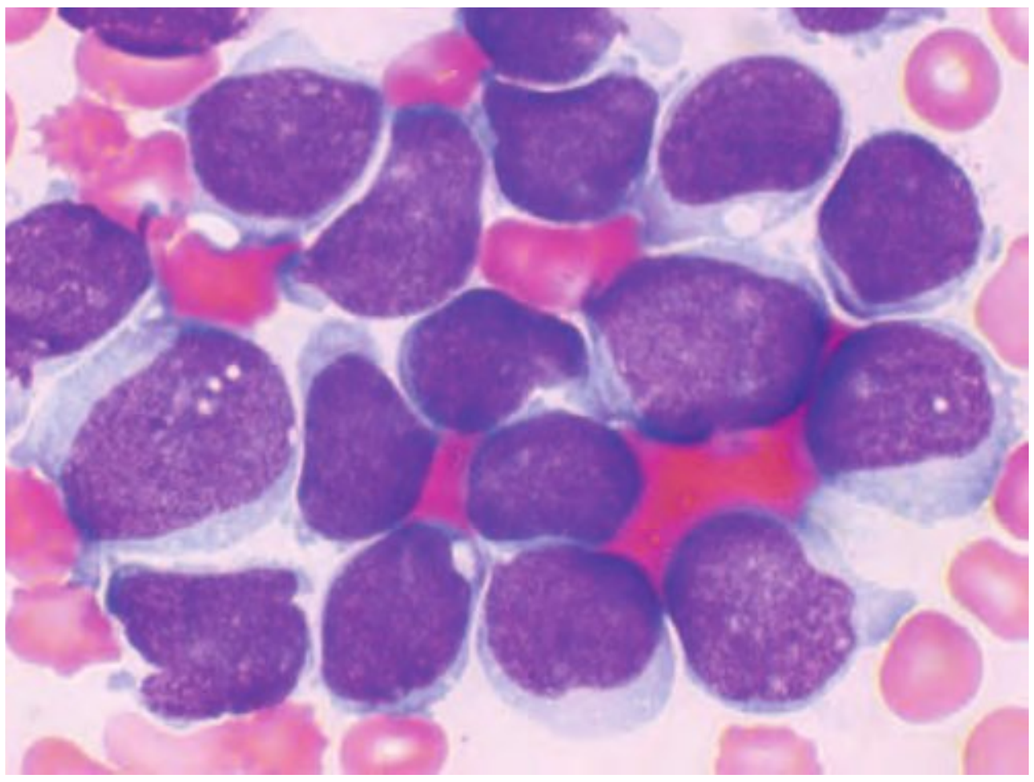
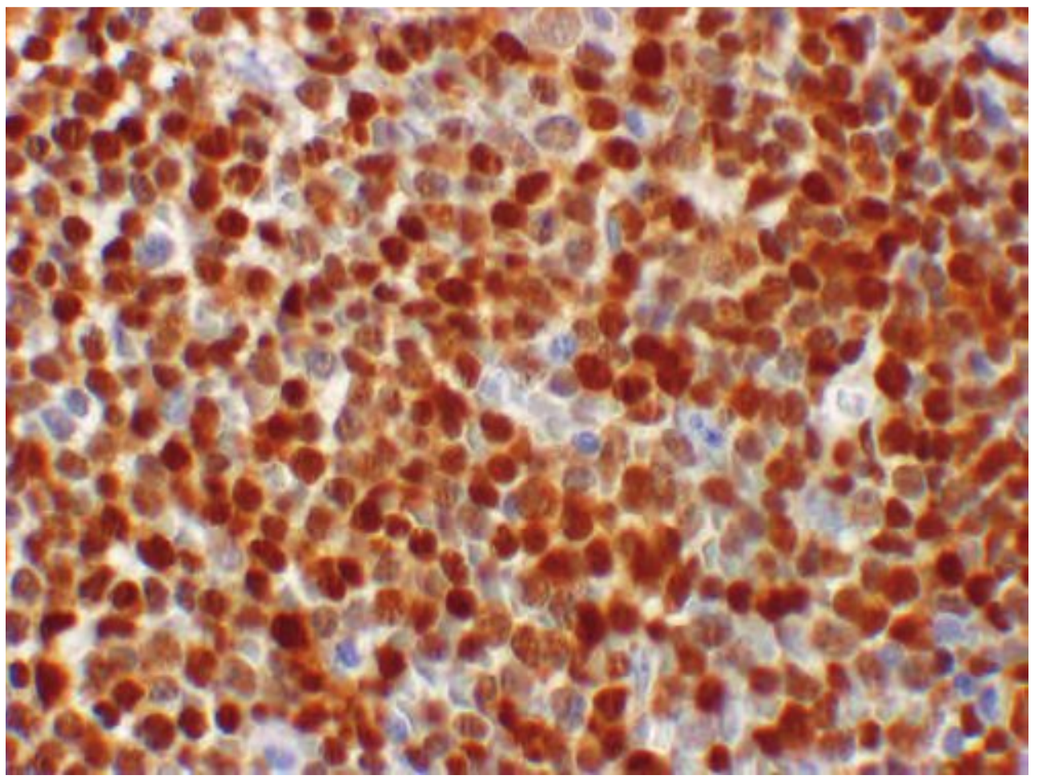


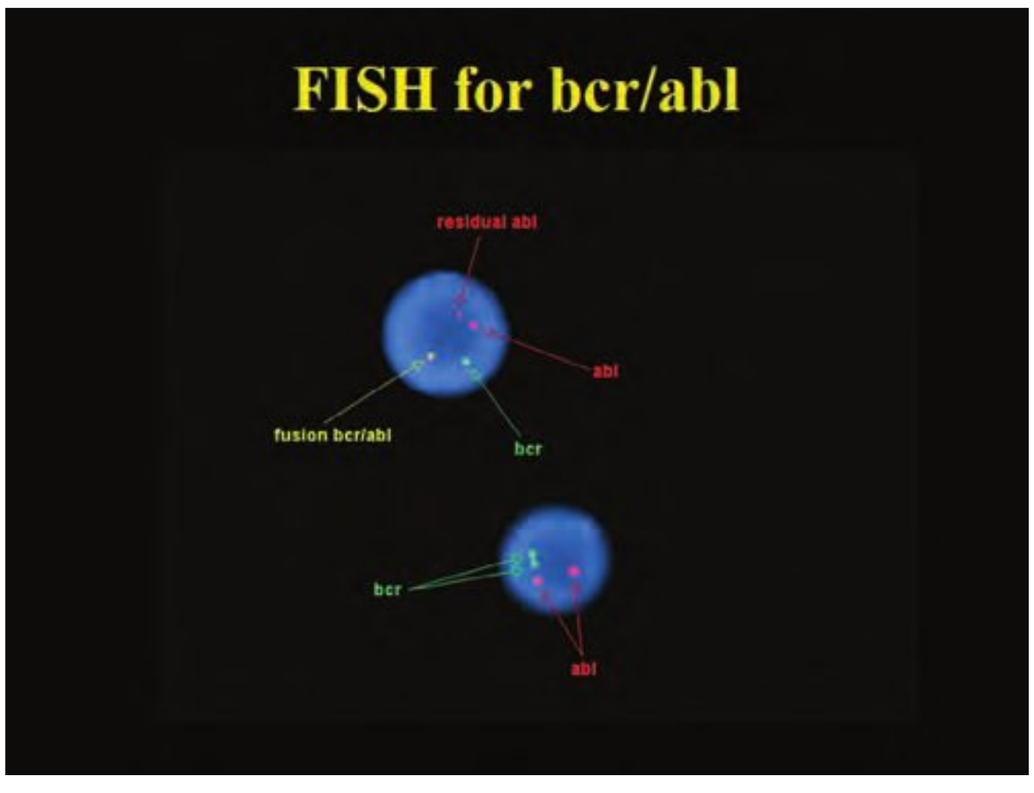
FIGURE 31-10. Cutaneous plasmacytoma. A: There is diffuse interstitial infiltration of the dermis associated with surface erosion. B: Higher magnification showing cellular infiltrate composed of plasmacytoid cells, some with binucleation. C: Atypical plasma cells in bone marrow aspirate from patient with multiple myeloma. D: Paraffin immunohistochemistry of cutaneous plasmacytoma for lambda light chains. E: Paraffin immunohistochemistry of cutaneous plasmacytoma for kappa light chains.

phase, where it is known as precursor B-cell acute lymphoblastic leukemia (B-ALL). Lymphoblastic lymphomas may be of either T- or B-cell lineage (see separate discussion of precursor T-cell lymphoblastic leukemia/lymphoma under secondary T-/NK-cell lymphoproliferative disorders, page 951). Although the majority of systemic lymphoblastic lymphomas are of T-cell lineage, those with a tendency for cutaneous involvement have shown a curious tendency toward B-cell lineage (65).

Clinical Features. B-LBL usually affects children and young adults who are younger than 35 years of age. Bone marrow involvement is generally extensive at time of presentation, with


A


B



C

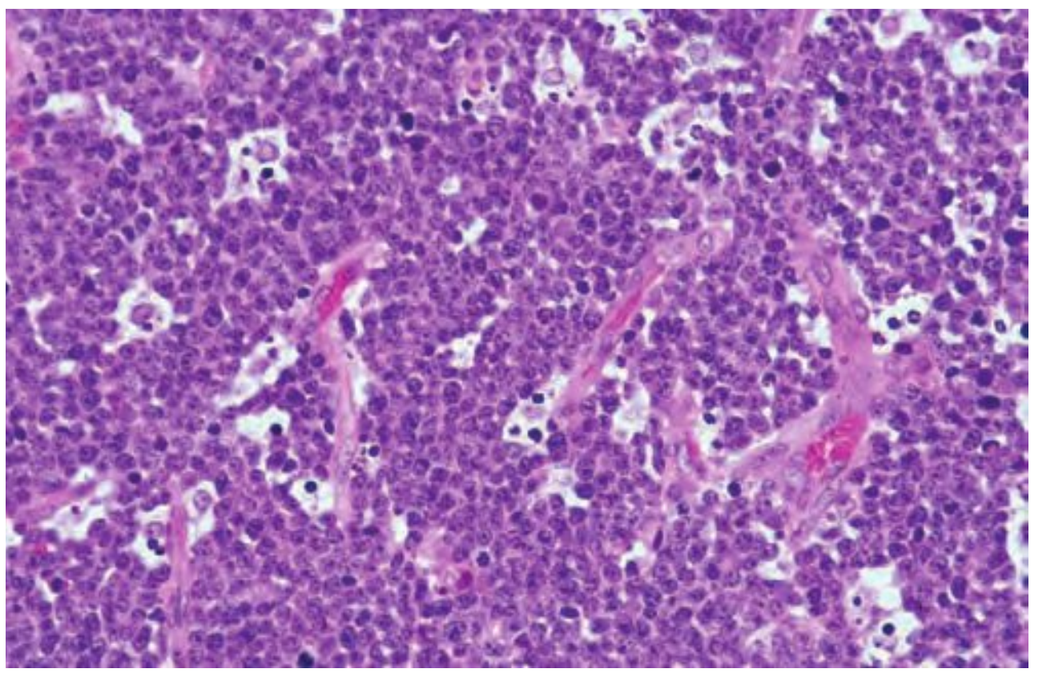

D

FIGURE 31-11. Precursor B-lymphoblastic lymphoma. A: Bone marrow aspirate showing malignant lymphoblasts. B: Nuclear reactivity for TdT. C: FISH in a patient with acute lymphoblastic leukemia who is positive for the Philadelphia chromosome (UPPER CELL: green dot, BCR gene on chromosome 22; lower right: red dot, normal ABL gene on chromosome 9; yellow dot, fusion BCR/ABL; upper left: red dot, residual ABL gene adjacent to breakpoint; LOWER CELL: normal gene pattern for comparison). D: Starry-sky pattern of Burkitt lymphoma that must be distinguished from mitotically active lesions of precursor B-LBL.

associated anemia and thrombocytopenia and symptoms related to bone or joint pain. Patients may show lymphadenopathy as well as hepatic and splenic enlargement on physical examination. Skin lesions, which may occasionally occur without blood or marrow involvement (66,67), may take the form of multiple papules and nodules often involving the head and neck. The outlook is favorable if skin is exclusively involved at the time of diagnosis, as compared to an unfavorable prognosis if disease is disseminated (68). There tends to be a high rate of remission, with median survival of approximately 5 years (66).

Histopathology. Skin involvement may be nodular or diffuse within the dermis, consisting of dense, homogeneous infiltration by mitotically active lymphoblasts with variably convoluted nuclei containing finely stippled chromatin and inconspicuous nucleoli (Fig. 31-11A). Cytoplasm is sparse and may be difficult to detect in routinely prepared tissue. The epidermis is spared, often separated from the region of dermal involvement by a thin subepidermal mantle of unaffected dermis (grenz zone). Further classification, including distinction between T- and B-cell lymphoblastic differentiation, requires immunohistochemical analysis.

Histogenesis. The neoplastic cells of B-LBL lack surface immunoglobulin expression and may harbor cytoplasmic μ chain (pre–B-cell leukemia) or no immunoglobulin at all (progenitor B-cell leukemia); thus, they are generally considered to be precursor B cells. The characteristic cytochemical/immunohistochemical profile consists of positive terminal deoxynucleotidyl transferase (TdT) (Fig. 31-11B), CD179a/b (69), CD19, cytoplasmic CD79a,

CD10 (also known as *common acute lymphocytic leukemia antigen* [CALLA]), and CD24 positivity and variable expression of CD22 and CD20. Stains for surface immunoglobulin and myeloperoxidase are characteristically negative. Cytogenetic abnormalities are numerous and frequently correlate with prognosis and treatment protocols, particularly in pediatric patients (70–72). The arsenal of tests assessing molecular abnormalities includes conventional cytogenetics, polymerase chain reaction (PCR), and fluorescence *in situ* hybridization (FISH). Hyperdiploid karyotypes with >50 chromosomes ordinarily convey favorable prognosis, while hypodiploidy predicts unfavorable outcome. Examples of lymphoblastic lymphoma with adverse outcomes include t(9;22) (Philadelphia chromosome), t(4;11) involving the mixed lineage leukemia (MLL) gene locus, and t(1;19). Along with chronic myelogenous leukemia, some lymphoblastic leukemias/ lymphomas express the chimeric bcr-abl gene that encodes for a tyrosine kinase that is constitutively activated, thus playing a key role in leukemogenesis (Fig. 31-11C).

Differential Diagnosis. Lesions may be differentiated from morphologically similar infiltrates of malignant T-cell lymphoblasts (refer to detail on page 935 under primary T-cell lymphoproliferative disorders) and myeloblasts by cytochemistry/ immunohistochemistry. Occasionally, mitotically active lesions in children may resemble the starry-sky pattern of Burkitt lymphoma (Fig. 31-11D), and lesions in adults may mimic MCL (Tables 31-4 and 31-5); TdT determination is of value in establishing a diagnosis of B-LBL in such cases (73,74) (Table 31-5).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

CLL/SLL is an indolent disseminated or solid neoplastic proliferation of a monotonous population of small lymphocytes of B-cell lineage.

Clinical Features. CLL/SLL is relatively common, generally affects older adults, and shows a male-to-female ratio of 2:1. Patients diagnosed with CLL have bone marrow and peripheral blood involvement, and the lymph nodes, liver, and spleen are also typically infiltrated. Other sites of occasional infiltration by leukemic cells are the skin, breast, and ocular adnexae. When tissue infiltration occurs without evidence of bone marrow involvement, a diagnosis of SLL can be made histologically. Although not usually curable, the disease tends to run an indolent course, unless transformation to a high-grade large B-cell lymphoma supervenes. This phenomenon, known as *Richter syndrome*, occurs in approximately 3.5% of cases. When cases with plasmacytoid differentiation (previously termed *immunocytoma* or *plasmacytoid lymphoma*) affect skin primarily, there is often a single nodule on the trunk or extremity and less frequently on the head and neck. Lesions tend to be multiple with secondary cutaneous involvement and may be associated with immunoglobulin production, resulting in autoimmune sequelae, or in the case of secretion of IgM, a Waldenstrom macroglobulinemia picture.

Cutaneous involvement may produce papules and nodules or occasionally more diffuse skin infiltration that results in irregular thickening and furrowing (75). Sometimes, leukemic cells may infiltrate sites of preexisting dermatitis where adhesive interactions with inflamed vessels are presumably augmented.

Histopathology. Involved tissues are infiltrated by uniform populations of small lymphocytes containing rounded hyperchromatic nuclei and a variably inconspicuous nucleolus (76,77) (Fig. 31-12). In lymph nodes and occasionally in other sites, pseudofollicles (alternatively termed *proliferation* or *growth centers*) that contain a continuum of small to large lymphocytes, including prolymphocytes and paraimmunoblasts, will produce a nodular pattern of regularly distributed pale-staining areas at scanning magnification. Cases with plasmacytoid differentiation may preferentially affect the superficial dermis or show a vertically oriented perifollicular distribution and be composed of heterogeneous populations of cells, including, in addition to plasmacytoid lymphocytes, immunoblasts, plasma cells, histiocytes, eosinophils, and reactive lymphoid follicles (17,78).

Skin involvement may take the form of an angiocentric pattern within the superficial and deep dermis and subcutis (Fig. 31-12A), an interstitial pattern where small lymphocytes are present among collagen bundles and adipocytes (Fig. 31-12B) as well as around vessels, and a mixed diffuse/nodular pattern (79). In the latter, proliferation centers similar to those typical of nodal involvement may occasionally be encountered. As with B-cell pattern infiltrates, the epidermis and follicular epithelium is spared, and the papillary dermis is usually uninvolved, producing a typical grenz zone. Cytologically, the infiltrating cells are identical to those that involve lymph nodes and other extranodal sites (Fig. 31-12C).

Histogenesis. The typical immunophenotype of the tumor cells consists of positivity for CD5, CD19, CD79a, CD23, and CD43. They generally only weakly express surface IgM or IgM and IgD, CD20, CD22, CD11c and are negative for CD10 and cyclin D1. It should be recalled that light chain restriction is confined to surface immunoglobulin in CLL/SLL; thus, unlike plasma cells that contain cytoplasmic immunoglobulin, immunoglobulin restriction can only be demonstrated in fresh, frozen (unfixed) sections. Heavy and light chain immunoglobulin genes are rearranged, and this can be demonstrated by molecular analysis using PCR. At the molecular level, two groups of CLL can be distinguished, one without somatic mutations in the immunoglobulin VH regions being the equivalent of recirculating $CD5^+$, $CD23^+$, IgM^+, IgD^+ naive B cells that are normally detected in blood and in primary follicles and mantle zones (80,81), and one with somatic mutations in the variable genes corresponding to post-germinal center

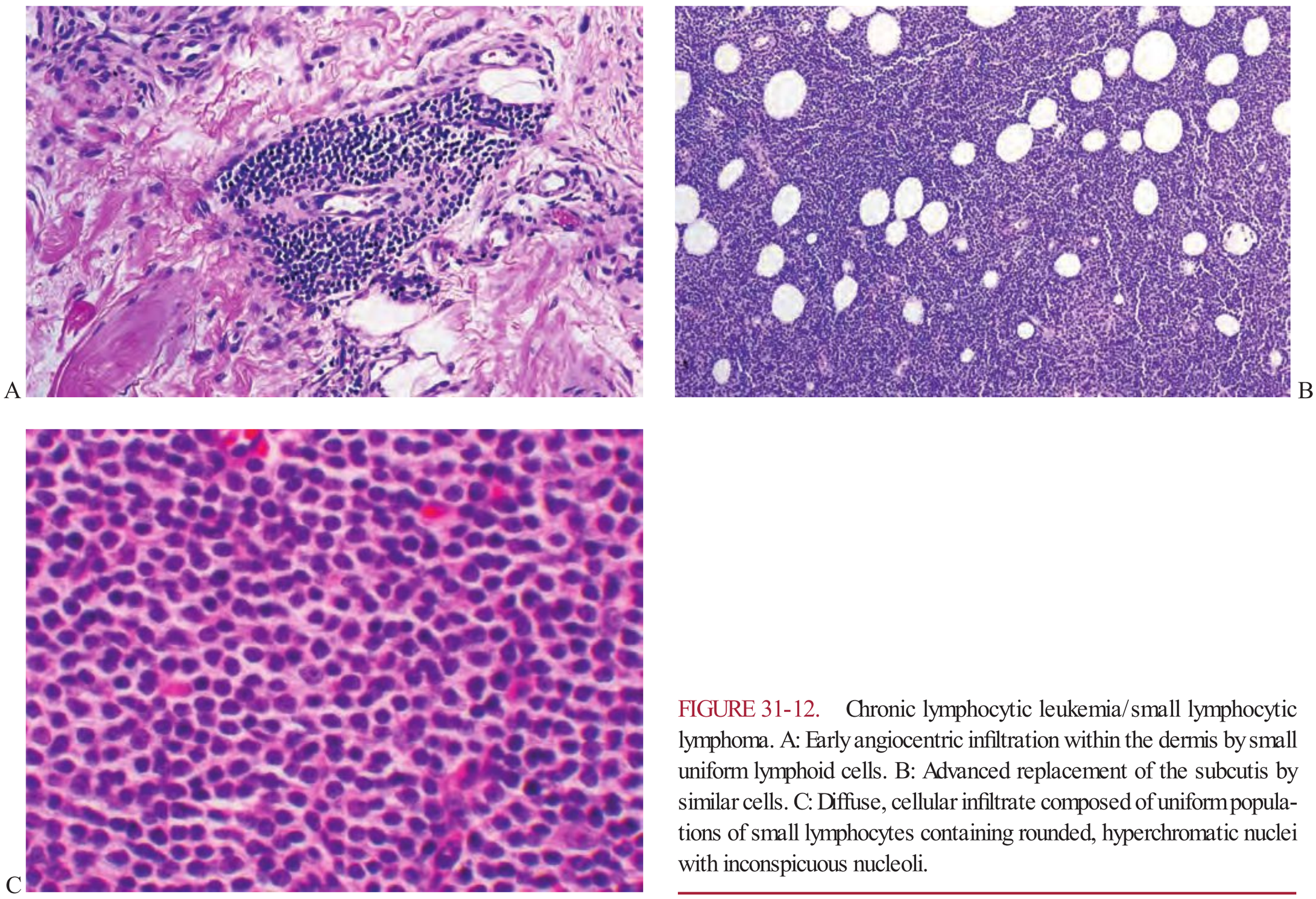


FIGURE 31-12. Chronic lymphocytic leukemia/small lymphocytic lymphoma. A: Early angiocentric infiltration within the dermis by small uniform lymphoid cells. B: Advanced replacement of the subcutis by similar cells. C: Diffuse, cellular infiltrate composed of uniform populations of small lymphocytes containing rounded, hyperchromatic nuclei with inconspicuous nucleoli.

B cells. The majority of CLL exhibit chromosomal abnormalities. Unmutated types of CLL are more commonly associated with trisomy 12, while the mutated forms may present with deletions at 13q14. Previous cases with reported clonal bcl-1 gene rearrangement may have been misdiagnosed cases of MCL. Distinguishing between the two ontogenetic types of CLL carries prognostic significance: the prospect of CLL with germ line VH genes is significantly less favorable than those with hypermutated VH genes. Flow cytometric detection of CD38 (82,83) and, more recently, of zeta-associated protein 70 (ZAP-70) (84–89), that appears to enhance signal transduction, have been utilized as surrogate markers to detect germ line VH gene types of CLL with predictable poor outcome.

Differential Diagnosis. In certain cases, the small lymphocytes of CLL/SLL may show moderate irregularity of nuclear contour, raising suspicion for MCL (Table 31-4). The presence of pseudofollicles or prolymphocytes and paraimmunoblasts, along with positive CD23 and negative cyclin D1 immunoreactivity, will permit a diagnosis of CLL/SLL in such instances (90,91). It should also be noted that in occasional cases, there may be plasmacytoid differentiation by the neoplastic lymphocytes, corresponding to so-called plasmacytoid immunocytoma of previous classification systems (92) and resulting in potential diagnostic confusion with MZL (15) (Table 31-4).

The perivascular pattern in CLL/SLL may result in confusion with forms of dermatitis characterized by a predominant or exclusive angiocentric architecture of inflammatory cell infiltration. This differential would therefore include polymorphous light eruption (see Chapter 12), dermal forms of lupus erythematosus (see Chapter 10), certain dermal delayed hypersensitivity responses to drug or injected antigen (see Chapter 11), and the family of gyrate erythemas (e.g., erythema annulare centrifigum and erythema chronicum migrans) (see Chapter 7). Although all of these conditions contain small lymphocytes, the cells of CLL/SLL tend to be more homogeneous at high magnification. Moreover, most forms of dermatitis are predominated by T cells, not B cells, and the B cells of CLL/SLL will also characteristically aberrantly express CD5.

Nodal Follicular Lymphoma

Nodal follicular lymphoma is a relatively common, often low-grade neoplasm of B lymphocytes differentiating toward follicle center cells (e.g., centrocytes [cleaved FCCs] and centroblasts [noncleaved FCCs]). These tumors at least focally show a nodular/follicular architecture on tissue infiltration.

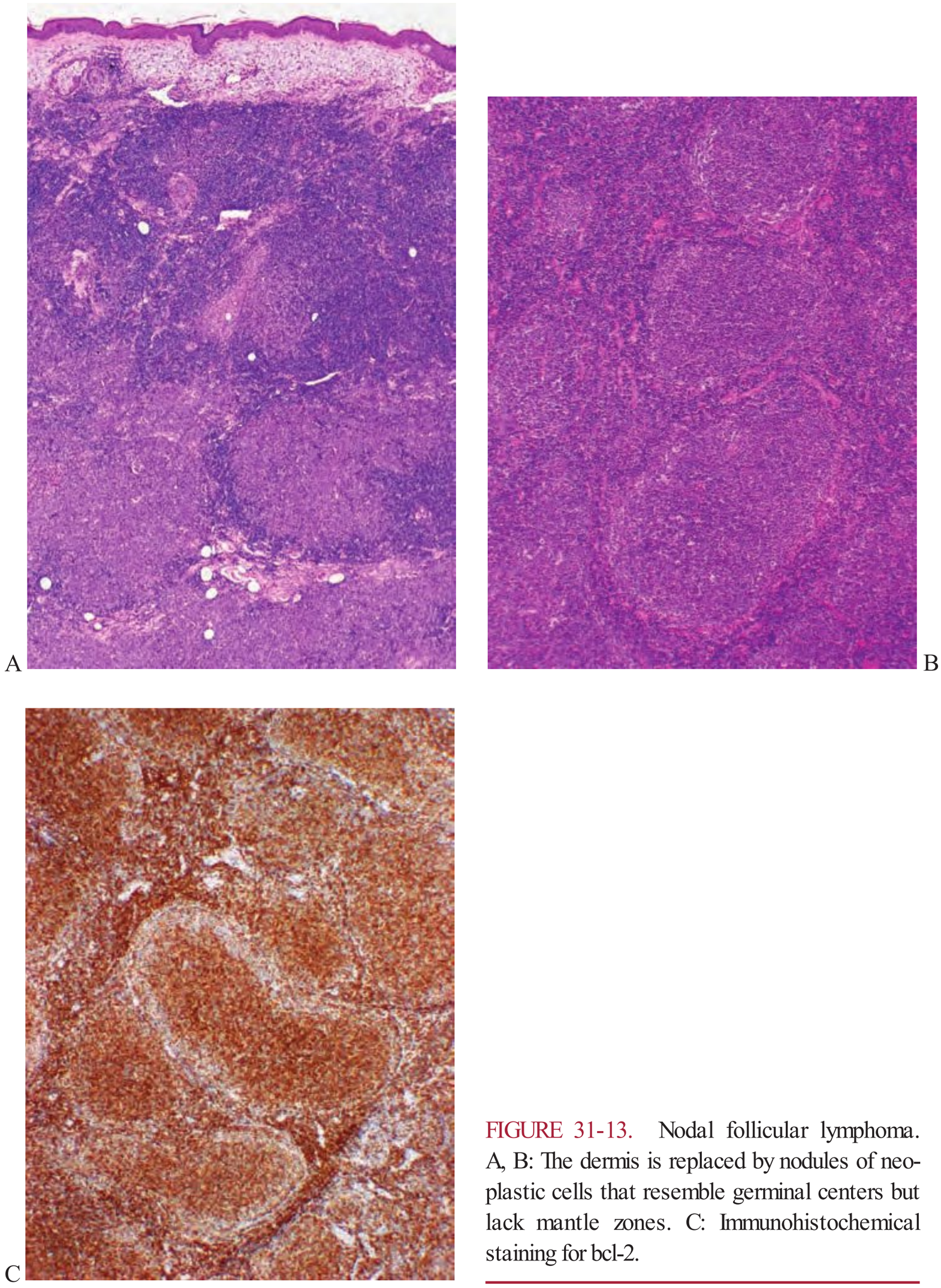


FIGURE 31-13. Nodal follicular lymphoma. A, B: The dermis is replaced by nodules of neoplastic cells that resemble germinal centers but lack mantle zones. C: Immunohistochemical staining for bcl-2.

Clinical Features. This type of lymphoma affects primarily older adults, with a median age of 59 and a male-to-female ratio of 1:1 (93). When children are affected, lesions tend to be localized to the head and neck, and approximately half of tumors are of the large cell type (see below). In addition to lymph node involvement, the bone marrow, spleen, blood, Waldeyer ring, gastrointestinal tract, skin, and soft tissues may be affected. Follicular lymphoma is generally incurable, showing an indolent waxing and waning course. The overall median survival is 7 to 9 years regardless of whether therapy is aggressive or symptomatic. Of all cases of nodal follicular lymphoma, approximately 4% will show evidence of secondary skin involvement, which must be differentiated from PCFCL because the latter tends to respond to local therapy and shows a more favorable prognosis.

Histopathology. The characteristic architecture consists of multiple closely packed nodules that initially may resemble germinal centers but that are composed of neoplastic cells devoid of mantle zones (17) (Fig. 31-13A, B). These follicular regions are devoid of polarization and do not show a prominent starry-sky pattern, and other regions may be characterized by a more diffuse pattern with associated sclerosis. Based on these architectural features, lesions may be classified as follicular (>75% follicular architecture), follicular

and diffuse (25% to 75% follicular architecture), and minimally follicular (<25% follicular). Rarely, exclusively diffuse follicle center cell lymphomas may also be seen, where the diagnosis must be based on cellular composition. Cytologically, two types of neoplastic lymphocytes are observed in follicular lymphoma. The predominant cell is the centrocyte, or cleaved FCC, a small- to medium-sized lymphocyte with scant cytoplasm as well as angulated, infolded, or twisted nuclear contours and inconspicuous nucleoli (Figure 31-7C). Similar but often smaller centrocytes may also be present in the interfollicular regions. Centroblasts, or noncleaved FCCs, are larger transformed lymphocytes with round to oval nuclei with vesicular chromatin and several visible nucleoli (Fig. 31-7C). On occasion, an even admixture of centrocytes and centroblasts or even a predominance of centroblasts may be encountered. These ratios provide the basis for a grading system based on proportional numbers of centroblasts in 10 neoplastic follicles, with grade 1 equal to the average count of 0 to 5/high power field (hpf), grade 2 equal to 6 to 15/hpf, and grade 3 equal to >15/hpf (94–96).

Secondary skin involvement, like PCFCL, presents as nodular dermal infiltrates that may initially resemble germinal centers (19). While secondary cutaneous involvement tends to have significant morphologic overlap with features seen in lymph nodes, nodal FCL may also show overlap to mucosal lymphoma (MALToma) and marginal zone lymphoma of the spleen.

Histogenesis. Germinal center B cells are believed to represent the cell of origin of follicular lymphoma. Tumor cells tend to express surface immunoglobulins (IgM, IgD, IgG, and rarely IgA), BCL2, and CD10 and the B-cell associated markers CD20, CD19, CD22, and CD79a. Most cases are negative for CD5 (in contrast to CLL/SLL) and CD43. Although BCL2 expression is useful in differentiating neoplastic follicles (Fig. 31-13C) from normally negative hyperplastic germinal centers, it should be noted that in contrast to nodal follicular lymphoma, PCFCL is frequently negative for BCL2. Rearrangement of immunoglobulin heavy and light chain genes is the rule, and cytogenetic abnormalities are almost always present (97), with the t(14;18)(q32;q21) rearrangement of the bcl-2 gene the most common. The BCL2 protein is situated on mitochondrial membranes and serves as an inhibitor of programmed cell death. Consequently, BCL2 expression in nodal follicular lymphoma appears to lend the tumor cells a distinct survival advantage when compared with their benign germinal center counterparts that undergo apoptosis.

Differential Diagnosis. Cutaneous involvement by nodal follicular lymphoma must be differentiated from B-CLH (26,27) and other conditions associated with the formation of reactive follicles (e.g., MCL and MZL) (Table 31-4). B-CLH often is clinically manifested by one or more erythematous to plum-colored plaques and nodules. Any site may be affected, but there is a predilection for skin of the face and scalp. The underlying cause is often unknown, although may involve a reaction to injected antigens, as may occur in insect bites or localized infection with the spirochete *B. burgdorferi* (28–30). Histologically, there may be a nodular to diffuse interstitial infiltrate that often involves the deep dermis and occasionally the subcutis. Germinal center formation may be variably pronounced; however, occasionally, these structures are indistinguishable from those encountered in reactive lymph nodes. Specifically, in addition to smaller lymphocytes with cleaved nuclei (centrocytes) and larger lymphocytes with noncleaved nuclei (centroblasts), they will contain an admixture of immunoblasts, antigen-presenting follicular dendritic cells, and macrophages containing phagocytized cellular debris (tingible body macrophages). Moreover, there tends to be aggregation of centroblasts and tingible body macrophages at one pole of the hyperplastic follicle and of centrocytes at the opposite pole, producing darker- and lighter-staining regions, respectively. Immunohistochemistry will reveal both kappa and lambda immunoglobulin light chain expression in B-CLH as opposed to monotypic expression in follicular lymphoma. Genotypic analysis may also be of assistance when establishing a diagnosis of B-CLH when it fails to reveal clonal immunoglobulin gene rearrangements. However, it must be noted that on occasion, cases of B-CLH appear to evolve over time into more aggressive clonal processes or may harbor a malignant clone in the midst of otherwise reactive histologic and immunophenotypic changes (31). Some of these differences are summarized in Table 31-4.

Mantle Cell Lymphoma

MCL is a B-cell neoplasm that is composed of uniform populations of small- to medium-sized lymphocytes that resemble FCCs, or centrocytes, but that tend to have somewhat less irregular nuclear contours (90–103). The normal cellular counterpart thus resides in the mantles that surround secondary lymphoid follicles in lymph nodes. Unlike follicular lymphoma, which accounts for approximately one third of all non-HLs in the United States, MCL is considerably less common, accounting for only 3% to 10%. Unlike B-CLL/SLL, proliferation centers are absent. Because it rarely involves skin, it is discussed here briefly.

Clinical Features. This disease affects middle-aged and older individuals with a male-to-female ratio of 2:1 (31,100, 101,104–106). Disease is usually advanced at time of detection (stage III or IV) and generally affects lymph nodes, spleen, bone marrow with or without peripheral blood involvement, and gastrointestinal tract (100,106–108). When multiple sites of polypoid gastrointestinal involvement by lymphoma are encountered, the diagnosis is generally MCL (109–111). Occurrence in the skin is rare but potentially underreported. Presentation in the skin is generally followed by development of overt extracutaneous involvement, consistent with the notion that cutaneous MCL is a more aggressive process than PCFCL or plasmacytoid B-CLL/SLL variants (19,112). Median survival is 3 to 5 years, and cure is unusual (105–108,113,114).

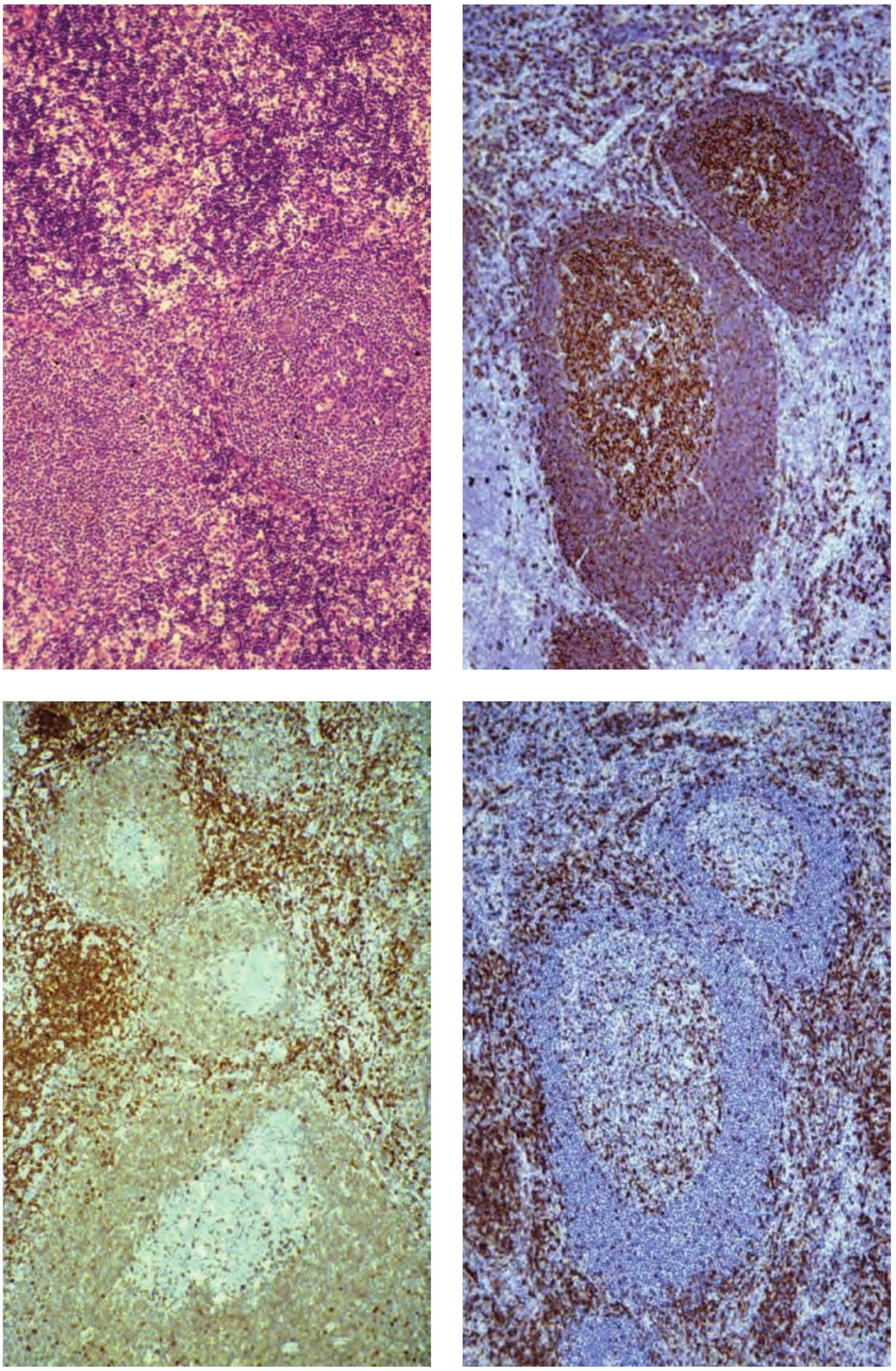


FIGURE 31-14. Mantle cell lymphoma. A: There is a vaguely nodular to diffuse infiltrate composed of small- to medium-sized lymphocytes. B: Immunophenotypically, the cells are characterized by strong reactivity for the B-cell marker CD20. C, D: Reactivity for CD5 that here compared with T cells (upper left) forms a mantle zone pattern about compressed lymphoid follicles (C) and negativity for T-cell marker CD3 (D).

Histopathology. The majority of cases show a vaguely nodular to diffuse pattern of growth composed of small- to medium-sized lymphocytes with variably irregular nuclear contours (Fig. 31-14A). The chromatin pattern is dispersed and nucleoli are inconspicuous. These cells most closely resemble centrocytes. Smaller cells resembling those of B-CLL/SLL may also be present. Transformed tumor cells (e.g., those resembling centroblasts, immunoblasts, or paraimmunoblasts) and pseudofollicles are not seen. Other cells that are sometimes admixed include occasional plasma cells, histiocytes dispersed in a pattern that may resemble the starry-sky of Burkitt lymphoma, and endothelial cells forming hyalinized vascular profiles. A characteristic feature of some lesions of MCL is the tendency of neoplastic lymphocytes to surround and compress nonneoplastic lymphoid follicles (so-called mantle zone pattern). Skin infiltration may be nodular to diffuse, and occasional lesions will show preferential infiltration of the more superficial dermal layers. Rarely, recurrent lesions will show more nuclear atypia and numerous mitoses, qualifying for the designation of "blastoid MCL."

Histogenesis. The tumor is believed to arise from a peripheral B cell of the inner mantle zone of the lymphoid follicle. Accordingly, the tumor is characterized by a clonal proliferation of $CD20^+$ B cells (Fig. 31-14B) that express surface IgM with or without associated IgD (99,100,103,113). They also tend to express CD5 (Fig. 31-14C), CD43, and BCL2 protein and are negative for CD10 and CD23 (100,113,115–120) (Fig. 31-14D). CD5 negativity does occasionally occur and may be associated with more indolent biologic behavior (121). Interestingly, gastrointestinal lesions are associated with expression of the gut homing receptor, alpha4 beta7 (122). The clonal nature of the process may be demonstrated via rearrangements of immunoglobulin heavy and light chain genes, and virtually all cases have cytogenetic abnormalities using FISH (123,124). Most cases of MCL have undergone clonal heavy and light chain gene rearrangement with germ line configuration in the VH gene region that is consistent with pregerminal center origin. The cytogenetic hallmark of MCL is t(11;14)(q13;q32) with participation of the cyclin D1 gene and the immunoglobulin heavy chain locus (113,125–129). Cyclin D1 (Prad-1, bcl-1) is an important cell cycle regulatory protein involved in restriction point control between the G1 and S phase. The genetic abnormality is detectable by conventional cytogenetics, FISH analysis, or PCR; overexpression of the gene product can be readily assessed by immunohistochemical stains with antibodies directed against the nuclear cyclin D1 protein. More recently, pathogenesis of MCL has been linked to alterations of the ataxia-telangiectasia mutated (ATM) gene that encodes a protein critically involved in the cellular response to DNA damage (130–132). It has been known for a long time that patients with hereditary ataxia telangiectasia are predisposed to develop malignant lymphomas. Of all malignant lymphomas, MCL is most commonly associated with mutations of the ATM gene, most of which are nonsense mutations resulting in truncated proteins followed by missense mutations. The underlying molecular mechanism leading to ATM mutations in MCL is unknown.

Differential Diagnosis. The most common differential diagnostic problem is differentiation of MCL from other processes where lymphoid follicles or their mimics are present. Table 31-4 summarizes the salient differential features for MCL compared with other cutaneous B-cell lymphoproliferative disorders.

Diffuse Large B-cell Lymphoma, Nodal Type

DLBCL is a relatively common type of non-HL that primarily affects adults and frequently presents with involvement of extranodal sites, including the skin. It is an aggressive lymphoma characterized by diffuse tissue infiltration by monotonous populations of large, "histiocytoid" malignant lymphocytes.

Clinical Features. Although elderly individuals are most often affected, with the median age in the seventh decade of life, the disease may affect a wide age range, and children are occasionally affected (104). Patients often present with signs or symptoms of a rapidly enlarging tumor at either a nodal or extranodal site, the latter of which commonly involves skin, soft tissue, and numerous viscera (2). On more thorough staging, disease is often found to be advanced and thus disseminated (30,85), although this aggressive lymphoma is potentially curable with aggressive chemotherapy. Lesions generally arise *de novo*, although some lesions represent transformation within preexisting more indolent lymphomas (e.g., CLL/SLL, follicular lymphoma, lymphomatoid granulomatosis [LYG], or marginal zone lymphoma). One important predisposing factor is immunodeficiency, particularly in the presence of seropositivity for Epstein-Barr virus (EBV).

In the skin, DLBCL forms red to purpuric papules, nodules, and infiltrated plaques. Occasionally, only the skin is found to be involved after careful staging work-up, and such cases may be considered to be primary in the skin (PCDLBCL), including skin of the back (114). Such lesions confined exclusively to the skin have proven to be more amenable to treatment (e.g., localized irradiation), although those involving the lower extremities have been noted to be more aggressive (21).

Histopathology. Tissue infiltration in DLBCL generally results in local destruction and effacement of preexisting structures (Fig. 31-15A), occasionally associated with zones of fibrosis. The dermal infiltrates may be diffuse or nodular. Frequently, deep dermis is preferentially affected, producing a so-called "bottom-heavy" pattern. Cytologically, there is a uniform, monomorphous population of large transformed lymphoid cells resembling centroblasts (Fig. 31-15B). These cells have scant cytoplasm, large nuclei with vesicular nuclear chromatin patterns, and often prominent nucleoli. Immunoblastic, T-cell/histiocyte-rich, and anaplastic variants have been described, but significant problems exist in terms of interobserver variability in subclassifying lesions according to variant forms (133).

Histogenesis. The presumed cell of origin is a peripheral germinal center or post-germinal center B cell. Accordingly, one or more pan-B-cell markers (e.g., CD19, CD20, CD22, CD79a) are expressed (Fig. 31-15C). Surface or cytoplasmic immunoglobulin is demonstrable in the majority of cases, the latter tending to correlate with plasmacytoid features of the large malignant B cells (134,135), and immunoglobulin gene rearrangements are regularly encountered. Anaplastic variants tend to express CD30 more consistently than their nonanaplastic counterparts (136). CD5 and BCL2 expression are also variably encountered in DLBCL (137). Twenty-five percent of DLBCLs demonstrate alterations of the BCL6 (LAZ-3) gene at 3q27, which encodes a zinc finger protein with homology to several Drosophila transcription factors (138–145). BCL6 protein is readily recognizable by immunohistochemistry and is expressed in normal germinal center lymphocytes. It should be emphasized that DLBCL represents a heterogeneous group of malignancies reflected in

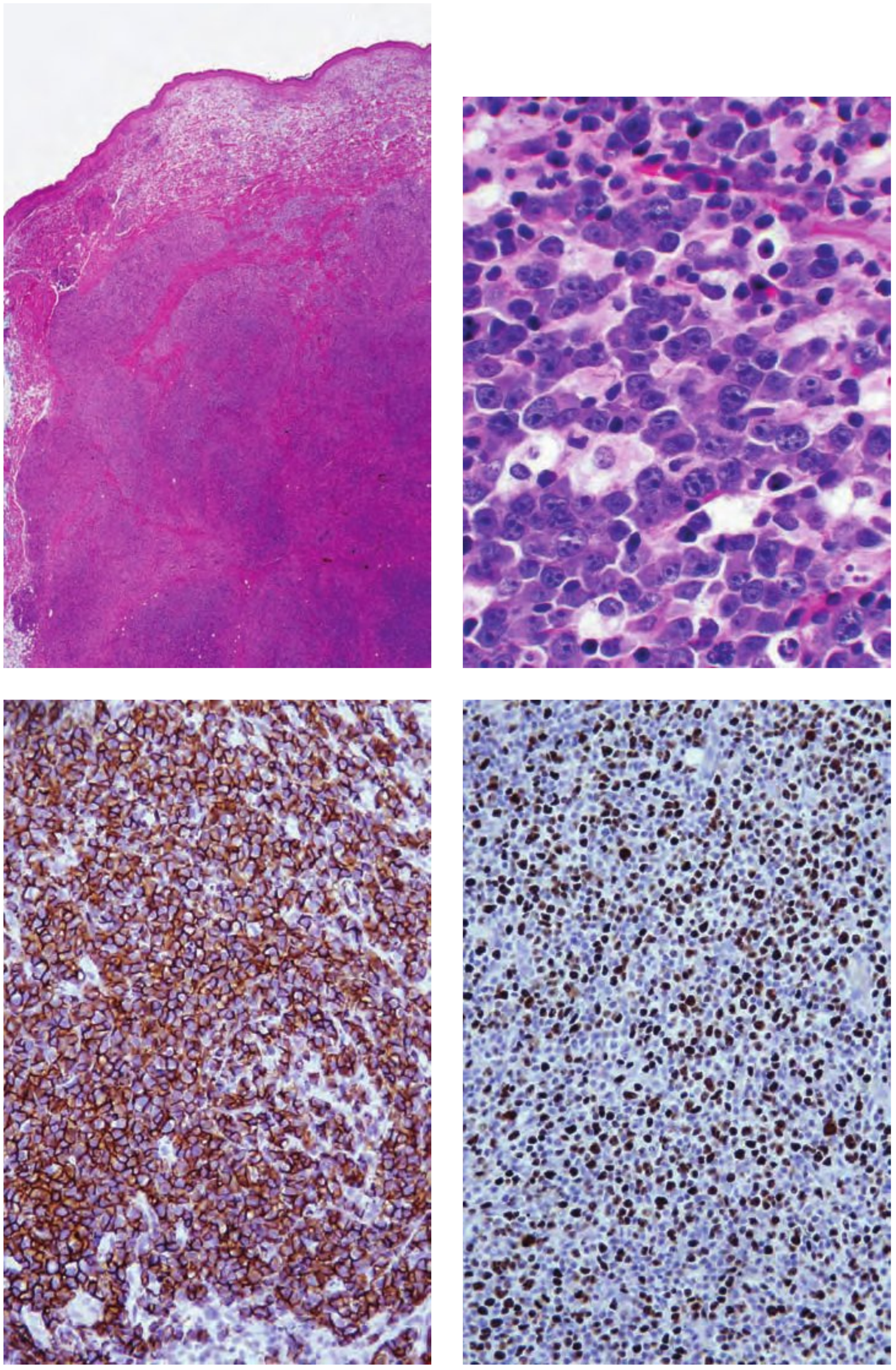


FIGURE 31-15. Diffuse B-cell lymphoma, nodal type. A: The dermis is diffusely effaced by a destructive infiltrate. B: High magnification showing infiltrate composed of large neoplastic lymphocytes. C, D: Immunohistochemistry shows the malignant cells to express CD20 (C) and evidence of a high proliferative rate based on Ki-67 reactivity (D).

variable immunophenotypical and genetic expression. Gene expression data obtained from microarrays suggest two distinct groups of DLBCL, one of which resembles the genetic makeup of germinal center cells (GCC), while the other one corresponds to the genetic makeup of nongerminal center B cells. DLBCL derived from GCC consistently express BCL6 and have a significantly better prognosis than DLBCL derived from non-GCC (146,147). High proliferative rates may be attested to on Ki-67 staining (Fig. 31-15D).

Differential Diagnosis. Occasional lesions may be dominated by medium-sized lymphoid cells, resulting in confusion with leukemia cutis or Burkitt lymphoma, and immunohistochemistry is required for definitive classification. Unlike blastoid variants of MCL, cells of DLBCL are negative for

cyclin D1 expression. Anaplastic lesions may raise the differential diagnosis of dermal involvement by anaplastic carcinoma and amelanotic melanoma, and in such cases, immunohistochemical screening for lineage-related markers (e.g., CD45, cytokeratins, Melan A) is a useful initial point of departure for diagnostic evaluation.

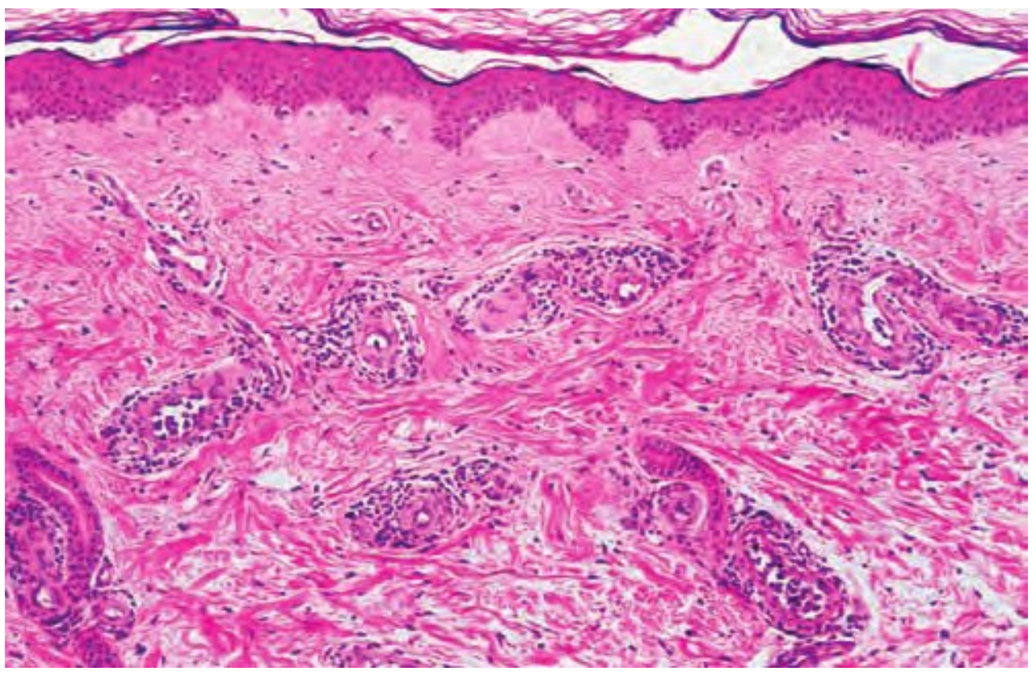
Intravascular Large B-cell Lymphoma

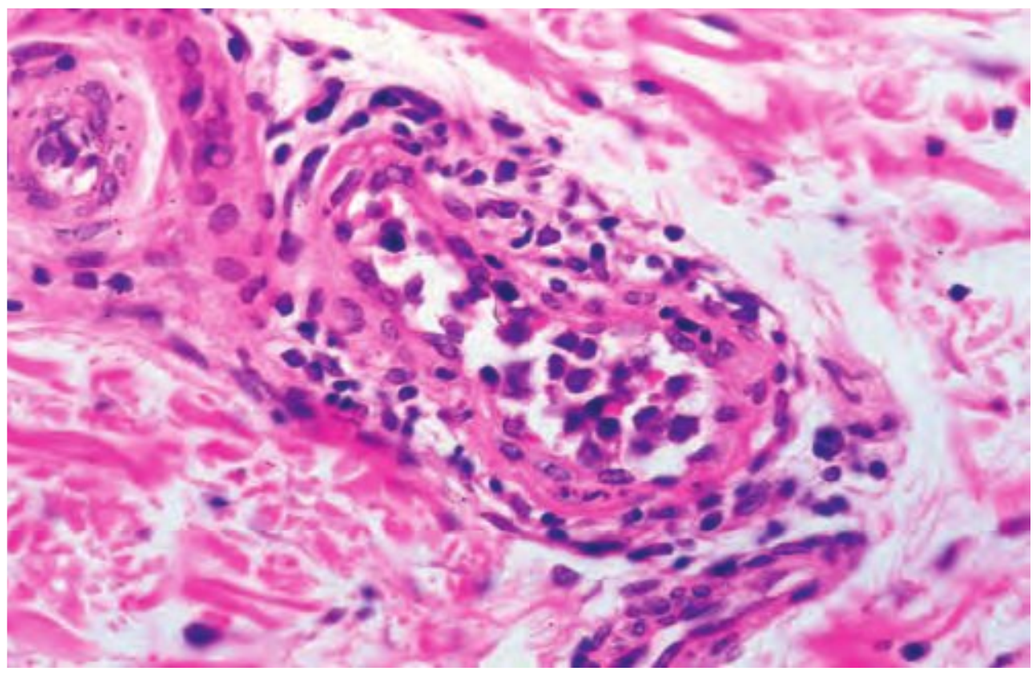
Considered a rare subtype of DLBCL, intravascular (angiotropic) B-cell lymphoma (formerly and mistakenly termed *malignant angioendotheliomatosis*) is an aggressive process that prototypically demonstrates intralumenal aggregation of large malignant B cells within vessels of involved tissues (148–153). The estimated 5-year survival is approximately 50% (13). It has long been postulated that the intravascular trapping of the neoplastic cells is associated with defects in homing receptors on the lymphoid cells and/or adhesion molecules on the endothelial cells. However, the precise mechanisms are still not fully elucidated.

Clinical Features. Intravascular large B-cell lymphoma is a disease of adults. It presents as widely disseminated involvement of extranodal tissues, including the skin, lung, central nervous system, kidney, and adrenal glands. Because signs and symptoms relate primarily to vascular occlusion, clinical presentation often is highly variable. Skin lesions tend to be red plaques and nodules. Telangiectasia and epidermal changes due to ischemia, including scaling and ulceration, also may be observed.

Histopathology. Involved vessels are either entirely or partially occluded by populations of large, malignant-appearing lymphoid cells enmeshed in fibrin (Fig. 31-16A). In the case of the latter, these cells may adhere to inconspicuous and attenuated underlying endothelium, producing the false impression of endothelial atypia or malignancy (Fig. 31-16B). Cytologically, tumor cells contain large nuclei with vesicular chromatin patterns and prominent nucleoli.

Histogenesis. The malignant B cells of peripheral germinal center or post-germinal center origin are believed to express defective homing receptors (e.g., CD11a/CD18), resulting in their tendency for intravascular accumulation due to impaired ability for diapedesis (154,155). Confirmation of B-cell origin may be accomplished by immunohistochemistry for CD20 (Fig. 31-16C). There is variable expression of CD5 and CD10 (150,156–164). Diffuse large B-cell lymphoma with hemophagocytic syndrome (BCL-HS) has been reported mainly in Asia and is regarded as a distinct variant of intravascular lymphoma. Rare cases of intravascular lymphoma with a T-cell phenotype have been documented (164,165).


A


B

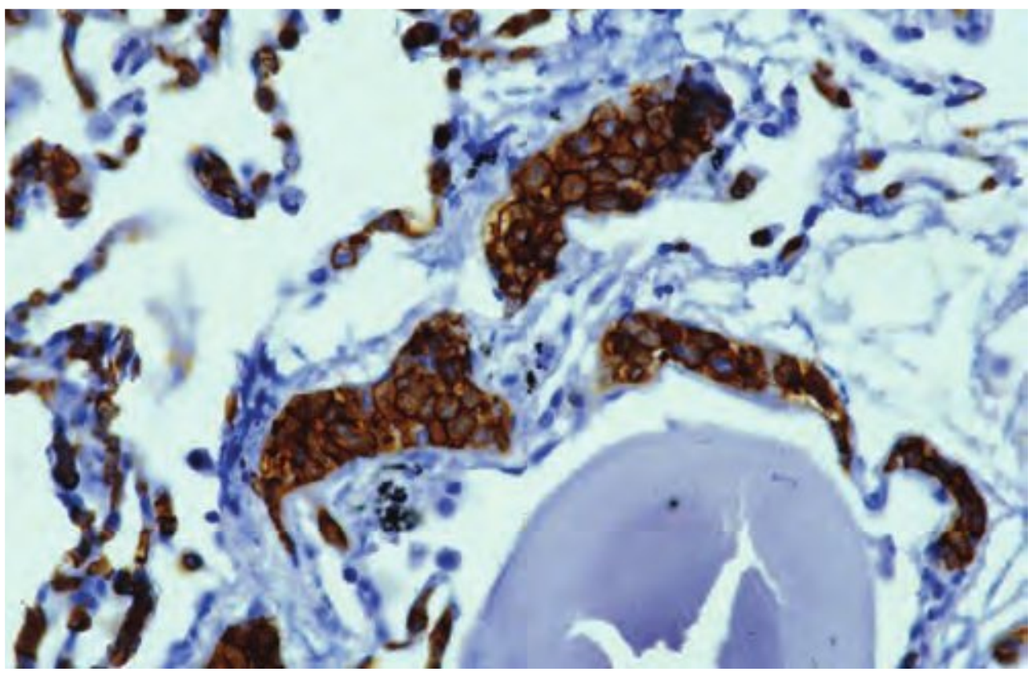

C

FIGURE 31-16. Intravascular large B-cell lymphoma. A: Superficial dermal vessels are partially occluded by hyperchromatic malignant cells. B: Higher magnification discloses malignant-appearing lymphocytes partially adherent to the endothelial surface of involved vessels. C: CD20 reactivity for malignant B cells within pulmonary vessels from a patient with diffuse extracutaneous involvement.

Differential Diagnosis. Because lesions typically show malignant cells to be exclusively confined to vascular lumens, the primary differential diagnosis involves differentiation of these cells from malignant and reactive endothelium (e.g., angiosarcoma and diffuse dermal angiomatosis/reactive angioendotheliomatosis [166,167]). In this regard, it should be remembered that both endothelial cells and many cells of hematopoietic origin express the CD34 marker. Differentiation from other intravascular malignant deposits (e.g., inflammatory carcinoma of the breast) may be confirmed by using lineage-related immunohistochemical markers.

Lymphomatoid Granulomatosis

LYG is a rare and variably aggressive lymphoproliferative disorder characterized by angiocentric and angiodestructive infiltration of extranodal tissues, including the skin, by EBV-transformed B cells and reactive T cells (168–170).

Clinical Features. Adult males are generally affected by LYG (male-to-female ratio of 2:1), although immunosuppressed children may also present with this disease. Although multiple organs may be involved, the lung is the most common and if not infiltrated at time of presentation tends to be affected at some point during the natural evolution of the disease. Skin involvement is quite common, being demonstrable in 25% to 50% of all cases. Nodal tissue and spleen are rarely affected (171–174).

Histopathology. Unlike most non-HLs, LYG shows an angiocentric and angiodestructive architecture and a polymorphous cytology (171,173) (Fig. 31-17). The infiltrating mononuclear cells show permeation and focal destruction and fibrinoid necrosis of vessel walls (175), and adjacent zones of ischemic necrosis may result. The cellular composition includes variably atypical lymphocytes with cleaved and elongated nuclear contours, immunoblasts, plasma cells, and histiocytes (176,177). Although MF may rarely produce angiodestructive lesions (178), the lymphoid cells in LYG tend not to have true cerebriform contours. Scattered immunoblasts and histiocytoid cells with some morphologic overlap with Reed-Sternberg variants may express B-cell markers as well as EBV protein. Occasional foci of epidermotropism may be observed in some lesions. Grading of lesions (I–III) based on proportion of EBV-positive cells, extent of atypia, and necrosis may correlate with biologic behavior for some lesions (179).

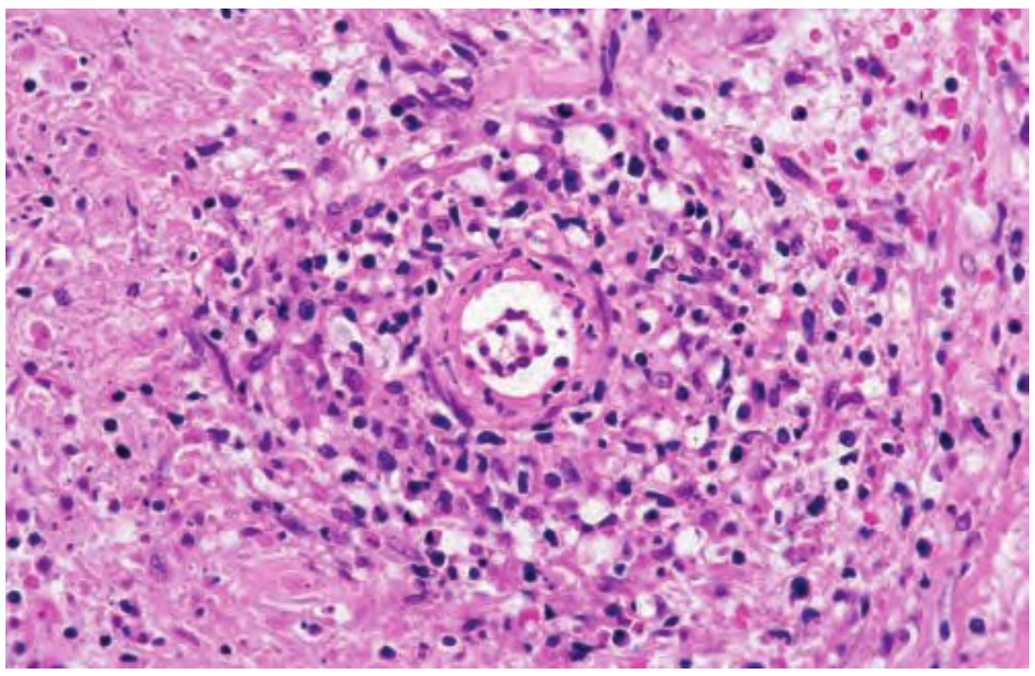


FIGURE 31-17. Lymphomatoid granulomatosis. Atypical lymphocytes have infiltrated and partially destroyed the involved vessel walls.

Histogenesis. The underlying cause of LYG appears to be related to EBV-driven abnormal B-cell proliferation in the setting of immunodeficiency (180,181). Large EBV-positive cells are also reactive for CD20, variably positive for CD30, and negative for CD15. The background lymphocytes are $CD3^+$, with CD4 >CD8. Higher-grade lesions tend to show clonality of immunoglobulin genes (174,182).

Differential Diagnosis. LYG must be differentiated from hematopoietic malignancies that also may show an angiodestructive growth pattern, such as extranodal NK-/T-cell lymphoma of the nasal type (182), and rare instances of MF with a vasculitic component (178). Identification of EBV-positive cells that express CD20 is helpful in separating LYG from these entities. There should not be diagnostic confusion with intravascular large B-cell lymphoma, which fails to show true primary vascular destruction.

Hodgkin's Lymphoma

HL constitutes a group of a relatively common type of lymphoproliferative conditions that share the common features of frequent origin in cervical lymph nodes, tendency toward occurrence in young adults, presence of Reed-Sternberg cells and their variants, and instances of rosette-like rimming of these cells by T lymphocytes. Although the skin is rarely involved, HL is discussed here briefly because it may be considered in the differential diagnosis of other cutaneous lymphoproliferative disorders (183–188).

Clinical Features. There are two major variants of HL: the common classical Hodgkin's lymphoma (CHL) and the far less frequently encountered nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL). The former consists of four histologic subtypes (see below). CHL tends to affect adolescents and young adults and typically presents as peripheral lymphadenopathy localized to one or several node groups. NLPHL affects young to middle-aged patients with a male predominance. Slightly less than half of these patients will also have systemic signs of disease (fever, sweats, and weight loss).

Histopathology. All forms of HL result in a polymorphous hematopoietic infiltrate that may efface nodal architecture and preexisting tissue structure. The histologic variant forms of

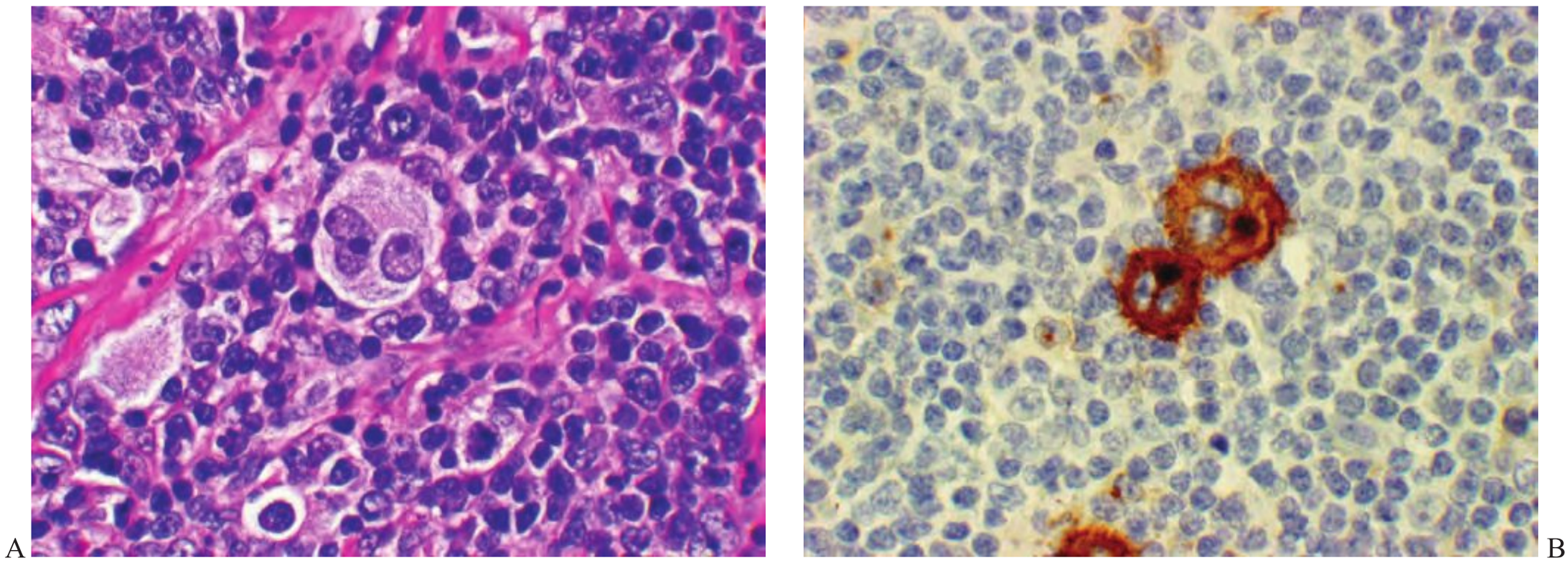


FIGURE 31-18. Hodgkin's lymphoma. A, B: CHL showing pleomorphic infiltrate and a characteristic Reed-Sternberg cell (A) that is reactive for the CD30 antigen (B).

CHL are lymphocyte rich (LRCHL), nodular sclerosis (NSHL), mixed cellularity (MCHL), and lymphocyte depleted (LDHL). CHL contains variable numbers of neoplastic Hodgkin's Reed-Sternberg (HRS) cells with abundant cytoplasm and at least two nuclear lobes, each containing prominent eosinophilic nucleoli and expressing CD30 by immunohistochemistry (Fig. 31-18A, B). By contrast, NLPHL is characterized by a cytologically and immunophenotypically distinct neoplastic cells known as the *L&H cells* (lymphocytic and/or histiocytic Reed-Sternberg cell variants). These cells have infolded and multilobed nuclei that may resemble popcorn, containing often multiple, small, basophilic nucleoli. The key features of each type of HL are summarized in Table 31-6. Skin involvement by HL generally resembles nodal disease. Architecturally, dermal infiltration is nodular or diffuse with absence of epidermotropism.

Histogenesis. The majority of cases of CHL are believed to be derived from mature germinal center B cells (189,190) that are rich in somatic mutations in the VH immunoglobulin genes. NLPHL is uniformly positive for B-cell markers (CD19, CD20, CD22, etc.), while classic types of HD express CD30 (191) in most instances. It appears that HL, despite morphologic similarities, represents a spectrum of disease entities rather than a single malady. NLPHL shows invariable expression of nuclear transcription factor Oct-2 that regulates the immunoglobulin promoter gene together with its cofactor BOB-1 (192–195). Classical types of HD tend to be positive

TABLE 31-6 Key Features of Each Type of Hodgkin's Lymphoma

	NLPHL	LRCHL	NSHL	MCHL	LDHL
Architecture	Nodular or nodular and diffuse	Usually nodular, rarely diffuse	Nodular, with collagen bands	Diffuse, no collagen bands	Highly variable
Cytology	Polymorphous, with L&H cells	Small lymphocytes, admixed with HRS cells	Polymorphous, HRS cells often in lacunar spaces	Polymorphous, HRS cells, granulomas	Variable, high ratio of HRS to lymphocytes
Immunophenotype	L&H cells $CD20^+$, $CD30^-$, $CD15^-$, $EMA^{+/-}$	HRS cells variably $CD20^+$, $CD30^+$, $CD15^+$, EMA^-	HRS cells variably $CD20^+$, $CD30^+$, $CD15^+$, EMA^-	HRS cells variably $CD20^+$, $CD30^+$, $CD15^+$, EMA^-	HRS cells variably $CD20^+$, $CD30^+$, $CD15^+$, EMA^-
EBV status	−	Many +	Many +	Many +	Many +

NLPHL, nodular lymphocyte-predominant Hodgkin's lymphoma; LRCHL, lymphocyte-rich classical Hodgkin's lymphoma; NSHL, nodular sclerosis Hodgkin's lymphoma; MCHL, mixed cellularity Hodgkin's lymphoma: LDHL, lymphocyte-depleted Hodgkin's lymphoma; L&H, lymphocytic and histiocytic; HRS, Hodgkin's Reed-Sternberg; EMA, epithelial membrane antigen; EBV, Epstein-Barr virus.

for PAX-5 encoded B-cell specific activator protein (BSAP) (194,196–199) and show variable expression for EBV in the tumor cells (200–203), either decorated by antibodies against latent membrane protein (LMP-1) and EBNA-1 or visualized by *in situ* hybridization to the RNA of EBV (EBER-1). A plethora of cytokines (interleukins, colony-stimulating factors, transforming growth factor-β, etc.) contribute to the variegated histologic appearance of HD (204–207).

Differential Diagnosis. HL only rarely involves the skin, and such events are almost always secondary to nodal disease. HL involving the skin may be confused, however, with T-cell–rich large B-cell lymphoma, DLBCL, anaplastic T-cell lymphoma, and reactive lymphoid hyperplasia. Careful correlation of clinical, histologic, and immunophenotypic features will generally assist in definitively excluding HL from these differential diagnostic considerations.

$CD30^+$ cells may occur in a variety of settings in addition to HL, including anaplastic T-cell lymphoma, MF, and lymphomatoid papulosis (LYP), and these conditions occasionally may develop in the same patient, resulting in speculation that they may be biologically interrelated (208). Careful evaluation and correlation of coexisting clinical parameters, immunohistochemical, and molecular studies may be necessary for accurate classification of atypical cutaneous infiltrates containing more than occasional $CD30^+$ large lymphoid cells. Fortunately, skin involvement by HL in the absence of overt nodal disease is so rare as to make its inclusion in this differential an academic one.

PRIMARY CUTANEOUS T-CELL LYMPHOPROLIFERATIVE DISORDERS

T-cell Lymphomatoid Hyperplasias

T-cell lymphomatoid hyperplasia refers to the occurrence of epidermotropic cutaneous immune responses composed of activated/proliferative T cells that produce a pattern that may mimic MF and its variants. It is arbitrarily divided into several clinicopathologic variants in order to better illustrate the patterns most likely to result in potential diagnostic confusion with T-cell malignancy.

Clinical Features. Because these conditions all share the feature of epitheliotropism, they—like various forms of MF—may be associated with the formation of scaling erythematous and variably indurated patches and plaques and occasionally with foci of alopecia. On occasion, subacute to chronic spongiotic or lichenoid dermatitis may be associated with lymphoid epidermotropism in the relative absence of intercellular edema or apoptosis, thus bringing to mind consideration of possible T-cell dyscrasia. Certain immune responses may also show a T-cell pattern in the setting of drug-induced immune dysregulation and therefore mimic T-cell dyscrasia or lymphoma.

Histopathology. Dermatitis with epidermotropism in the relative absence of associated spongiosis or evidence of cytotoxic injury will generally show more typical findings on evaluation of deeper sections. Multiple biopsies may occasionally be required to better assess the sequential evolution of lesions and to identify stages where more characteristic inflammatory changes predominate. The finding of Langerhans cell microgranulomas (209) favors a reactive process, although care must be taken not to confuse these structures with true Pautrier microabscesses (see page 937) (Fig. 31-19A). Importantly, many examples of T-cell pattern lymphomatoid dermatitis will lack the uniform cytologic atypia within the epidermotropic component more characteristically seen in MF. An exception to this, however, are T-cell pattern reactive infiltrates occurring in patients with altered immune function, as may be seen in certain lymphomatoid drug eruptions (Fig. 31-19B), as described by Brady and associates (210). In these settings, cytologically atypical epidermotropic infiltrates may closely mimic MF and even may show immunophenotypic (e.g., diminished CD7

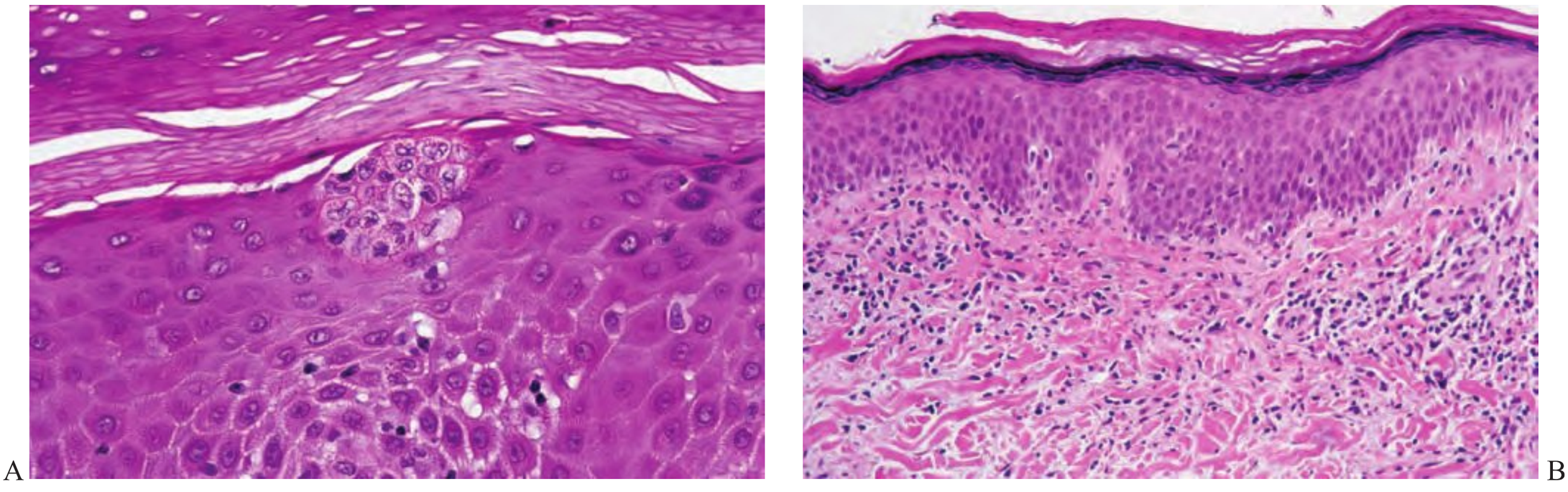


FIGURE 31-19. T-cell lymphomatoid hyperplasia. A: Langerhans cell microgranuloma associated with T-cell immune response may mimic Pautrier microabscess. B: Lymphomatoid drug eruption, with papillary dermal interstitial and focally epidermotropic infiltrate of variably activated lymphocytes in a characteristic T-cell pattern.

expression) or genotypic (e.g., T-cell receptor [TCR] gene rearrangements) abnormalities that are reversible on drug cessation (211).

Histogenesis. The histogenesis of T-cell pattern drug-induced lymphoid dyscrasia seems to relate to the concurrence of cutaneous hypersensitivity reactions caused by drugs that themselves are capable of inciting some level of immune dysregulation. These drugs include anticonvulsants, antidepressants, phenothiazines, calcium channel blockers, and angiotensin-converting enzyme inhibitors.

Differential Diagnosis. The primary differential diagnosis is the T-cell pattern immune response in the setting of immune dysregulation. Careful consideration of clinical factors, including duration of lesions, response to previous therapy, and potential relationship to drugs that influence lymphocyte function should be undertaken before definitively excluding a lymphomatoid drug eruption in the differential diagnosis of epidermotropic T-cell malignancies.

T-/NATURAL KILLER–CELL NEOPLASMS

Mycosis Fungoides

MF is the prototype of CTCL that typically begins as slowly progressive dermatitis-like patches and plaques, and if untreated evolves to nodules and eventual systemic dissemination. The patch/plaque stage of the disease is the result of intraepidermal and superficial dermal infiltration by small- to medium-sized malignant T cells with characteristically cerebriform nuclear contours, while the more advanced stages develop as a consequence of exclusively dermal involvement by nonepidermotropic, often cytologically more atypical malignant T cells.

Clinical Features. MF is relatively rare, accounting for $<1\%$ of non-HLs. However, of lymphomas that arise primarily in skin, it is the most common (13), comprising approximately 44% of cutaneous lymphomas. It is a disease predominantly of adult males (male-to-female ratio of 2:1), although children are occasionally affected. MF has a plethora of clinicopathologic manifestations. Typical lesions initially present as large erythematous scaling patches and plaques (many centimeters in diameter and may show arcuate or polycyclic configurations) that generally are resistant to antiinflammatory therapy (Fig. 31-20A). Zones of alopecia may occur due to infiltration and mucinous degeneration of hair follicles (alopecia mucinosa). Occasional lesions may show epidermal atrophy, prominently dilated superficial dermal blood vessels, and patchy hyper- and hypopigmentation (poikiloderma vasculare atrophicans variant), while others may show excessive epidermal thickening and scaling (psoriasiform variant). In one rare form of the disease, lesions are generally solitary, involve acral skin, and clinically resemble squamous neoplasia as a result of epidermal thickening and scale formation (pagetoid reticulosis variant). The dermal component is occasionally associated with granulomatous inflammation that compromises the integrity of elastic fibers (granulomatous slack skin [GSS] variant).

The natural history of MF is one of slow progression, with the patches and plaques giving rise over time to nodules that may eventually ulcerate (Fig. 31-20B). Rarely, nodules are documented from the outset (d'emblee variant), although this rare presentation is not well characterized, and some of these patients may have other forms of T-cell malignancy (e.g., adult T-cell leukemia/lymphoma [ATLL]; primary cutaneous peripheral T-cell lymphoma; unspecified, primary cutaneous $CD4^+$ medium-sized pleomorphic T-cell lymphoma; and $CD30^+$ large T-cell lymphoma) (212). Diffuse erythroderma may be associated with systemic dissemination and may represent either a manifestation of late evolution of localized disease (213) or blood involvement from the outset (Sézary syndrome). When extracutaneous spread eventuates, the lymph nodes, spleen, liver, and lungs are often involved, in addition to the peripheral blood. Lymph node enlargement at such advanced stages must

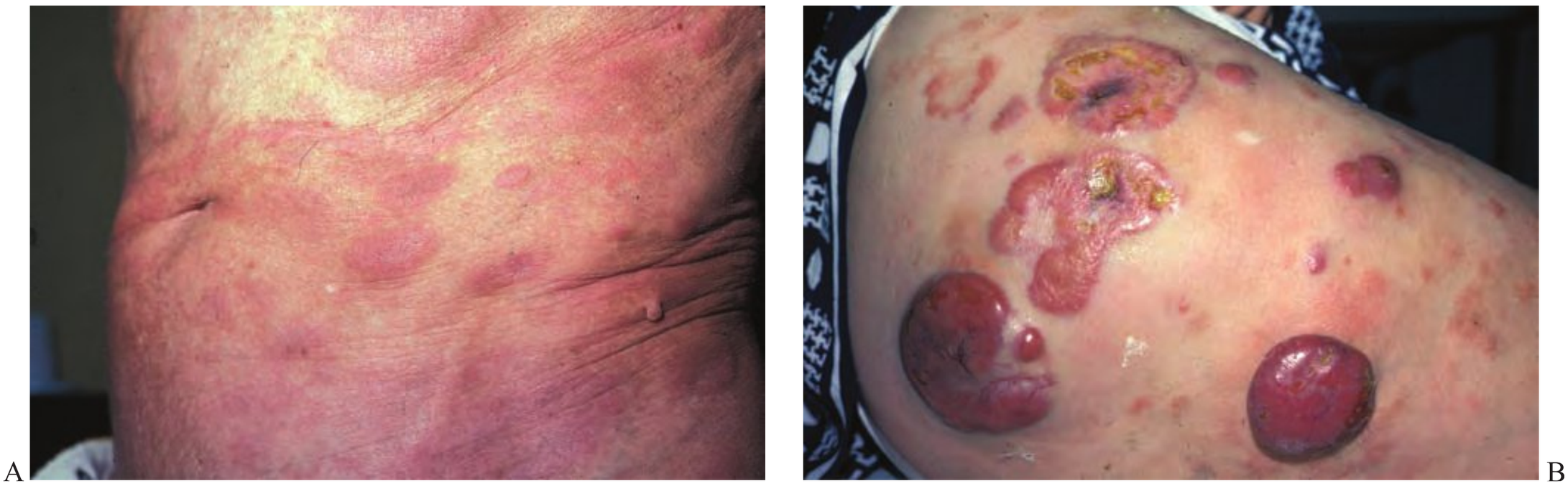


FIGURE 31-20. Mycosis fungoides: clinical features. A: Erythematous scaling patches and plaques of early disease. B: Plaques and nodules of advanced disease.

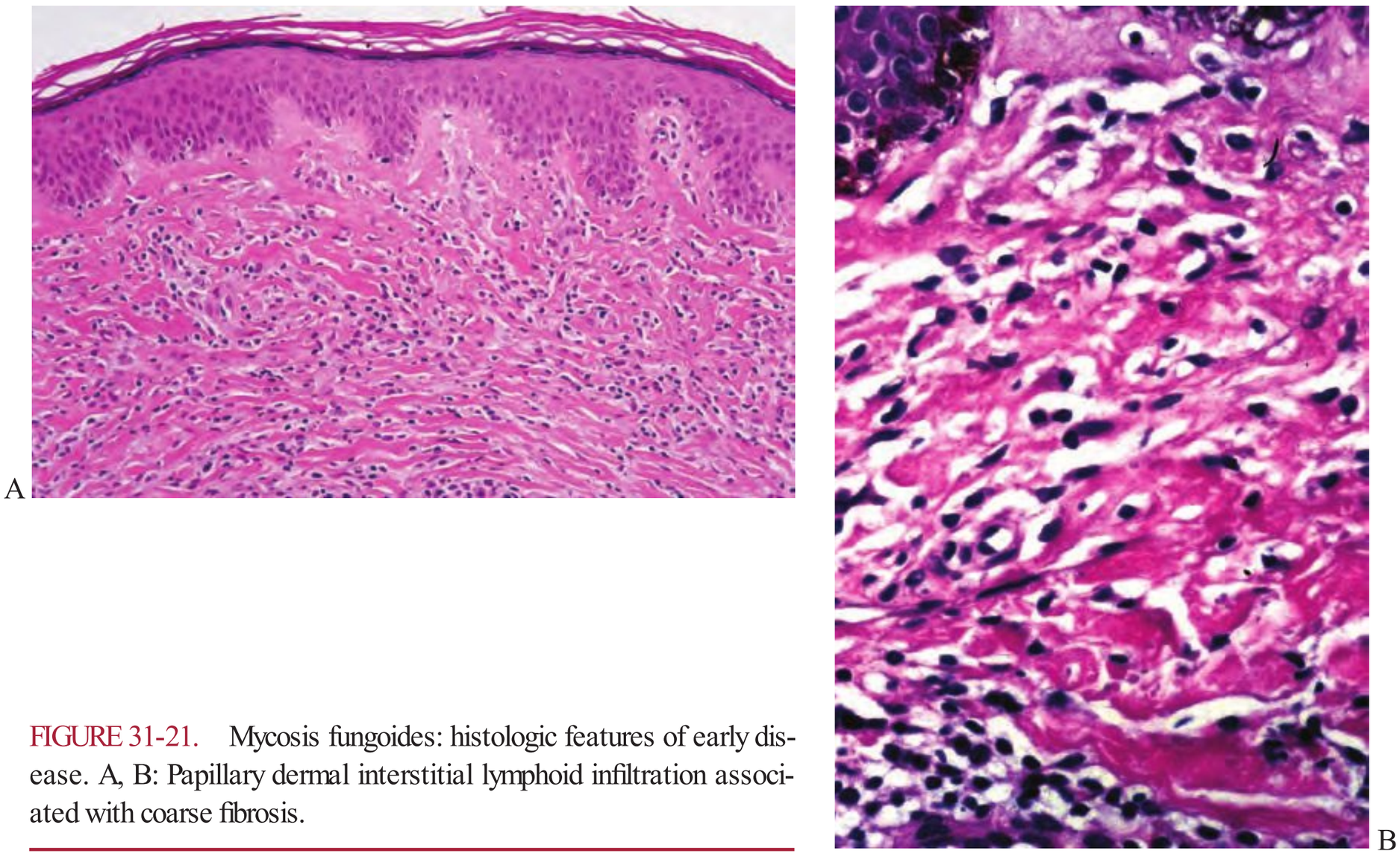


FIGURE 31-21. Mycosis fungoides: histologic features of early disease. A, B: Papillary dermal interstitial lymphoid infiltration associated with coarse fibrosis.

be differentiated from nodal hyperplasia resulting from chronic drainage of involved sites (dermatopathic lymphadenopathy).

Clinical staging of MF involves four categories: stage I indicates disease confined to skin as localized (<10% body surface, stage IA) or disseminated (≥10% body surface involvement, stage IB) patches/plaques; stage II signifies nodal enlargement without histologic evidence of nodal lymphoma (generally dermatopathic changes only, IIA) or cutaneous tumors (IIB); stage III implies generalized erythroderma; and stage IV connotes nodal or visceral dissemination (214). Prognosis is directly related to extent of disease progression, with stage I and II lesions having an excellent outcome and more advanced presentations (nodules and extracutaneous dissemination) showing aggressive courses (13,213,215–218).

Histopathology. Early lesions of MF show a patchy bandlike lymphocytic infiltrate within the papillary dermis, often associated with coarse fibrosis (Fig. 31-21A, B). The lymphocytic component may in part be reactive, with an admixture of eosinophils, plasma cells, and monocytes, and in this mixture of cells, the characteristic cytology of MF cells may be difficult to document. Care must be taken to identify foci of epidermotropism or folliculotropism that generally involve the malignant T-cell clone. These foci may consist of a lentiginous pattern (linear accumulation associated with the basement membrane zone, frequently described as *tagging*) (Fig. 31-22A, B) or a pagetoid pattern with either single-cell infiltration (Fig. 31-22C) or clustered epidermotropic atypical lymphocytes, also known as *Pautrier microabscesses*, into a "passive" epidermal layer (Fig. 31-22D). Lymphoid epidermotropism in MF, unlike lymphoid exocytosis in dermatitis, is generally unassociated with significant epidermal or follicular spongiosis or evidence of cytotoxicity (basal cell layer vacuolization or apoptosis). Rather, the epithelium may appear passive, resulting in seemingly permissive accumulation of atypical lymphocytes within lacunar spaces that separate seemingly indifferent keratinocytes. These spaces appear by sequential analyses to result from minute regions of epithelial mucinosis. When hair follicles are infiltrated by malignant T cells, accumulation of mucin may produce widened intercellular spaces between epithelial cells and ultimately result in inability of follicles to support existing or recycle new hair shafts (follicular mucinosis).

Cytologically, the malignant T cells in MF are small- to medium-sized lymphocytes that characteristically contain nuclei with dense heterochromatin and elaborately indented (cerebriform) nuclear contours (Fig. 31-23A, B). Occasionally, these cells may be difficult to differentiate from cytokine-activated T cells, although one helpful feature is the tendency for epidermotropic malignant T cells to predominantly or exclusively show cerebriform nuclear features and clear perinuclear halos. However, intraepithelial aggregates of malignant T cells in MF must be differentiated from similar aggregates of larger mononuclear cells also with irregular, frequently indented, nuclear profiles (so-called Langerhans cell microgranulomas [8], commonly associated with dermatitis; also see differential diagnosis and Table 31-7). Malignant T cells with cerebriform nuclei, although present predominantly in the epidermis, also may be detected within the dermal component of lesions. However, their frequent admixture with reactive lymphocytes and mononuclear cells may make their reliable identification more difficult, especially in early lesions. With advanced disease, when lesions become nodular and there is often loss of

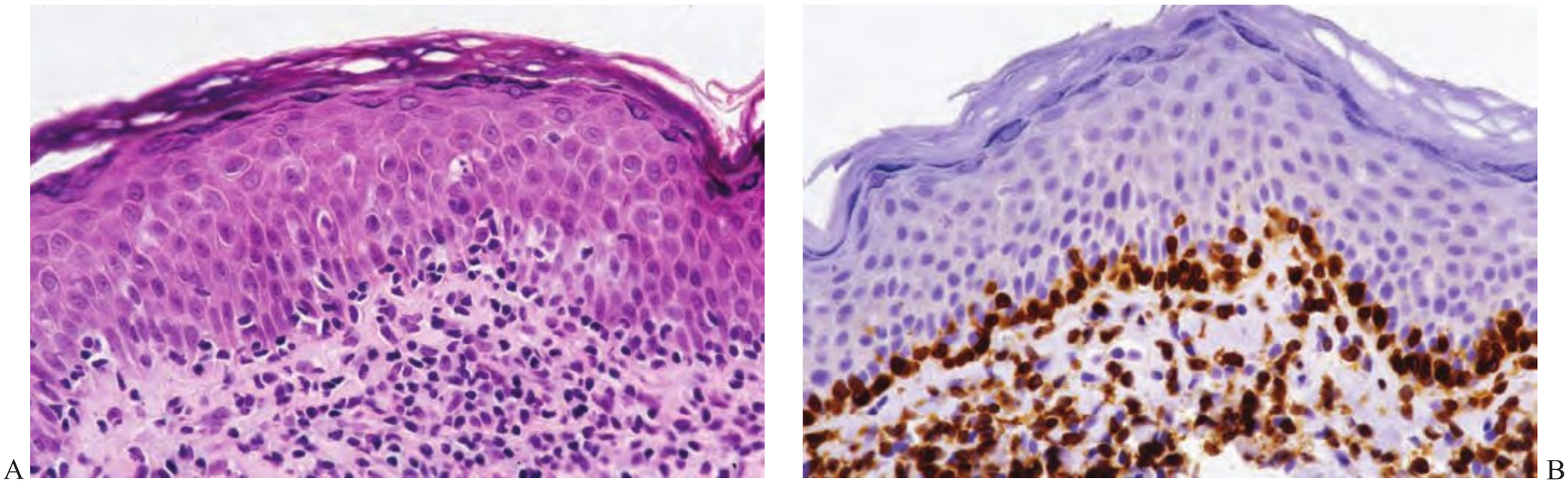


FIGURE 31-22. Mycosis fungoides: architectural patterns of epidermotropism. A: Papillary dermal interstitial infiltrate associated with linear aggregation of neoplastic lymphocytes along the dermal–epidermal junction. B: Adjacent section stained for CD4 emphasizing this linear pattern of early epidermotropism. C: Early plaque-stage disease with single cell epidermotropism by atypical lymphocytes into a "passive" epidermal layer. D: Plaque-stage disease characterized by prominent clusters of atypical lymphocytes within the epidermis (Pautrier microabscesses).

FIGURE 31-23. Mycosis fungoides: cytology. A: Oil immersion conventional microscopy of atypical lymphocytes within the epidermal layer. B: One-micron, toluidine blue–stained section of epidermotropic malignant lymphocytes showing characteristically infolded nuclear contours.

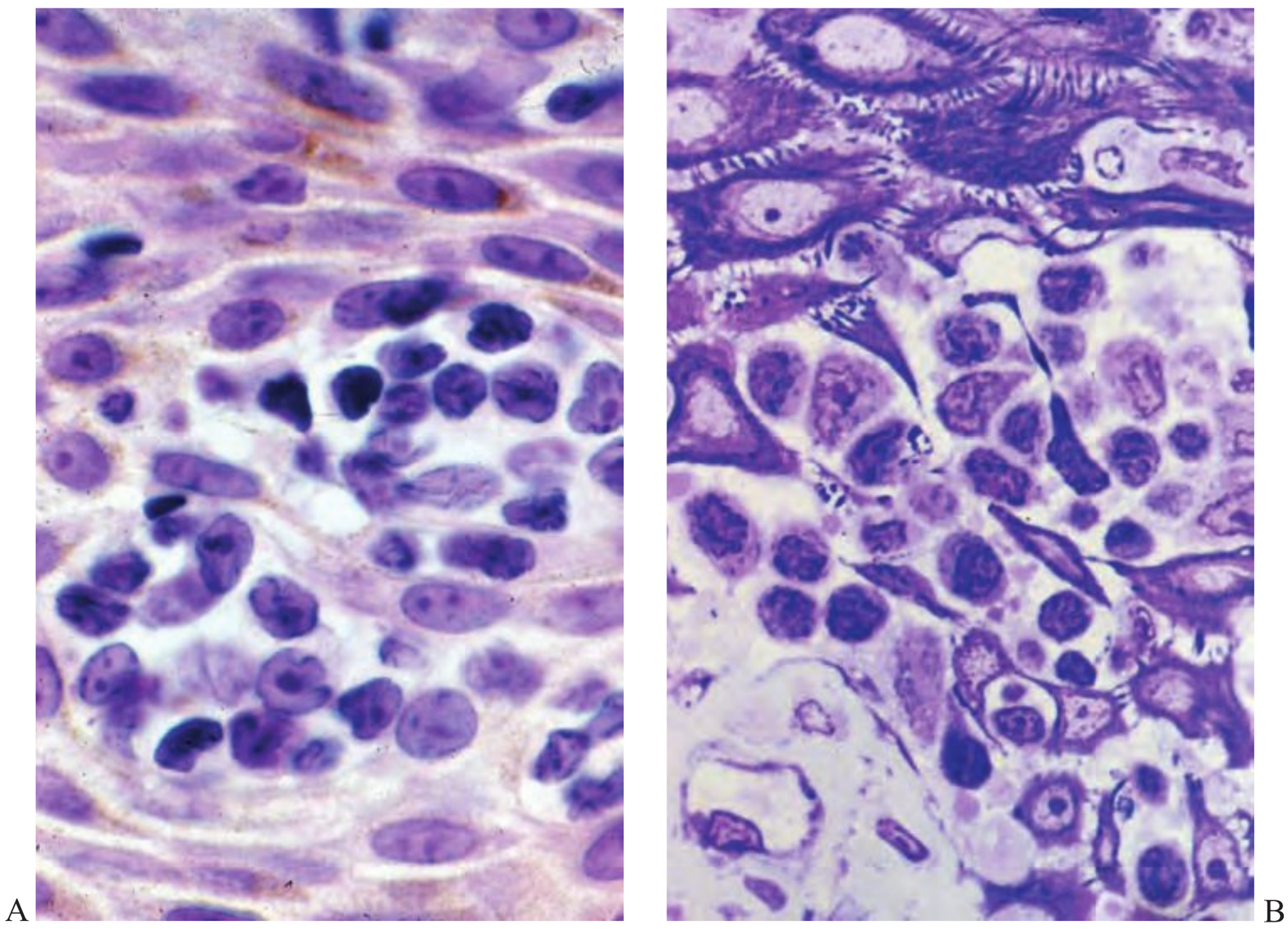


TABLE 31-7 Differential Diagnosis of Mycosis Fungoides and Dermatitic Mimicks

	Mycosis fungoides	Reactive dermatitis
Architecture of infiltrate	• Early/Patch stage: patchy bandlike • Plaque stage: lichenoid • Tumor stage: nodular/diffuse	• Superficial perivascular • Superficial and deep perivascular
Pattern of infiltrate	Epidermotropism with Pautrier microabscesses	Exocytosis with Langerhans cell microgranulomas
Composition of infiltrate	Predominance of atypical lymphocytes	Admixed lymphocytes, macrophages, eosinophils, mast cells, and plasma cells
Epidermal changes	Psoriasiform hyperplasia without associated spongiosis or apoptotic keratinocytes	• Associated spongiosis and apoptotic keratinocytes • Psoriasiform hyperplasia may be seen in chronic disease
Papillary dermal changes	Coarse fibrosis	May be fibrotic if long standing or previously traumatized
Cytology of lymphoid cells	• Small to medium • Cerebriform hyperchromatic nuclei • Perinuclear halos	• Small, round, and regular
Immunophenotyping	$CD2^+$, $CD3^+$, $CD4^+$, $CD5^+$, and $CD8^-$ with loss of CD7 (rare $CD8^+$ variant reported)	Mixed $CD4^+$ and $CD8^+$
TCR gene rearrangement	Clonal	Polyclonal (rarely clonal)

TCR, T-cell receptor.

epidermotropism, the dermal infiltrate is composed of nodular to diffuse interstitial populations of more uniformly atypical T cells (Fig. 31-24A, B). Transformation to large, highly atypical CD 30^+ lymphocytes in the dermal component is associated with development of an aggressive biologic course (219,220).

Apart from the classic MF described previously, there are a number of clinicopathologic variants and subtypes of MF, some of which are recognized by the WHO/EORTC consensus classification. These include the following:

Adnexotropic mycosis fungoides (221). This form of the disease may occur anywhere, although the skin of the face and the scalp as well as sun-exposed extremities are often involved. Epidermotropism may be minimal to absent, and diagnosis may be overlooked when biopsies are too superficial. Infiltration of hair follicles by characteristically atypical T cells (222) (folliculotropic MF) may result in Pautrier microabscesses and be associated with follicular mucinosis where keratinocytes forming affected follicles produce intracellular mucin and eventually degenerate, culminating in alopecia (Fig. 31-25A–C). There are no reliable clinical, histopathologic, or molecular criteria that allow a distinction to be made between "benign" alopecia mucinosa and MF-associated follicular mucinosis (folliculotropic MF [223]). Eccrine involvement (syringotropic MF) may also be observed, with or without follicular lesions. Infiltration of the eccrine coil

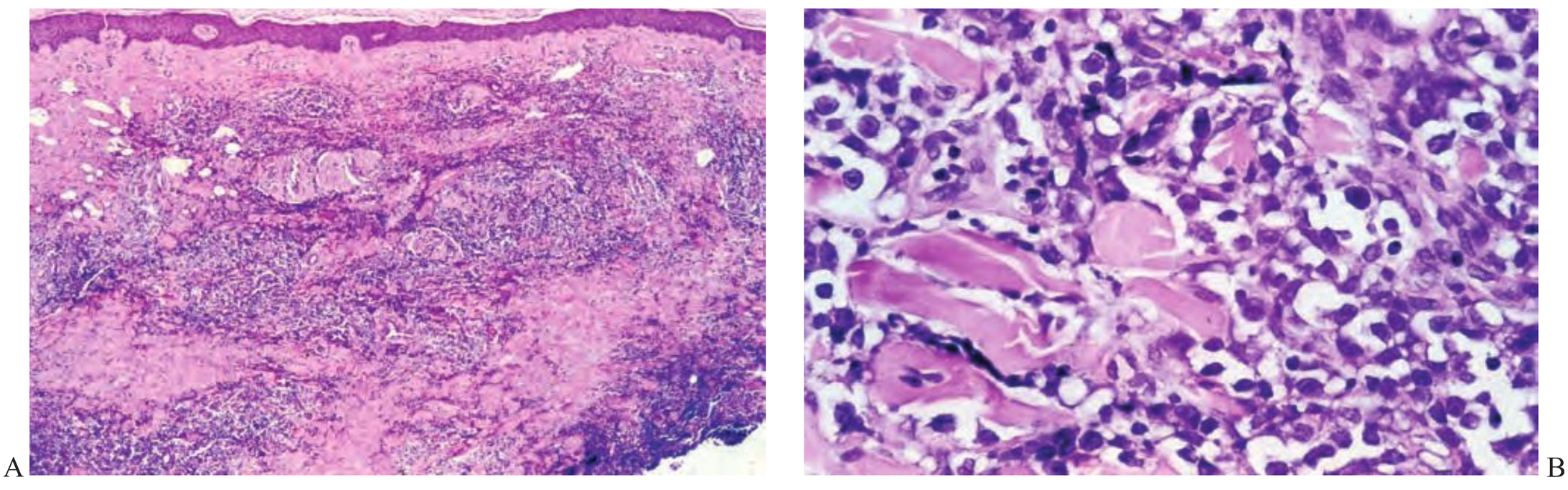


FIGURE 31-24. Mycosis fungoides: nonepidermotropic. A: There is a nodular to diffuse dermal infiltrate with relative sparing of the superficial dermis and epidermis. B: Cytologically, atypical lymphocytes produce an interstitial pattern of dermal infiltration.

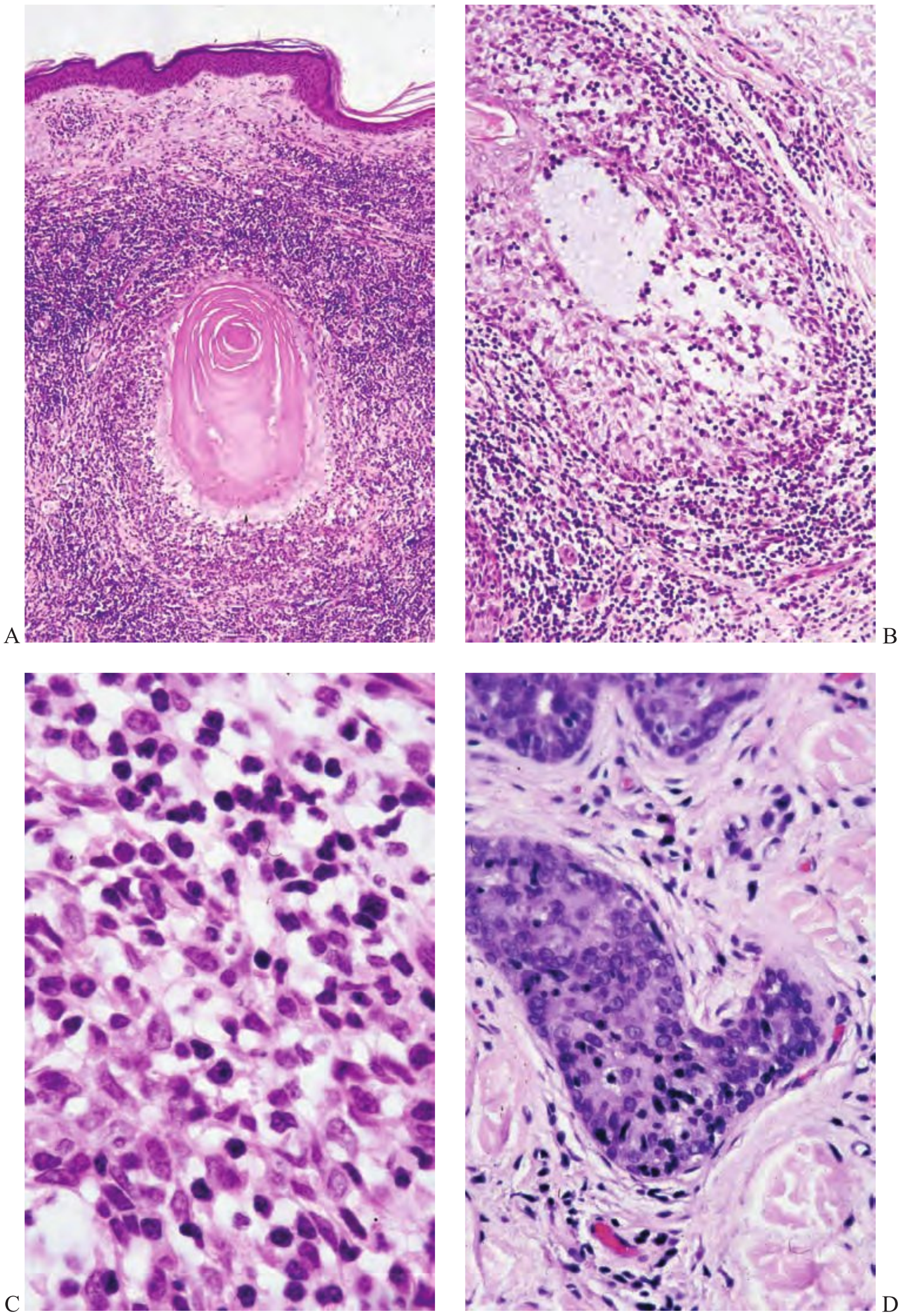


FIGURE 31-25. Adnexotropic mycosis fungoides. A: Infiltration is associated with architectural distortion and destruction of follicular structures. B: Follicular mucinosis characterized by pools of pale blue–staining mucin. C: Atypical T cells in a mucinous background. D: Eccrine involvement by atypical lymphocytes, associated with syringosquamous metaplasia.

may be associated with syringometaplasia but not mucinosis (Fig. 31-25D). Prognosis is generally favorable, although potentially less so than in early evolutionary stages of classic epidermotropic patch/plaque-stage disease (13). From the clinical point of view, an additional relevant feature of adnexotropic MF includes the deeper localization of neoplastic infiltrate, which may render reduced response to skin-targeted therapies.

Solitary pagetoid reticulosis (Woringer-Kolopp disease). In the past, cases of pagetoid reticulosis were considered to be a distinct entity. Only recently, phenotypic criteria have allowed them to be reclassified. Solitary pagetoid reticulosis (Woringer-Kolopp disease) is now regarded as a rare variant of MF, whereas cases of generalized pagetoid reticulosis (Ketron-Goodman disease) represent, for the most part, examples of aggressive $CD8^+$ T-cell lymphoma (56). Solitary pagetoid reticulosis (Woringer-Kolopp disease) is a rare low-grade and peculiar form of MF associated with exclusively epidermal infiltration by medium- to large-sized malignant T cells with abundant pale cytoplasm, often in the form of a solitary acral

lesion where associated epidermal acanthosis and hyperkeratosis results in the clinical impression of a squamous neoplasm. The pagetoid growth pattern of the neoplastic T cells may be attributed to their strong expression of adhesion molecules, cutaneous lymphocyte-associated antigen (CLA) and αEβ7, in particular, which facilitate interactions with endothelial cells and keratinocytes, respectively (224). Immunophenotypic studies have also disclosed the malignant T cells to be either $CD4^+$, $CD8^+$, or double negative for both epitopes, and TCR gene rearrangements may be demonstrated (225). Histopathologically, because of the pronounced epidermotropism, pagetoid reticulosis may mimic superficial spreading melanoma, pagetoid squamous carcinoma *in situ*, Paget's as well as extramammary Paget's disease. However, differential diagnosis can be readily achieved based on cytomorphologic and immunophenotypic features (CD45, S100, pan-cytokeratin, epithelial membrane antigen [EMA], and carcinoembryonic antigen [24,226,227]).

Granulomatous mycosis fungoides. This unusual variant accounts for up to 4% of MF. Clinically, the lesions present as papules, plaques, and tumors that are not distinctive from classical cases (228). Histopathologically, granulomatous MF is characterized by the presence of variable granulomatous inflammation, which may take the forms of interstitial, tuberculoid/sarcoidal, or palisading granulomata reminiscent of granuloma annulare and/or necrobiosis lipoidica (229–231). Multinucleated giant cells, usually of the foreign body type (although Langerhans and Touton giant cells have been described as well) with or without focal elastophagocytosis, may be seen (228,232,233). Recent studies suggest that granulomatous MF may have an aggressive course, with nearly 40% of patients dying from the disease and 50% within 5 years of the onset of cutaneous lesions (234,235). Special stains for microorganisms are useful in excluding concurrent infection in a patient with classical MF. Despite rare cases showing overlapping features, granulomatous MF can be differentiated from GSS clinically by the absence of bulky skin lesions and histologically by the lack of extensive elastolysis/elastophagocytosis and dense infiltrate with deep subcutaneous involvement (236).

Granulomatous slack skin (GSS). This subtype indicates the presence of elastolytic granulomas that develop in association with the dermal lymphomatous component, which is typically dense and extends deep into the subcutis. Histologically, atypical T-cell infiltrates, often associated with epidermotropism or folliculotropism, are intimately associated with noncaseating dermal granulomas formed by histiocytes and multinucleated giant cells that may contain ingested elastic fibers (237) or engulfed lymphocytes (emperipolesis). In established lesions, there is marked reduction of elastic fibers. Clinically, zones of skin with increased folding and decreased elasticity gradually develop, with preferential involvement of intertriginous sites, as a result of loss of elastic fibers. Despite therapy, lesions generally progress slowly over time.

In addition to the variants and subtypes listed by the WHO/EORTC consensus classification, other variants of MF have been described. Despite characteristic features that allow for their distinction, these variants share a similar clinical course and prognosis with classical MF and may represent a clinicohistopathologic spectrum of the disease. Nonetheless, because of their clinical and histopathologic similarity to reactive dermatoses, recognition of these variants will facilitate differential diagnosis (212).

Poikiloderma vasculare atrophicans. This is a reaction pattern that may occur in lesions of MF, although it is not synonymous with T-cell lymphoma and may be seen in other settings. Early lesions may involve either large plaques or small papules arranged in a netlike configuration. Lesions show erythema, mild scaling, epidermal thinning, mottled hypo- and hyperpigmentation, and telangiectasia, and the clinical picture may resemble changes of radiodermatitis. Histopathology discloses epidermal atrophy; epidermal infiltration by atypical lymphocytes; a variable band of lymphocytes, histiocytes, and melanophages in the papillary dermis; and ectasia of superficial dermal vessels. The finding of atypical lymphocytes, potentially supported by a characteristic immunophenotypic and molecular profile for MF, should assist in separating this rare variant from other causes of acquired poikiloderma, including dermatomyositis and lupus erythematosus.

Psoriasiform mycosis fungoides. In the authors' experience, this variant is rare and may in some instances be the consequence of superimposed lichen simplex chronicus. Epidermotropism is present, consisting of accumulation of single and clustered atypical small- to intermediate-sized lymphocytes within the epidermal layer (Fig. 31-26). However, there is marked acanthosis frequently in association with coarse papillary dermal

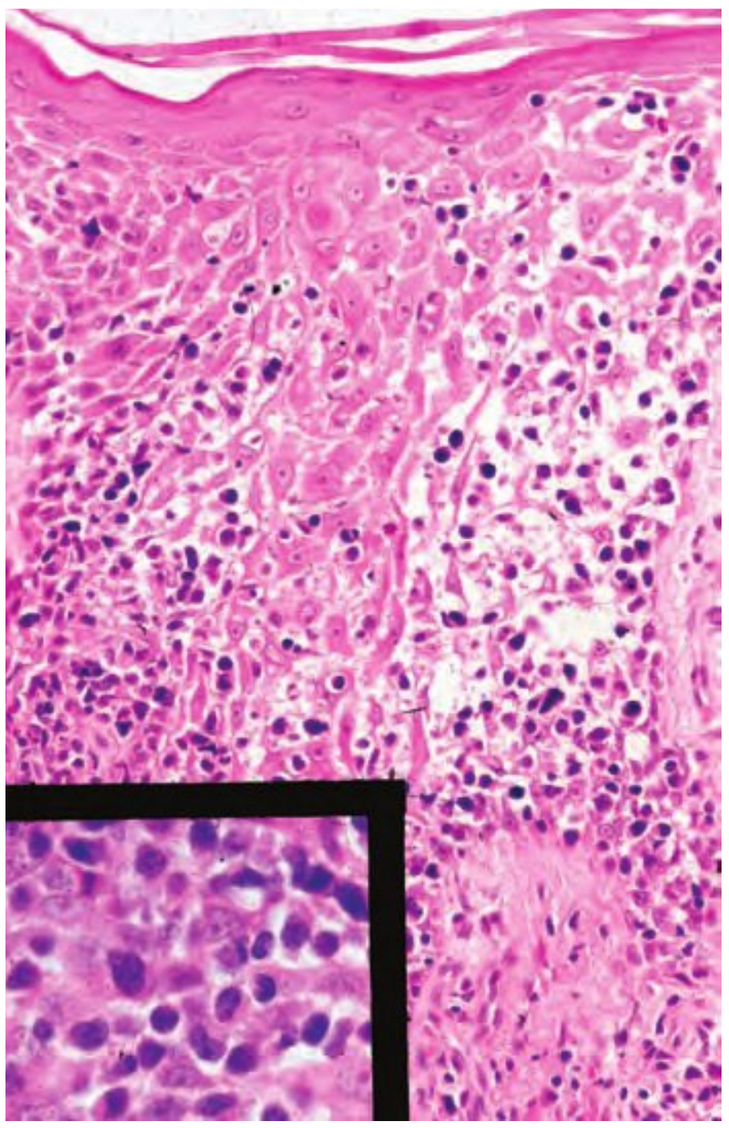


FIGURE 31-26. Psoriasiform mycosis fungoides. There is epidermal hyperplasia associated with pronounced epidermotropism by atypical lymphocytes (inset).

fibrosis. In one study of 222 biopsies where MF produced patterns that mimicked various forms of dermatitis, including psoriasiform dermatitis, diagnostic clues included epitheliotropism in the relative absence of spongiosis, alignment of atypical lymphocytes in association with the basal cell layer (so-called "tagging"), lymphoid atypia, and broad areas of compact hyperkeratosis with subtly interspersed parakeratosis (238).

Bullous/Vesicular mycosis fungoides. Bullous MF manifests clinically as blisters that may develop on normal skin or within typical plaques and tumors of MF (239–242). This variant may be of significant clinical relevance in terms of prognosis, as in one study, almost 50% of patients died within a year following the onset of blisters (240). In addition to common histologic features of classical MF, there is associated clefting, which may occur at different planes—subcorneal, intraepidermal, and subepidermal. Although the precise mechanism of the blister formation is not clear, it has been proposed that the subcorneal and intraepidermal separation may result from confluence of Pautrier microabscesses, and the subepidermal blister may be secondary to reduced keratinocyte adherence to the basement membrane in response to cytokines produced by the lymphoma cells (243). Unlike immunobullous disorders, immunofluorescence studies are consistently negative in bullous MF.

Hypopigmented mycosis fungoides. This variant is predominantly seen in young patients with dark skin (244,245). The lesions appear as asymptomatic or slightly pruritic, hypopigmented patches that may or may not be accompanied by typical patches and plaques of classical MF. The underlying mechanisms leading to hypopigmentation have been a subject of controversy. Some studies have found degenerative changes in melanocytes secondary to nonspecific cellular injuries (228,229), while others demonstrated impaired melanosome transfer to keratinocytes (246). Apart from prominent pigment incontinence, hypopigmented MF is indistinguishable from classical MF histopathologically. Although a recent report described a frequent $CD8^+$ phenotype in the former, the two variants share similar clinical course and prognosis (247).

Hyperpigmented mycosis fungoides. This is a rare variant characterized by diffuse macular hyperpigmentation (248,249). Histopathologically, there is often marked elongation of the rete ridges with basal hyperpigmentation and dermal melanophages superimposed on features of classical MF (248). Ultrastructural studies have revealed giant melanin granules in the tumor cells, keratinocytes, Langerhans cells, and macrophages (248).

Mycosis fungoides palmaris et plantaris. This variant defines cases where the MF lesions are limited to, predominantly affecting, or initially presenting on the palms and/or soles (250). The lesions may present as annular hyperpigmented patches and plaques (250,251), vesicles (239), pustules (252–254), hyperkeratotic/verrucous plaques (255–257), psoriasiform plaques (258), ulceration (259), and nail dystrophy (257). Regardless of the associated variable secondary epidermal changes that may complicate the clinical differential and microscopic interpretation, the presence of histopathologic findings of classical MF and clonal rearrangement of the TCR genes will help in reaching the correct diagnosis.

Verrucous/Hyperkeratotic mycosis fungoides. Typical lesions are hyperkeratotic/verrucous and occur on lower extremities, face, and trunk (260). There may or may not be associated classical patches and plaques of MF. Histologically, lesions are characterized by classic features of MF in a background of epidermal hyperplasia with hyperkeratotic scale (260–262).

Acanthosis nigricans–like (vegetating/papillomatous) mycosis fungoides. As the name implies, the lesions often resemble acanthosis nigricans or seborrheic keratosis clinically and have the predilection for the flexural sites (axillae and groin), neck, nipple, and areolae (263–265). Microscopically, the lesions have combined features of seborrheic keratosis and typical MF (e.g., a bandlike atypical lymphoid infiltrate with epidermotropism, elongated interconnected rete ridges, and pseudohorn cysts) (263–265).

Pustular mycosis fungoides. Pustular MF presents as pustular eruptions that may be limited to the palmoplantar areas (MF palmaris et plantaris) or generalized (252–254,266). Intraepidermal collections of atypical lymphocytes with neutrophils and eosinophils constitute the characteristic histopathologic findings (253,267). Production of high levels of interleukin-8 by the lymphoma cells has been implicated in the formation of pustular lesions (268).

Ichthyosiform mycosis fungoides. This is another rare variant of MF, which accounts for 1.8% of cases (269). The lesions are pruritic and ichthyosiform, often with excoriations. There may be accompanying comedo-like areas and/or follicular keratotic papules. Microscopically, the ichthyosiform areas show typical features of MF with compact orthohyperkeratosis and hypergranulosis, whereas the follicular papules exhibit cystic dilatation of hair follicles with keratotic plugs and folliculotropic atypical lymphocytes (212,269).

Histogenesis. The cell of origin in MF is believed to be a peripheral epidermotropic T cell. The immunophenotype is $CD2^+$, $CD3^+$, $CD4^+$, $CD5^+$, and $CD8^-$ (Fig. 31-27A–E), although rare cases have been described that are $CD8^+$ (270,271). Lesions often show absence of CD7, particularly in the atypical epidermotropic T cells (the admixed nonneoplastic lymphoid infiltrate in the dermis may preserve CD7 reactivity), even at early evolutionary stages of the disease, although this finding in itself does not reliably permit differentiation of MF cells from reactive T cells (270). The skin-homing antigen, CLA (recognized by HECA-452 antibody), is expressed in most cases, consistent with association of the malignant clone with a peripheral epidermotropic T cell. Although occasional $CD30^+$ cells may be identified in the dermal infiltrates, this epitope is not expressed by most cells comprising the malignant clone. However, in advanced tumor-stage disease, especially with

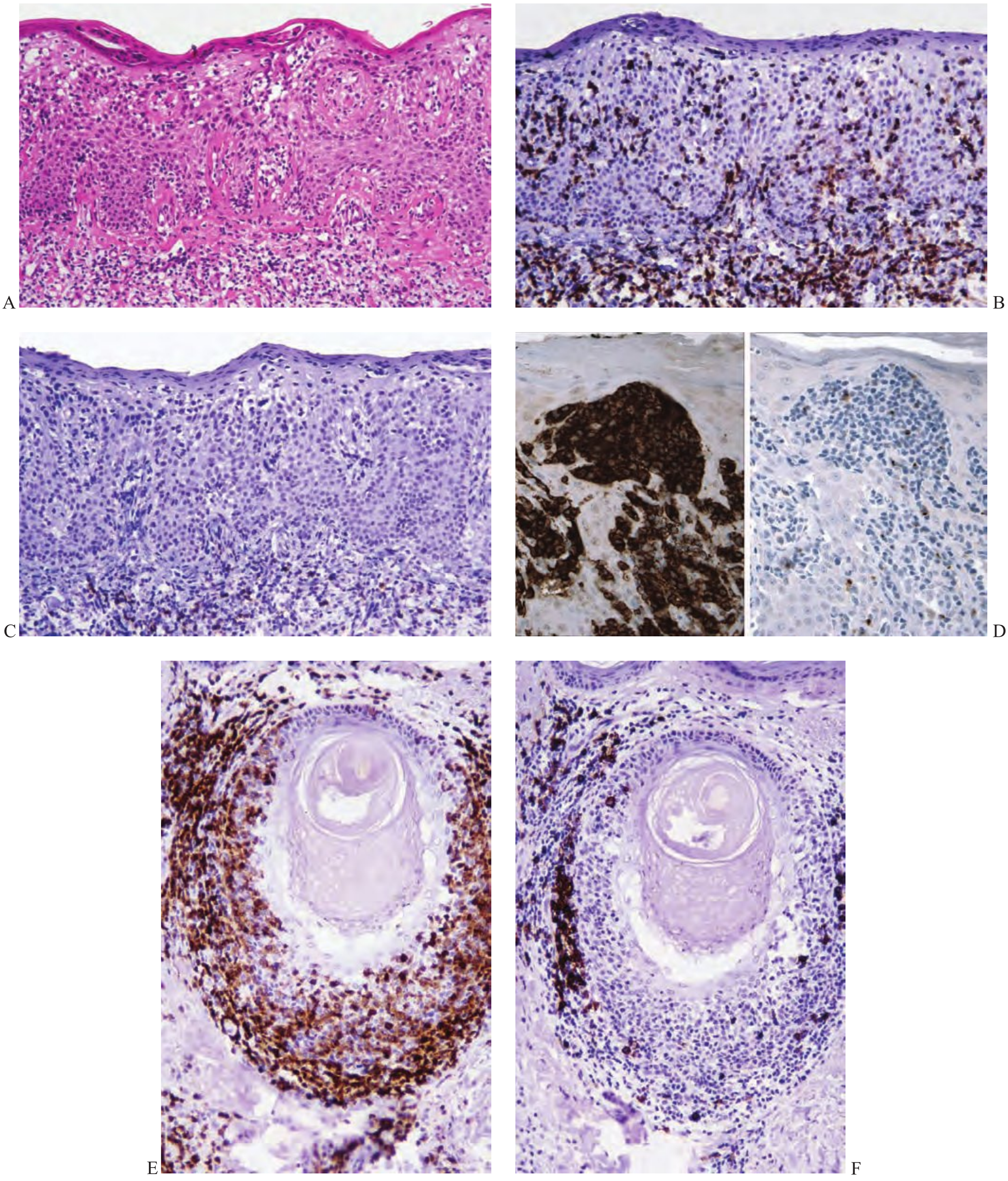


FIGURE 31-27. Immunophenotypic features of mycosis fungoides. Serial sections through a plaque-stage lesion with marked epidermotropism (A) reveal that most of the epidermotropic cells (in particular, those displaying nuclear atypia) express CD4 (B) but not CD8 (C). In addition, the epidermotropic CD4^{+} malignant T cells (left panel, D) may exhibit aberrant loss of other T-cell markers, such as CD7 (right panel, D). Similar findings are observed for folliculotropic T cells (E, CD4, F, CD8).

large cell transformation, the cells may acquire CD30 expression as well as a cytotoxic phenotype and thus cytotoxic granule-associated proteins, such as TIA-1, granzyme B, and perforin, also may be demonstrated (272). TCR genes are clonally rearranged, and this may be a helpful, albeit not entirely specific, diagnostic adjunct in early disease.

Differential Diagnosis. The practical differential diagnosis of classical epidermotropic MF involves primarily reactive T-cell infiltrates with exocytosis or an abnormal papillary dermal homing pattern (Table 31-7). True dermatitis may show lymphoid exocytosis and development of Langerhans cell microgranulomas that superficially may resemble Pautrier microabscesses. However, the former is generally associated with spongiosis or evidence of cytotoxic epidermal injury, and CD1a positivity by immunohistochemistry (209) and the latter with large cells containing ample cytoplasm, pale-staining infolded nuclei. Adnexotropic lesions must be separated from forms of dermatitis primarily centered about hair follicles and sweat glands. Again, the finding of uniformly atypical epitheliotropic lymphocytes and their tendency to be predominantly $CD4^+$ by immunohistochemistry should assist in this differential. While occasional cases of dermatitis show TCR gene rearrangements, most do not. Accordingly, PCR analysis is also an important adjunct in differentiating MF from its inflammatory imitators. As discussed previously, careful clinical history is required to access the relationship of onset of atypical T-cell pattern epidermotropic infiltrates to drugs that may produce immune dysregulation and eruptions that are morphologically, immunophenotypically, and even genotypically difficult to differentiate from MF. Clearing of the skin lesions following discontinuation of the offending drugs or lack of correlation of TCR gene rearrangement among lesions is also helpful in establishing the diagnosis. Other common histologic mimickers of MF include persistent arthropod bite reaction, secondary syphilis, nodular scabies, actinic reticuloid, fungal infection, lichen sclerosus in the early inflammatory stage, lichen striatus, lichenoid keratosis, pigmented purpuric dermatitis, connective tissue disorders, inflamed vitiligo, and regressed melanoma (273).

It is possible that very early evolutionary stages of MF involve a dysplastic phase in tumor progression. Such lesions may fulfill some but not all of the features required for a diagnosis of patch-stage disease. The authors generally refer to such lesions as being compatible with possible evolving T-cell dyscrasia, close follow-up and interval biopsy sampling to assess disease evolution are recommended. Some such lesions may be referred to by a variety of potentially confusing clinical descriptors, including *large plaque parapsoriasis*. The notion that small plaque parapsoriasis is an indolent form of MF is questionable in view of the accepted requirement for most malignant cells to exhibit features of tumor progression over time.

Late-stage disease, where epithelial involvement is minimal to absent and cytologic features may be higher grade, must be distinguished from B-cell lymphomas involving the skin. Distinction between aggressive $CD30^+$ transformed tumor stage MF (MF with large cell transformation) and primary cutaneous anaplastic large cell lymphoma (PC-ALCL) relies mainly on clinical history of presence or absence of typical patches and plaques of classical MF.

Sézary Syndrome

Sézary syndrome refers to a potentially aggressive leukemic form of CTCL characterized by generalized redness and scaling of the skin (erythroderma), lymphadenopathy, and presence of malignant T cells in the skin and peripheral blood (274). Because these malignant T cells have phenotypic and antigenic overlap with those of MF, Sézary syndrome is sometimes regarded as a MF variant. However, important clinical and histopathologic differences exist between classical MF and Sézary syndrome, and in the new WHO-EORTC classification, the term *Sézary syndrome* is restricted to cases that do not have a history of MF.

Clinical Features. Patients generally present with diffuse skin erythema and lymphadenopathy. There may also be itching, hair loss, nail dystrophy, and hyperkeratosis affecting the skin of the palms and soles (12). In addition to lymph node, skin and blood involvement, malignant T cells may also infiltrate viscera in late stages, although bone marrow is often spared (12,193). The prognosis is poor, with a median survival between 2 to 4 years (275).

Histopathology. Affected skin may show changes similar to those of patch/plaque-stage MF, although the infiltrate is often sparse and multiple sections may be required in some cases to identify convincing epidermotropism by atypical lymphocytes (Fig. 31-28A). Involved lymph nodes are characterized by effacement of their architecture by infiltrates of atypical cells. The peripheral blood contains atypical lymphocytes with cerebriform nuclear contours, with smaller versions referred to as *Lutzner cells* and larger ones as *classical Sézary cells* (Fig. 31-28B). Diagnosis of Sézary syndrome requires at least 1,000 such cells per mm^2 in most series (13,213). Flow cytometry will generally indicate elevation in a CD4: CD8 ratio of 10 or higher and increased numbers of cells with a $CD4^+/CD7^-$ phenotype (276). Molecular analysis will show clonal rearrangement of the TCR gene in most cases (13,277).

Histogenesis The neoplastic peripheral epidermotropic T cells generally are $CD2^+$, $CD3^+$, $CD4^+$, $CD5^+$, and $CD7^{+/-}$. Aberrant T-cell phenotypes are common, often with loss of T cell markers such as CD2, CD3, CD4, CD5, and CD7; rare $CD8^+$ variants have been described (13).

Differential Diagnosis. Sézary syndrome must be differentiated from other dermatitic causes of erythroderma (e.g., atopic dermatitis, seborrheic dermatitis, pityriasis rubra pilaris, and psoriasis). Because the histopathology of skin involvement in Sézary syndrome may be subtle, it is often critical also to

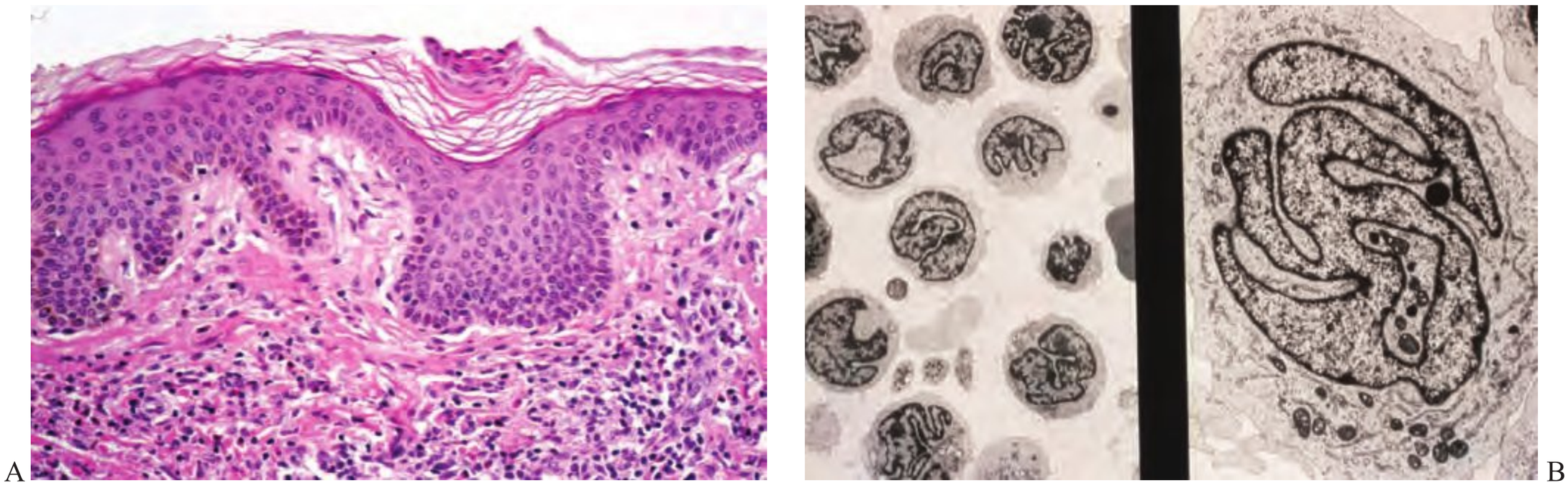


FIGURE 31-28. Sézary syndrome. A: There is a bandlike papillary dermal lymphoid infiltrate with minimal epidermotropism. B: Ultrastructural examination of peripheral blood buffy coat revealing numerous Sézary cells.

examine routine buffy coat preparations as well as flow cytometry of peripheral blood in establishing a diagnosis of Sézary syndrome. Immunohistochemistry to identify epidermotropism by predominantly to exclusively $CD4^+$ T cells, loss of CD7, and molecular analysis for TCR gene rearrangements are also important adjuncts to correct diagnosis. Although patients with advanced MF also may develop leukemic dissemination by malignant cerebriform T cells, the clinical course and presence of advanced plaques and nodules should separate these individuals from patients with true Sézary syndrome. Patients with ATLL have circulating atypical T cells. However, these tend to be polylobated rather than cerebriform, and cutaneous lesions are generally multiple nodules rather than diffuse erythroderma. Finally, detection of human T-cell lymphoma/leukemia virus-1 (HTLV-1) confirms the diagnosis.

Primary Cutaneous CD30-positive T-cell Lymphoproliferative Disorders

Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders is a category that refers to a spectrum of related, relatively low-grade disorders that primarily affect the skin and develop from an activated or transformed large T cell that expresses the CD30 antigen (142,278). Although these conditions may occur together in a given patient and show clinical, histologic, and antigenic overlap, the clinicopathologic features are sufficiently distinctive for considering them in the context of the following categories: (a) PC-ALCL, (b) LYP, and (c) borderline lesions.

Clinical Features. Skin lesions of PC-ALCL consist of one or more localized nodules or occasionally papules (13,278). Lesions must be differentiated by careful staging from systemic anaplastic large cell lymphoma (ALCL) with secondary skin involvement and from high-grade large cell lymphomas that may also express CD30, since these latter conditions have a considerably worse prognosis. Partial or complete regression of individual lesions may occur, although relapse is common (279). Eventual extracutaneous dissemination to lymph nodes occurs in about 10% of patients with primary skin involvement, particularly in individuals who have multiple primary lesions (276,278). Primary cutaneous anaplastic large cell lymphoma (PC-ALCL) is associated with a favorable prognosis with a 10-year survival >90% (278). LYP typically develops as multiple diffusely distributed "juicy" red papules and nodules that usually regress within one to several months (217,279) (Fig. 31-29). Lesions are generally <2.5 cm in diameter, and extracutaneous dissemination only occurs in a minority of cases (4%) that progress to overt lymphoma, such as MF, PC-ALCL, or HL (217). Although clinically typical cases of LYP can be easily distinguished from classical cases of PC-ALCL, a huge area of overlap exits, and these two entities are better understood as a continuum.



FIGURE 31-29. Primary $CD30^+$ lymphoproliferative disorders: lymphomatoid papulosis. Lesions clinically present as multiple "juicy" red papules and nodules.

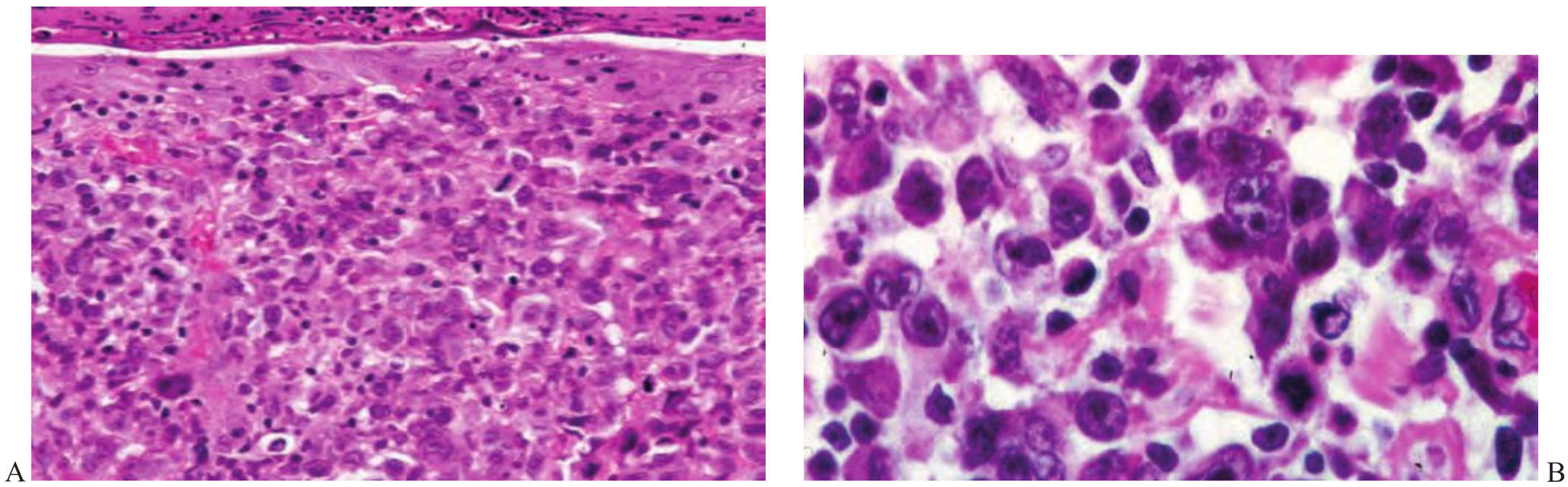


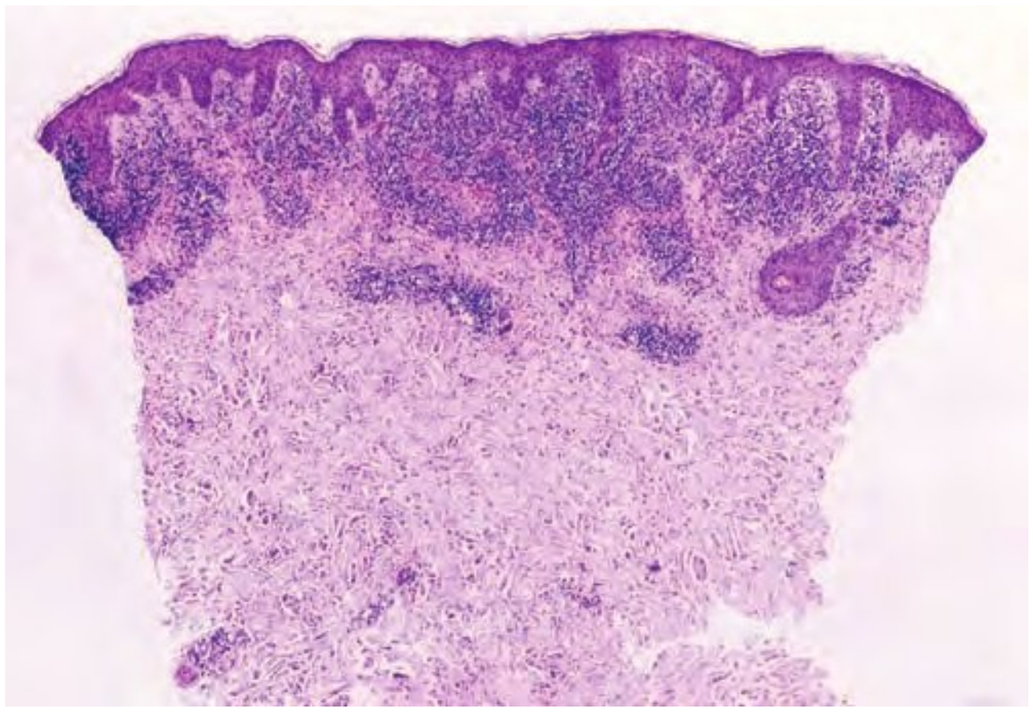
FIGURE 31-30. Histology of primary cutaneous anaplastic large cell lymphoma. A: Skin infiltrate composed of tumoral infiltrate of large atypical lymphocytes with associated incipient epidermal erosion. B: High magnification of the large anaplastic lymphocytes forming an infiltrate in PC-ALCL

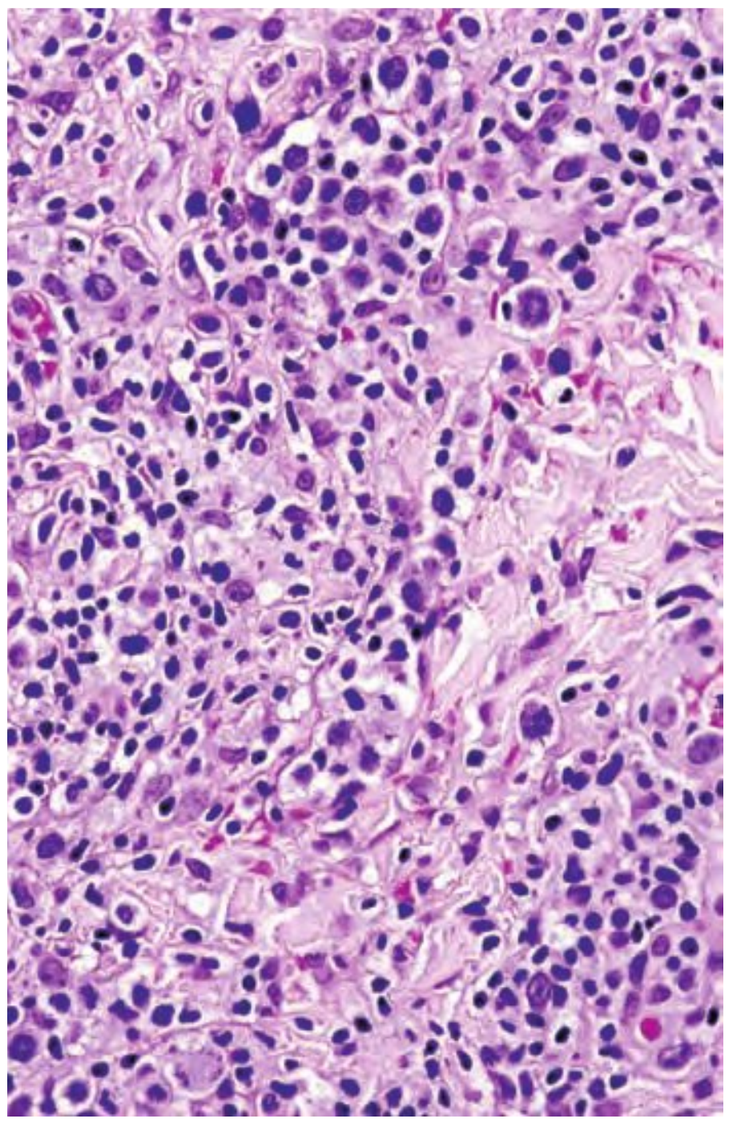
Histopathology. Nodules are formed by infiltrates that typically involve the superficial and deep dermis and occasionally the subcutis, in a diffuse, interstitial pattern (13) (Fig. 31-30A). Cytologically, biopsies of PC-ALCL may closely resemble those of systemic ALCL with secondary skin involvement (Fig. 31-30B), although Reed-Sternberg–like cells and highly pleomorphic, multinucleated giant cells may be more numerous in the former. The large atypical cells should account for the majority of cells composing the infiltrate, although a background of secondary inflammatory elements may be observed. Marked epidermal hyperplasia, sometimes with keratoacanthoma-like features; invasion by atypical cells; and ulceration are often present.

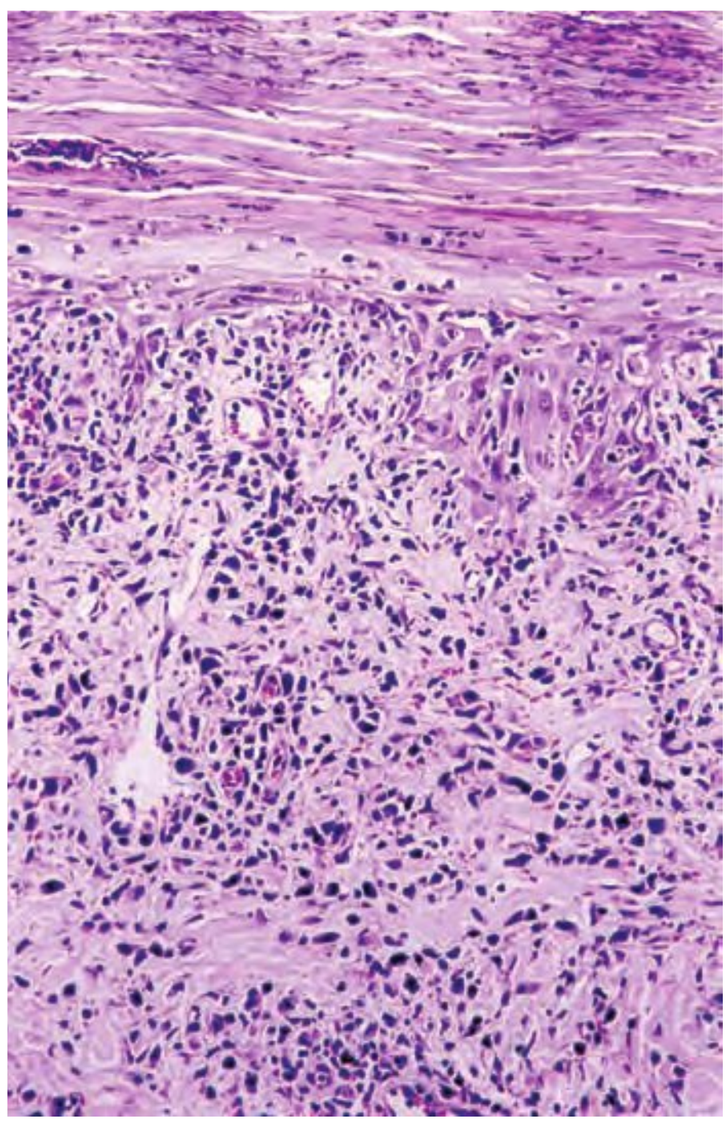
By contrast, the architecture of LYP tends to be more restricted, forming a wedge-shaped infiltrate extending from the superficial into the mid and deep dermis (Fig. 31-31A). This is composed of an admixture of various cell types, including variably activated lymphocytes, histiocytes, neutrophils, and eosinophils. However, an admixed minority population composed of atypical large lymphocytes is required for the diagnosis, and these may either resemble Reed-Sternberg–like cells (type-A LYP) or the cerebriform cells of MF (type-B LYP). In the latter, epidermotropism similar to that seen in patch/plaque-stage MF may be present. Occasional biopsies will show hybrid features between these two types of LYP. There is an angiocentric deposition of infiltrating atypical cells (Fig. 31-31B), often accompanied by vascular injury. Epidermal changes include hyperkeratosis, parakeratosis, and occasional foci of neutrophil infiltration and central erosion/shallow ulceration (Fig. 31-31C). In rare instances, clinical features of LYP may be present in the setting of histologic characteristics of PC-ALCL (predominance of large atypical cells), and these lesions are referred to as *borderline* or *type-C LYP*. Rarely, a solitary tumor more in keeping with PC-ALCL will show histopathology more like LYP (atypical cells in the minority), and such lesions have been termed *anaplastic lymphoma, LYP-like* (278).

Histogenesis. All forms of primary cutaneous $CD30^+$ T-cell lymphoproliferative disease are believed to be derived from an activated skin-homing T cell. In PC-ALCL, in addition to CD30 positivity by >75% of the cells forming the infiltrate (13,279), there is CD4 expression as well as frequent expression of cytotoxic granule proteins (granzyme B, perforin, TIA-1) (279,280). Aberrant T-cell phenotypes with loss of CD2, CD3, and/or CD5 may be observed. Importantly, unlike many cases of systemic $CD30^+$ lymphomas, most primary cutaneous lesions are negative for EMA (13) and rarely carry the t(2;5) translocation, hence negative for ALK-1. However, a positive ALK-1 does not necessarily imply a secondary cutaneous manifestation of extracutaneous ALCL (281). A similar immunophenotype is expressed by the minority population of large atypical cells in type-A LYP (Fig. 31-31D), although CD30 expression may not be detected in type B lesions, in which Reed-Sternberg–like cells are infrequent to absent. Most cases of PC-ALCL and about half of cases of LYP (predominantly the type A variant) show clonal rearrangements of the TCR.

Differential Diagnosis. The single most important consideration in the diagnosis of primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders is their differentiation from primary systemic lymphomas that may express CD30 and show a considerably worse prognosis. This may generally be accomplished by careful assessment of correlative clinical and histologic and immunohistochemical parameters (see above) as well as by meticulous clinical staging. Distinction of PC-ALCL from LYP is similarly possible by evaluation of clinical parameters and assessment of lesion architecture and


A


B


C

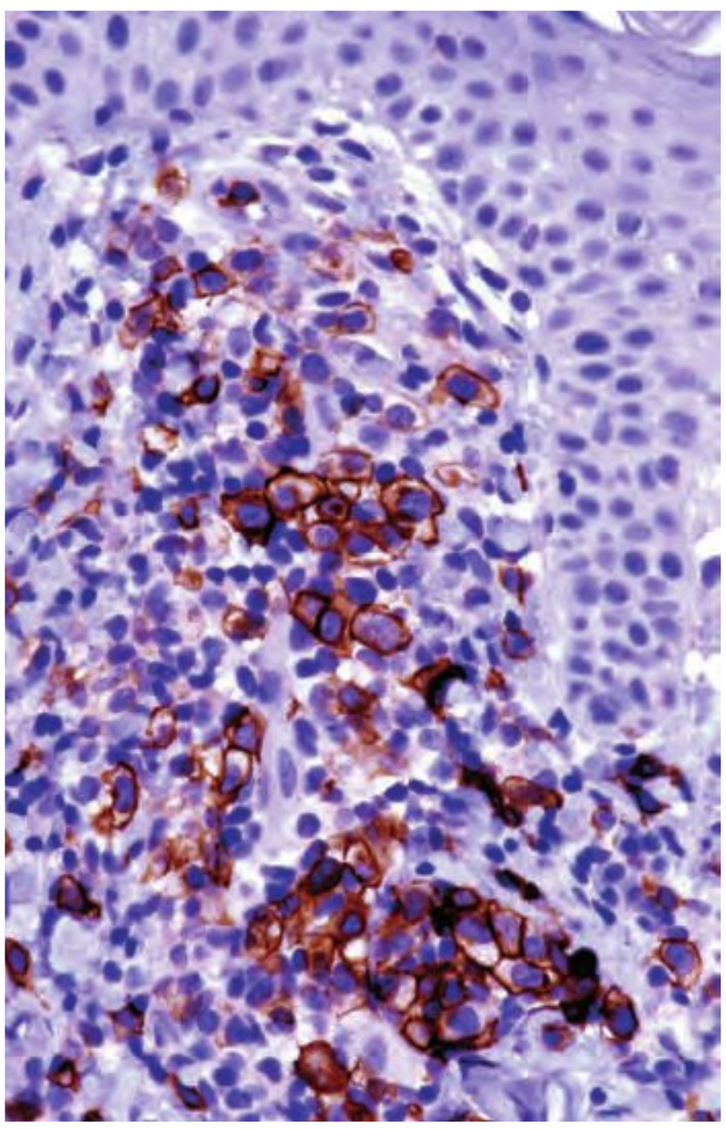

D

FIGURE 31-31. Histology of lymphomatoid papulosis. A: Low power of localized infiltrate in superficial and mid dermis, forming what will become a wedge-shaped angiocentric architecture. B: Variably atypical lymphoid cells in the dermis. C: Epidermal infiltration with associated scale abnormalities and neutrophil infiltration. D: CD30+ cells are numerous within the superficial dermal component of the infiltrate.

relative percentages of large atypical $CD30^+$ cells within the cutaneous infiltrates (>75%). In addition, CD30 positivity may be observed in tumor-stage MF, particularly in cases with large cell transformation (typically with a history of conventional patches and plaques of MF), and other reactive conditions, including arthropod bites, drug erruptions, and viral infection (e.g., herpes simplex virus 1 and 2) (282). Unlike HL, the Reed-Sternberg–like cells in PC-ALCL generally do not express CD15 (283).

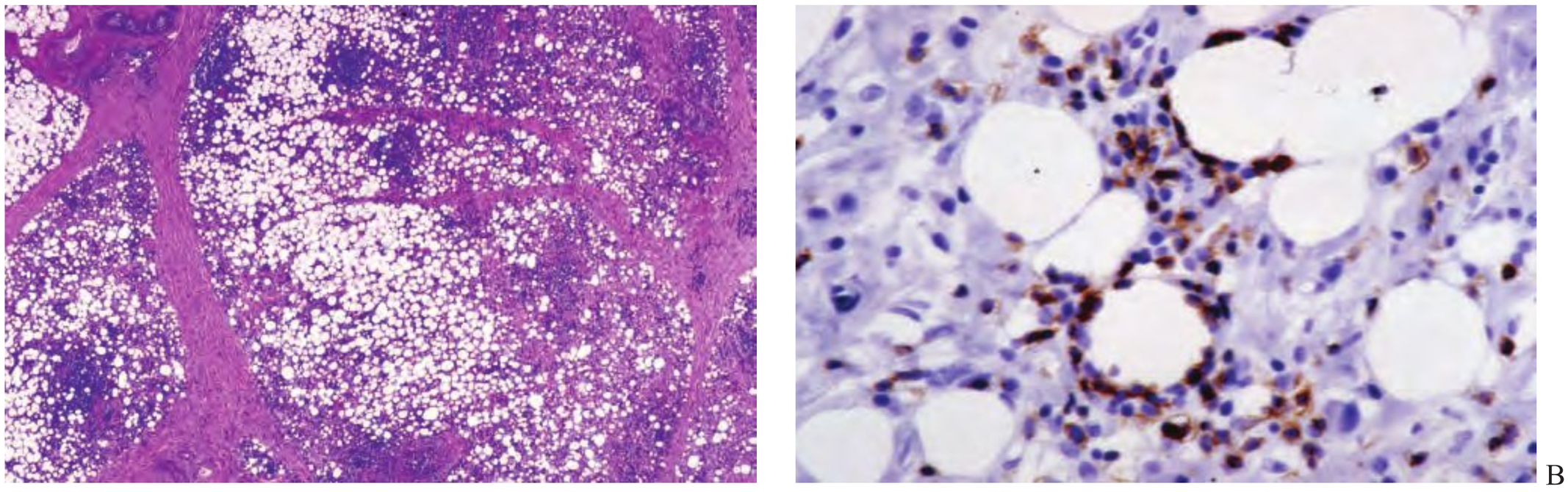


FIGURE 31-32. Subcutaneous panniculitis-like T-cell lymphoma. A: Lobular and septal pattern of subcutaneous infiltration. B: TIA-1 immunohistochemistry showing characteristic rimming about individual adipocytes.

Subcutaneous Panniculitis-like T-cell Lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is defined as a rare lymphoma that (a) primarily infiltrates subcutaneous tissue, (b) shows high-grade cytologic features, and (c) is composed of $CD8^+$, α/β^+ T cells with a cytotoxic phenotype.

Clinical Features. While the majority of cases occur in young adults, a broad age range has been reported, and the disease tends to show an equal gender distribution (284). Affected individuals generally present with symptoms related to formation of deeply seated and variably sized cutaneous nodules often involving the extremities and/or trunk. The disease has a protracted but indolent course with a 5-year survival of 82% (285). Rare systemic symptoms and signs of fever, fatigue, and weight loss, when present, may relate to hemophagocytic syndrome and a more rapidly progressive course (286).

Histopathology. There is a diffuse, variably cellular infiltrate involving both septae and lobules within the subcutis (Fig. 31-32A), with relative sparing of the overlying dermis. The infiltrate is composed of smaller lymphocytes with visible cytoplasm admixed with larger transformed cells with hyperchromatic nuclei. Initial biopsy in which the more atypical elements are not well represented may appear deceptively banal. Cells characteristically show peripheral alignment (rimming) about individual adipocytes (Fig. 31-32B). Fat necrosis, karyorrhexis, and associated infiltration of reactive histiocytes may also be noted. Necrosis, nuclear fragmentation, and vascular injury may all be observed. A hemophagocytic syndrome, which is associated with a rapidly progressing course, may occur but is much less common than in γ/δ^+ T-cell lymphoma with panniculitis-like lesions (286) (see page 950).

Histogenesis. The malignant cells express a mature $CD2^+$, $CD3^+$, $CD4^-$, $CD5^+$, $CD8^+$ T-cell phenotype. In keeping with their presumed derivation from a cytotoxic T cell, they also are reactive for the following proteins: granzyme, perforin, and T-cell intracellular antigen (TIA-1). TCR genes are rearranged, and EBV sequences cannot be demonstrated. In the WHO/EORTC classification, SPTCL is restricted for cases derived from α/β T cells, whereas those with a γ/δ T-cell phenotype are included in the category of cutaneous γ/δ T-cell lymphoma. The latter often exhibit both CD4 and CD8 negativity but reactivity for CD56 (287) and have a poor prognosis.

Differential Diagnosis. SPTCL should be differentiated from benign panniculitis, such as lupus erythematosus panniculitis. The presence of plasma cells and lymphoid follicles with germinal centers and the lack of clonality in TCR gene rearrangement studies favor the latter. *In situ* hybridization for EBV should be performed to rule out NK-/T-cell lymphoma, nasal type, which frequently exhibits subcutaneous involvement and is positive for EBV.

Extranodal Natural Killer–/T-cell Lymphoma, Nasal Type

Extranodal NK-/T-cell lymphoma, nasal type is characterized by angiocentric and angiodestructive infiltrates of malignant cells with NK- or cytotoxic T-cell phenotype that often but not invariably involve tissues of the nasal cavity (288–291). It has been known by numerous appellations, including pleomorphic reticulosis and lethal midline granuloma. Besides the nasal cavity, skin is the second most commonly affected site, and cutaneous involvement may be the primary manifestation of the disease. Regardless of whether the cutaneous involvement is primary or secondary, the disease runs an aggressive course and requires the same treatment (291–295).

Clinical Features. Extranodal NK-/T-cell lymphoma tends to more often affect adult males, with a geographical distribution showing concentration in Asia, Mexico, Central

America, and South America. Sites most often affected include the nasal cavity and nasopharynx, skin and soft tissues, gastrointestinal tract, and testis and has secondary lymph node involvement (296–304). Nasopharyngeal involvement is often associated with extensive destruction of soft tissue and bone, and rapid and widespread dissemination may occur. Skin may be either a site of secondary spread or a primary manifestation of the disease. Cutaneous nodules, often with ulceration, are most often encountered. Advanced disease is the rule at the time of presentation, and an associated hemophagocytic syndrome may also be noted (300,305), with fever, cachexia, and other systemic symptoms (291,298,299,306). In those advanced cases where marrow and peripheral blood involvement are encountered, there is overlap with aggressive NK-cell leukemia. As mentioned previously, although patients presenting with only skin lesions have a better prognosis than those with both cutaneous and extracutaneous disease (median survival of 27 months vs. 5 months), both groups exhibit a highly aggressive clinical behavior and require the same treatment (291–293, 307).

Histopathology. The characteristic histopathology involves a diffuse, focally angiocentric and angiodestructive dermal/subcutaneous infiltrate of variably sized, mitotically active lymphoid cells with moderate quantities of pale cytoplasm and nuclei with irregular and occasionally elongated profiles. Chromatin tends to be coarsely granular, and nucleoli are inconspicuous. Some cases will show an admixture of reactive inflammatory cells, including activated lymphocytes, plasma cells, and eosinophils. Infiltration and fibrinoid necrosis of affected vessel walls and zones of necrosis and apoptosis are characteristic findings (175). The epidermis or squamous epithelial mucosa may be ulcerated or in some instances may show florid pseudoepitheliomatous hyperplasia.

Histogenesis. In most instances, the cell of origin is believed to be an NK cell or a cytotoxic T cell. The typical immunophenotype is $CD2^+$, $CD56^+$, and surface $CD3^-$ (182,297, 308–310). Cytotoxic granule–associated proteins (TIA-1, granzyme B, perforin) are usually detected, and CD4, CD5, and CD8 are generally negative. Interestingly, TCR and immunoglobulin genes are in the germ line configuration in most cases of extranodal NK-/T-cell lymphoma, although a variety of cytogenetic abnormalities have been recorded. There is a strong association with EBV, suggesting a possible causal role for this agent (311–316). In rare $CD56^-$ cases, detection of EBV by *in situ* hybridization and expression of cytotoxic proteins are required for diagnosis (317).

Differential Diagnosis. The differential diagnosis includes other neoplastic lymphocytic infiltrates that are angiocentric and angiodestructive. LYG has historically been considered in the context of extranodal NK-/T-cell lymphoma, although the former is now recognized to represent a form of EBV-positive B-cell lymphoproliferative disorder that may contain numerous reactive T cells (310). Vasculitic variants of MF have been described, although these can be distinguished by the absence of cytotoxic markers that characterize most cases of extranodal NK-/T-cell lymphoma. One caveat is that tumor stage MF may acquire a cytotoxic phenotype. In such patients, clinical history of previous conventional MF lesions allows differentiation from extranodal NK-/T-cell lymphomas.

Primary Cutaneous Peripheral T-cell Lymphoma, Unspecified

Primary cutaneous peripheral T-cell lymphoma, unspecified (PC-PTCL-u) accounts for approximately 10% of all CTCL and is designated for all CTCLs that do not fit into any of the better defined subtypes of CTCL, including the three provisional entities described below (24). The majority of cases in this category were classified as primary cutaneous $CD30^-$ large T-cell lymphoma in the EORTC classification.

Clinical Features. Patients are middle-aged to elderly individuals (median age 68 years) with a male-to-female ratio of 2.5:1.0 (318). Lesions may present as solitary or localized but more frequently generalized nodules or tumors (318–320). The prognosis is generally poor, with a 5-year survival $<$20% (318–321).

Histopathology. Diffuse or nodular infiltrates with variable numbers of medium-sized to large pleomorphic or immunoblast-like T cells are typical. For the designation of PC-PTCL-u, the large cell component should constitute at least 30% of the neoplastic infiltrate (refer to differential diagnosis with the provisional entity, primary cutaneous $CD4^+$ small- to medium-sized pleomorphic T-cell lymphoma, next page, in which $<$30% admixed large cells can be seen). Epidermotropism is generally mild or absent.

Histogenesis. Most cases show an aberrant $CD4^+$ T-cell phenotype with variable loss of pan-T-cell markers, such as CD5 and CD7. CD30 staining is negative or restricted to few scattered tumor cells. Rare CD56 expression or cytotoxic proteins (granzyme B, TIA-1) may also be observed (318). TCR genes are rearranged, but cytogenetic alterations are largely uncharacterized.

Differential Diagnosis. Distinction from MF with large cell transformation relies on the lack of clinical history of MF.

Primary Cutaneous Aggressive CD8-positive T-cell Lymphoma (Provisional Entity)

This provisional entity primary cutaneous aggressive $CD8^+$ T-cell lymphoma is characterized by a proliferation of epidermotropic $CD8^+$ cytotoxic T cells and an aggressive clinical course (322,323), which includes cases of generalized pagetoid reticulosis (Ketron-Goodman disease). Cases of this provisional entity were grouped together with the PTCL-u category in the old WHO classification (317).

Clinical Features. Primary cutaneous aggressive $CD8^+$ T-cell lymphoma affects middle-aged to elderly patients with a median age of 53 years and a male-to-female ratio of 1.4:1.0 (322). Clinically, patients present with localized or disseminated eruptive papules, nodules, or tumors with central ulceration and necrosis or hyperkeratotic patches and plaques on the face or upper arms (291,322). Spreading to other visceral sites, such as the lung, testis, central nervous system, and oral mucosa, has been documented, but lymph nodes are often spared (322). The clinical course is aggressive, with rapid progression and a median survival <32 months (4).

Histopathology. Early lesions are characterized by epidermotropic atypical pleomorphic T lymphocytes ranging from small to medium size that are scattered throughout the epidermis in a pagetoid pattern. In fully developed lesions, the atypical lymphocytes may form bandlike or diffuse infiltrates with angiocentricity/angioinvasion as well. The epidermis may be acanthotic or atrophic with variable numbers of apoptotic keratinocytes and spongiosis. Occasionally, associated ulceration or blister formation may be observed. Adnexal and subcutaneous involvement is frequently present. The atypical lymphoid infiltrate may be accompanied by a variable number of reactive histiocytes and dendritic cells as well as rare eosinophils and plasma cells (322,324).

Histogenesis. The neoplastic cells display a $CD3^+$, $CD4^-$, $CD8^+$, $CD7^{-/+}$, $CD45RA^+$, granzyme B^+, perforin$^+$, TIA-1^+ phenotype, characteristic of cytotoxic T cells. With disease progression, the malignant clone may acquire CD7 or lose CD2 expression. A recent study showed association of the $CD2^-$, $CD7^+$ phenotype with a more aggressive course (323). TCR gene rearrangement studies are typically positive, and the lesion is absent for EBV (322).

Differential Diagnosis. Differentiation from other types of CTCLs expressing a $CD8^+$ cytotoxic T-cell phenotype, such as rare cases of MF, LYP, and PC-ALCL, is largely based on clinical presentation and disease course (322).

Primary Cutaneous CD4-positive Small-/Medium-sized Pleomorphic T-cell Lymphoma (Provisional Entity)

Primary cutaneous $CD4^+$ small-/medium-sized pleomorphic T-cell lymphoma is an entity that is defined as small- to medium-sized, $CD4^+$, pleomorphic CTCL without a history of classic patches and plaques of MF and a favorable clinical course (320). In the past, the majority of cases were diagnosed as idiopathic T-cell lymphomatoid hyperplasia.

Clinical Features. The median patient age is 69 years with a male-to-female ratio of 0.5:1.0 (318). The clinical lesions range from multiple reddish papules to solitary plaque/nodules, generally involving the upper half of the body without a history of patches or plaques to suggest MF (325–327). Despite that the entity is not very well characterized, patients seem to have a very good prognosis, with a disease-specific 5-year survival rate of up to 75% and an overall 5-year survival rate of 60% to 80% (328).

Histopathology. Typically, there is a dense diffuse or nodular infiltrate of predominantly small- to medium-sized pleomorphic T-cells with a tendency to involve the subcutis. Epidermotropism may be seen focally (4). The infiltrate may contain a small percentage (<30% by definition) of large pleomorphic cells (320) and admixed small reactive B cells or histiocytes, eosinophils, and plasma cells (328,329).

Histogenesis. The neoplastic cells are of helper T-cell phenotype and express CD3 and CD4 but not CD8, TIA-1, granzyme B, and CD30. Pan-T-cell markers are lost in some cases (325,330). TCR genes are rearranged, but no consistent cytogenetic abnormalities have been observed (24).

Differential Diagnosis. Differential diagnosis includes T-cell lymphoid hyperplasia, PC-PTCL-u, and MF. Demonstration of an aberrant T-cell phenotype and clonality are useful criteria to differentiate these from reactive T-cell lymphoid hyperplasia (331). PC-PTCL-u has a large cell morphology (with large cells representing at least 30% of total tumor cell population) (321,322) rather than the predominance of small- to medium-sized T-cells in primary cutaneous $CD4^+$ small-/medium-sized pleomorphic T-cell lymphoma, which may harbor a small percentage of admixed large cell component. Because morphologic and immunophenotypic distinction between primary cutaneous $CD4^+$ small-medium-sized pleomorphic T-cell lymphoma and MF can be difficult, by definition, the diagnosis of primary cutaneous $CD4^+$ small-/medium-sized pleomorphic T-cell lymphoma should only be entertained after exclusion of MF by clinical history.

Cutaneous γ/δ T-cell Lymphoma (Provisional Entity)

Cutaneous γ/δ T-cell lymphoma (CGD-TCL) was previously characterized as subcutaneous panniculitis-like T-cell lymphoma (SPTCL) with a γ/δ phenotype (13,317). The new WHO/EORTC classification defined this provisional entity as a cutaneous lymphoma originated from a clonal proliferation of mature, activated γ/δ T cells with a cytotoxic phenotype and with an aggressive clinical behavior.

Clinical Features. Young to middle-aged adults (median age of 49 years) are affected with a male-to-female ratio of 1.5:1.0. Typical lesions include disseminated scaly plaques and ulcerated nodules/tumors often on the extremities (291,332–334). Systemic involvement of mucosal and other extranodal sites is common, but the lymph nodes, spleen, or bone marrow are generally spared (292,335,336). A hemophagocytic syndrome with associated constitutional symptoms, such as fever, malaise, fatigue, chills, and weight loss, has been described in patients

with panniculitis-like lesions (286,337). The prognosis is disappointing even with systemic chemotherapy, with a median survival of 15 months (334,336). Patients with subcutaneous disease have a worse prognosis compared with those with epidermal or dermal infiltrates only (334).

Histopathology. The infiltrate may be epidermotropic, diffusely dermal, panniculitic, or combinations of the above patterns either in one biopsy or in different specimens (334,338). The cytomorphology is monomorphous, medium to large in size, with irregular nuclei, prominent nucleoli, and coarsely clumped chromatin. Angiocentricity and angiodestruction are common (339). Subcutaneous involvement may show rimming of adipocytes, similar to SPTCL. In cases associated with hemophagocytic syndrome, phagocytosis of blood cells by histiocytes are observed (336).

Histogenesis. The neoplastic cells display a $CD3^+$, $CD2^+$, $CD4^-$, $CD5^-$, $CD7^{+/-}$, $CD8^-$, and $CD56^+$ phenotype with strong expression of cytotoxic proteins such as TIA-1, granzyme B, and perforin (336,340,341). Consistent with the γ/δ T-cell lineage, the neoplastic cells are strongly positive for TCR γ/δ in frozen sections, and the TCR γ/δ genes are rearranged. Isochromosome 7q is the most common cytogenetic abnormality (336). EBV sequences cannot be demonstrated.

Differential Diagnosis. Differential diagnosis includes SPTCL and extranodal NK-/T-cell lymphoma. In the new WHO/EORTC classification, SPTCL is designated to tumors with an α/β phenotype, while CGD-TCL characterizes those with a γ/δ phenotype. In contrast to CGD-TCL, extranodal NK-/T-cell lymphoma is positive for EBV.

SECONDARY T-/NATURAL KILLER–CELL LYMPHOPROLIFERATIVE DISORDERS AFFECTING SKIN

Peripheral T-cell Lymphoma, Unspecified

PTCL-u corresponds to a relatively large group of predominantly nodal T-cell lymphomas that occur in Western countries and that frequently also show involvement of the bone marrow, liver, spleen, peripheral blood, and skin (13,342–344). The modifier "unspecified" emphasizes that most cases are clinicopathologically heterogeneous and thus do not fit well into better defined entities of T-cell neoplasia. In the skin, these lesions are separate from MF and Sézary syndrome, possessing distinctive histologic, antigenic, and genotypic attributes.

Clinical Features. The majority of cases involve adults without gender predilection, although reports exist of children being affected. Clinical presentation generally involves constitutional symptoms and lymphadenopathy. The lymphoepithelioid cell variant (see below) is a low-grade variant of peripheral T-cell lymphoma where systemic signs may include enlargement of cervical lymph nodes, hepatosplenomegaly, fever, and skin involvement in <10% of cases (345). Skin lesions may take the form of eczematous plaques or erythematous tumors; pruritis, peripheral eosinophilia, and hemophagocytic syndromes have also been described (217). The 5-year survival rate ranges from 30% to 35%, even with standard chemotherapy (346).

Histopathology. There are two variant forms of this entity: the *lymphoepithelioid cell variant* (previously referred to as *Lennert's lymphoma*) and the *T-zone variant*. The lymphoepithelioid variant is characterized by small lymphocytes with variable, often minimal, irregularities in nuclear contour, admixed with clusters of epithelioid histiocytes, eosinophils, plasma cells, and occasional Reed-Sternberg–like cells (347). These cells may infiltrate the dermis in a nodular or diffuse pattern, and the papillary dermis and epidermis may also be involved (348). The T-zone variant derives its name from its pattern of nodal involvement that primarily involves the interfollicular zones, with preservation of lymphoid follicles. Tumor cells are small to intermediate in size and often lack significant pleomorphism (Fig. 31-33). As with the lymphoepithelioid variant, reactive cells, including plasma cells, epithelioid histiocyte, eosinophils, and Reed-Sternberg–like cells, may also be noted. It is likely that definitive separation of these two variants will require evaluation of lymph node rather than skin involvement.

Histogenesis. The tumor is a malignancy of T cells, and the most common nodal immunophenotype is $CD4^+$, $CD30^{+/-}$, and $CD8^-$, with frequently aberrant T-cell antigenic profiles (e.g., loss of pan-T-cell differentiation markers) (349,350). Moreover, there tend to be clonal rearrangements of TCR genes (351), as documented by PCR analysis. While there is no consistent trend in karyotypic abnormalities, an association between trisomy 3 and the lymphoepithelioid variant (Lennert's lymphoma) has been reported (352).

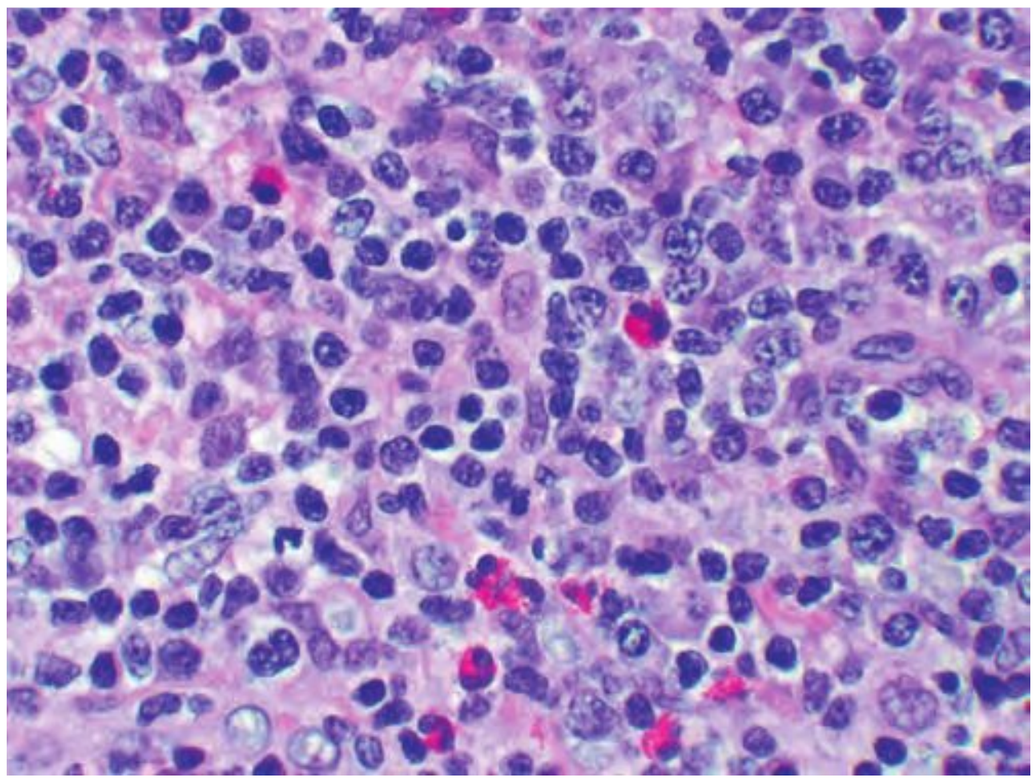


FIGURE 31-33. Peripheral T-cell lymphoma. Note relatively monomorphic lymphoid cells of intermediate size.

Differential Diagnosis. The lymphoepithelioid variant may occasionally mimic the granulomatous variant of MF, although the latter is characterized by clinical lesional evolution that involves initial formation of inconspicuous patches. Because lesions may be $CD30^+$, they should not be confused with ALCLs that differ cytologically. Whereas nodal cases also differ in that ALCLs often express cytotoxic granule associated proteins (287,353–357), it must be noted that extranodal involvement by peripheral T-cell lymphoma may also have a cytotoxic T-cell phenotype, including CD56 expression (296). EBV is generally absent on tumor cells but may be noted in the reactive components of lesions, in particular the Reed-Sternberg–like cells (358). Because these cells may be noted, along with a polymorphous reactive component, care must be taken not to mistake lesions as the rare event of cutaneous involvement by HL.

Angioimmunoblastic T-cell Lymphoma

Angioimmunoblastic T-cell lymphoma (AITL) accounts for approximately 15% to 20% of peripheral T-cell lymphomas.

Clinical Features. The disease typically affects middle-aged to elderly patients and presents with generalized lymphadenopathy and hepatosplenomegaly as well as constitutional symptoms such as high fever, night sweats, and weight loss (318,359–361). Laboratory findings typically show hemolytic anemia, leukocytosis, and polyclonal hypergammaglobulinemia. About 50% of patients develop cutaneous eruptions, most commonly macules and papules over the trunk and extremities. In rare cases, purpura, infiltrated or urticarial plaques, papulovesicular lesions, nodules, and erythroderma have been reported (362). AITL has an aggressive clinical course, with a median survival $<$3 years (317).

Histopathology. The involved lymph nodes show partial or complete architectural effacement with an interfollicular mixed polymorphous infiltrate of small- to medium-sized lymphocytes, plasma cells, eosinophils, epithelioid histiocytes, and immunoblasts as well as prominent arborizing high-endothelial venules (317,360, 361). The cutaneous lesions are generally subtle and vary considerably histologically. The most common features comprise a superficial perivascular infiltrate with or without atypical lymphocytes. Additional patterns documented include a dense superficial and deep perivascular atypical lymphoid infiltrate, leukocytoclastic vasculitis (362), and necrotizing granulomas (359).

Histogenesis. Immunohistochemical studies demonstrate a $CD3^+$ T-cell infiltrate with a predominance of $CD4^+$ over $CD8^+$ phenotype. TCR gene rearrangement of cutaneous lesions may display an identical clonal population to that detected in lymph nodes (361–363). EBV is positive in the majority of lymph nodes but rarely is detected in cutaneous lesions (362).

Differential Diagnosis. Because of the subtle and wide spectrum of histopathologic manifestations, the histologic differential diagnosis is broad and includes inflammatory dermatoses with superficial or superficial and deep perivascular patterns, leukocytoclastic vasculitis, infection, sarcoidosis, and other primary granulomatous conditions.

Anaplastic Large Cell Lymphoma

ALCL is a nodal T-cell malignancy that is characterized by homogeneous proliferation of large atypical lymphocytes that express the CD30 (Ki-1) antigen. It must be differentiated from PC-ALCL, which is a lesion with a considerably better prognosis.

Clinical Features. Of non-HLs, approximately 3% of adult lymphomas and 10% to 30% of lymphomas in children are accounted for by ALCL (364). Lesions may be further divided according to expression of ALCL kinase (ALK), with most positive cases affecting males in the second to third decades of life and most negative cases occurring in older individuals with relatively equal distribution according to gender. Of extranodal sites, the skin is involved in more than 20% of cases, followed by the bone, soft tissue, lung, and liver (364,365). Fever and adenopathy are common, with presentation in advanced stages of disease the rule.

Histopathology. Although a wide morphologic spectrum has been described (133,366–371), most cases share the presence of large anaplastic mononuclear cells containing abundant cytoplasm and an eccentric, reniform nucleus (370) (Fig. 31-34A, B). Occasional intranuclear cytoplasmic inclusions ("doughnut" cells) and multinucleated forms may be observed (372). The chromatin pattern is generally finely aggregated, and nucleoli are variably prominent and usually multiple. In addition to lesions where these cells predominate (the common variant), others may show these cells to be admixed with large numbers of histiocytes (lymphohistiocytic variant) or with cytologically similar, albeit smaller atypical lymphocytes (small cell variant). In general, however, the hallmark large anaplastic lymphocytes are recognizable cytologically and as a result of their tendency to aggregate about blood vessels. The dermal infiltrates tend to have a nodular architecture. The presence of epidermal hyperplasia tends to correlate with primary cutaneous ALCL rather than systemic ALCL.

Histogenesis. The presumed cell of origin for ALCL is a mature cytotoxic T cell. The majority of cases express T-cell antigens, and even those without T-cell antigen expression ("null cell" phenotype) have evidence of T-cell lineage at a genomic level (356). Pan-T-cell maturation markers (e.g., CD3, CD5, and CD7) are frequently negative, which is consistent with an aberrant T-cell phenotype. The majority of cases show strong CD30 reactivity on the cell membrane and in association with the Golgi zone (Fig. 31-34C). This reactivity is especially prominent on the hallmark large anaplastic cells and less pronounced on the smaller variant forms (241). ALK expression (see below) is present in 60% to

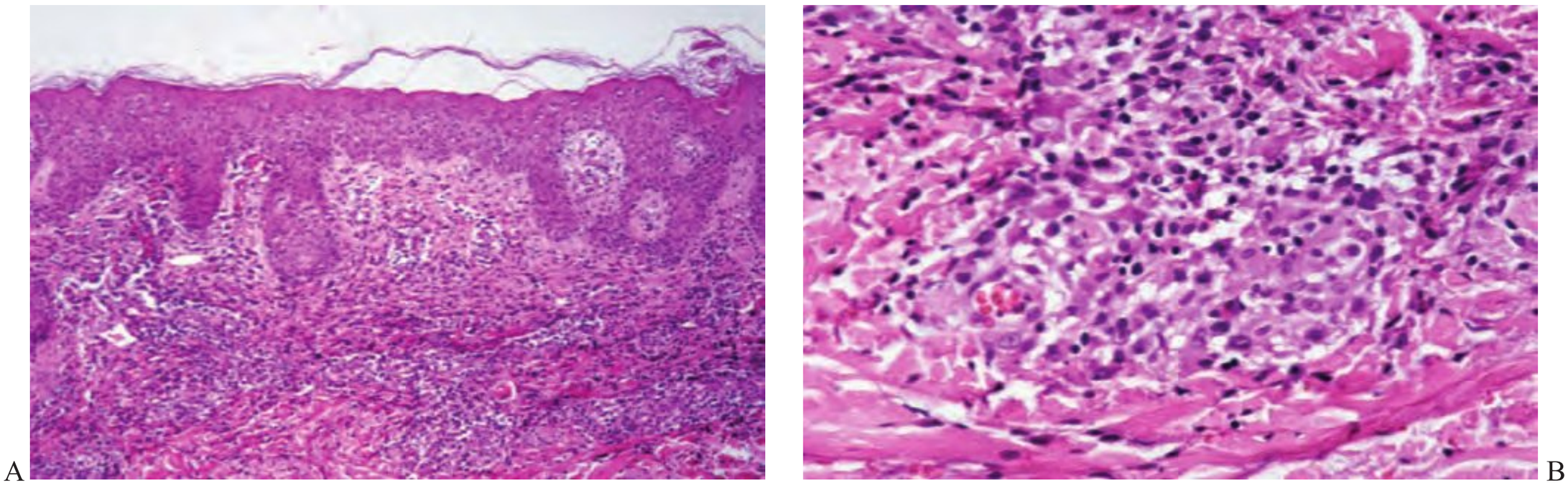


FIGURE 31-34. Anaplastic large cell lymphoma. Low (A) and higher (B) magnification showing dermal infiltrate by large anaplastic lymphoid cells. C: Immunohistochemistry for CD30.

80% of cases, and the majority of these are also positive for EMA (366,370). In addition, most cases show positivity for cytotoxic-associated markers, including TIA-1, granzyme B, and/or perforin (355,356). Tumor cells are consistently negative for EBV, although they may show perinuclear staining for lysosomal enzymes as well as reactivity with some probes that identify CD68, and accordingly, caution must be exercised in not assuming histiocytic lineage in such instances (372). The majority of cases demonstrate clonal rearrangements in the TCR irrespective of expression of T-cell markers.

Overexpression of the ALK protein is caused by alterations of the ALK gene at chromosome 2. Most commonly, t(2;5)(p23;35) is seen with the participation of the ALK gene on chromosome 2 and nucleophosmin (NPM) gene on chromosome 5. However, breakpoints on chromosomes other than 5 can partner with the ALK gene. Classic t(2;5) leads to ALK protein overexpression resulting in both cytoplasmic and nuclear stain with antibodies directed against this molecule. The ALK protein functions as a tyrosine kinase receptor, and its gene belongs to the insulin receptor superfamily. ALCL are invariably negative for EBV genomes, separating them from EBV+ classic types of HL.

Differential Diagnosis. The primary differential diagnostic considerations include HL, particularly when Reed-Sternberg–like cells are present. However, the immunophenotypic profile of ALCL is sufficiently distinctive to permit distinction of ALCL from the rare occurrence of HL with skin involvement. Systemic ALCL (discussed here) presents in the skin in advanced stages and therefore may be further differentiated from PC-ALCL and its regressing variants (e.g., LYP) based on clinical parameters and immunoreactivity to ALK-1 (discussed in greater detail previously under PC-ALCL).

Adult T-cell Leukemia/Lymphoma

ATLL is a peripheral high-grade lymphoid neoplasm caused by the human retrovirus HTLV-1.

Clinical Features. ATLL occurs most often as an endemic disorder, primarily in Japan, the Caribbean basin, and Central Africa, with the disease distribution mirrored by the prevalence of HTLV-1 infection (373). The disease is also detected in populations in certain parts of the southeastern United States where HTLV-1 seropositivity is high. The virus may be transmitted by blood and body fluids, including breast milk, and the disease is believed to have a long latency period before becoming overt. The median age is 55 years, with males slightly more affected than females (374). Widespread lymphadenopathy and peripheral blood involvement are present from the outset. The skin is the most common extralymphatic site of involvement, with lesions documented in more than half of the cases. *H*ypercalcemia, *o*steolytic bone

lesions, *T*-cell leukemia, and *s*kin lesions (HOTS) represents a clinical syndrome that along with lymphadenopathy represents a prototypical presentation for ATLL. Skin lesions generally take the form of multiple papules, plaques, and nodules that may be explosive in onset (Fig. 31-35A). Clinical course is variable, and acute (leukemia, rash, hypercalcemia), lymphomatous (lymphadenopathy without leukemia or hypercalcemia), and chronic/smoldering (skin lesions without leukemia or hypercalcemia) variants have been described. Cutaneous lesions may be seen in all variants. In general, individuals afflicted with the acute and lymphomatous types have a significantly worse prognosis (375). The 4-year survival rates are 5.0% for the acute type, 5.0% to 7.0% for the lymphomatous type, 26.9% for the chronic type, and 62.8% for the smoldering type (376).

Histopathology. Skin lesions may show nodular to diffuse infiltrates of atypical lymphocytes, with or without papillary dermal involvement or epidermotropism. Lesions thus are generally indistinguishable from MF in plaque to nodular stages of evolution (Fig. 31-35B). Cytologically, the neoplastic lymphocytes contain enlarged hyperchromatic nuclei with irregular, often convoluted nuclear profiles (Fig. 31-35C). Anaplastic cells with clumped nuclear chromatin and prominent nucleoli may also be observed (374,377). The peripheral blood contains atypical cells with characteristically hyperlobated nuclear profiles ("flower cells"), a feature that may serve to distinguish ATLL cells from those of Sézary syndrome and systemically disseminated forms of MF (Fig. 31-35D).

Histogenesis. Tumor cells are $CD4^+$ T cells that also express T-cell–associated antigens CD2, CD3, CD5, and CD25, but generally lack CD7 and CD8. As in all cases of T-cell lymphoma, rare cases that express CD8 but not CD4 or double-negative ($CD4^-/CD8^-$) cases may occur. Tumor cells may also express CD30 but unlike ALCL lack ALK, TIA-1, and granzyme B (378,379). TCR gene rearrangements are present (380). Interestingly, the $CD3^+/CD4^+$ neoplastic cells of ATLL may demonstrate suppressor, rather than helper/inducer, function *in vitro*. Clonally integrated HTLV-1 is present. The HTLV-1 transactivator, Tax, has been implicated as the viral oncoprotein (381).

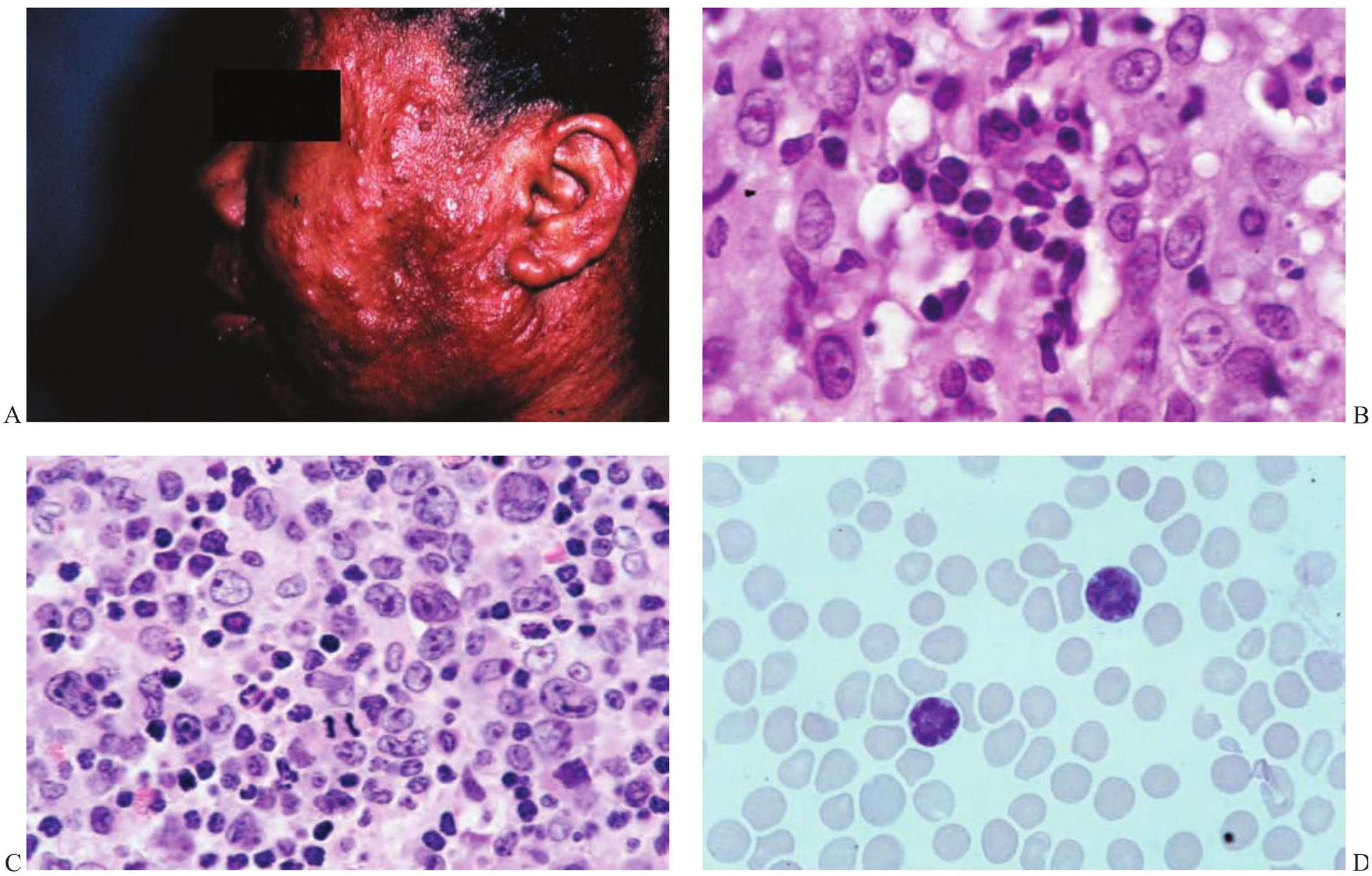


FIGURE 31-35. Adult T-cell leukemia/lymphoma. A: Clinical appearance, where multiple nodules explosively developed within several weeks in this patient with hypercalcemia. B: Epidermotropic atypical lymphocytes are indistinguishable by conventional paraffin histology from MF. C: Tissue infiltration by tumor cells with variably hyperchromatic and convoluted nuclear contours. D: Peripheral blood showing enlarged lymphoid cells with characteristically hyperlobated nuclear contours.

Differential Diagnosis. The differential diagnosis includes primarily MF and Sézary syndrome. The presence of patch-stage disease, both clinically and/or histologically, is of assistance in differentiating MF from ATLL. However, in more advanced lesions, distinction by histology alone may be impossible. Because most ATLL patients are not erythrodermic, this clinical feature may assist in differentiating this condition from Sézary syndrome. It should also be noted that the cytology of peripheral blood involvement in ATLL is distinctive, showing cells with hyperlobated, "flower-like" nuclear contours rather than the cerebriform nuclei of Sézary cells. In suspected cases of ATLL, HTLV-1 serology should be performed (382), although definitive diagnosis ultimately will depend on demonstration of HTLV-1 gene integration within the malignant cells in skin or blood by Southern blot analysis (383).

Precursor T-lymphoblastic Leukemia/Lymphoblastic Lymphoma

Precursor T-lymphoblastic leukemia (T-ALL)/lymphoblastic lymphoma (T-LBL) is a high-risk neoplasm that is derived from pre- and intrathymic T lymphocytes. The distinction between the designation of leukemia and lymphoma is somewhat arbitrary, with the former preferred when there is extensive marrow and blood involvement and the latter when there is a mass lesion at presentation and $<$25% lymphoblasts in the marrow and minimal peripheral blood involvement (384).

Clinical Features. The most typical presentation is that of a mediastinal mass in children and young adults. Involvement of bone marrow and peripheral blood is frequent. The lymph nodes, liver, spleen, Waldeyer ring, central nervous system, gonads, and skin may all be involved. Infiltration of the skin results in erythematous to hemorrhagic papules and nodules, with skin of the head and neck region preferentially involved (68). Whereas the leukemic counterpart tends to affect children, the lymphomatous phase is more often encountered in men (38).

Histopathology. As with other poorly differentiated T-cell infiltrates of skin, the dermis is preferentially involved by a diffuse interstitial infiltrate, with little or no epidermotropism. Cytologically, the tumor cells are uniformly atypical, with scant cytoplasm and nuclei characterized by slightly irregular, sometimes grooved contours and moderately condensed to evenly dispersed chromatin patterns with inconspicuous nucleoli (68,385) (Fig. 31-36A). Occasionally, eosinophils will be present within the dermal infiltrate.

Histogenesis. The cell of origin is believed to be a precursor T-lymphoblast. The tumor cells are TdT^+ and may express CD1a, CD2, CD3, CD4, CD5, CD7, and/or CD8 to variable degrees. Of these, reactivity for CD3 and CD7 are the most common (Fig. 31-36B, C). Lineage ambiguity of these primitive cells may occur, however, as evidenced by occasional expression of the B-cell marker CD79a or myeloid markers CD13 and/or CD33. Clonal rearrangements of the TCR are also commonly observed.

Differential Diagnosis. Skin involvement by T-ALL/T-LBL must be differentiated from B-cell lymphoblastic leukemia/lymphoma and acute myeloid leukemia, and this requires immunohistochemistry and/or histochemistry for lineage-associated antigens and enzymes. In children, extranodal involvement by Birkitt lymphoma, and in adults, by the blastoid variant of MCL, may enter into the differential diagnostic algorithm. Because lymphoblastic lymphoma is the only lymphoma that shows nuclear TdT positivity, these possibilities may be readily eliminated. Primary neuroendocrine carcinoma of the skin may occasionally be confused with T-ALL/T-LBL, especially when the former shows a diffuse interstitial pattern of dermal involvement. Again, immunohistochemistry will establish the hematopoietic and lineage characteristics of T-ALL/T-LBL in this setting.

T-cell Prolymphocytic Leukemia

T-cell prolymphocytic leukemia (T-PLL) is a relatively rare, aggressive form of T-cell leukemia composed of cells of mature, postthymic phenotype, that tend to involve the lymph nodes, liver, spleen, and skin (20% of cases) in addition to the blood and bone marrow (386).

Clinical Features. The vast majority of afflicted individuals are adults who present with generalized lymphadenopathy and enlargement of the spleen and liver. Anemia, thrombocytopenia, and atypical lymphocytosis are present; HTVL-1 serology is negative. Unlike Sézary syndrome, skin lesions are not erythrodermic but rather infiltrative. The leukemic infiltrates tend to form plaques and nodules that are variably erythematous to hemorrhagic in appearance.

Histopathology. Skin involvement takes the form of dense dermal infiltrates with a focal tendency for periadnexal localization. However, epidermotropism is not present (387,388). Peripheral blood in most cases contains numerous (often $>100 \times 10^3$/L) small- to intermediate-sized lymphoid cells characterized by basophilic cytoplasm and nuclei with irregular contours and detectable nucleoli. Occasional cases will show such prominent irregularities in nuclear contour that the cells may resemble Sézary cells (389), while others will show a predominance of small lymphocytes with inconspicuous nucleoli (small cell variant). Important common features, however, are the presence of cytoplasmic blebs from the plasma membranes and Golgi region staining for alpha-naphthyl acetate esterase (281). Bone marrow will contain these cells as well, although the characteristic diagnostic features may be more difficult to establish in this tissue.

Histogenesis. Cases show various combinations of CD4 and CD8 reactivity, with most expressing CD4 and showing clonal rearrangements of TCR gamma and beta chains. Strong CD7 staining and coexpression of CD4 and CD8 in 25% of patients along with weak reactivity for CD3 suggest that T-PLL may be differentiating toward a stage intermediate between a cortical thymocyte and a mature peripheral blood

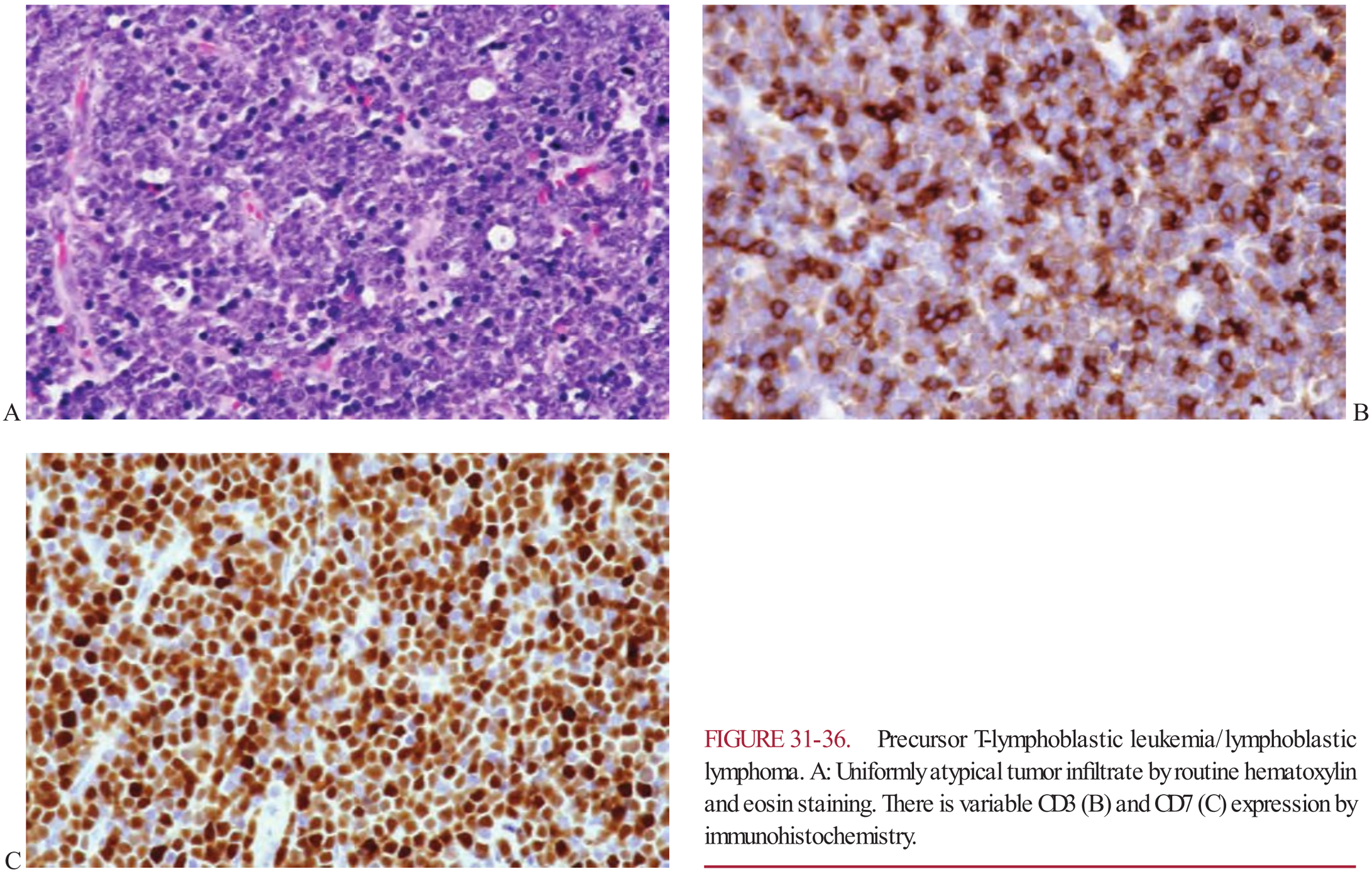


FIGURE 31-36. Precursor T-lymphoblastic leukemia/lymphoblastic lymphoma. A: Uniformly atypical tumor infiltrate by routine hematoxylin and eosin staining. There is variable CD3 (B) and CD7 (C) expression by immunohistochemistry.

T cell. Eighty percent of patients show inversion of chromosome 14 with breakpoints involving the long arm at q11 and q32 (390,391). Additional cytogenetic alterations, such as trisomy 8 and cMyc amplification have also been documented (388).

Differential Diagnosis. T-PLL must be differentiated from other forms of T-cell lymphoma showing skin involvement and a leukemic phase, such as Sézary syndrome, ATLL, T-CLL, and T-ALL. The clinical features at presentation, absence of epidermotropism, absence of HTLV-1 positivity, characteristic cytoplasmic blebbing in peripheral blood smears, and coexpression of CD4 and CD8 (a feature virtually unique to T-PLL) should all assist in differential diagnostic exclusion of this rare yet aggressive condition.

PRIMARY CUTANEOUS MYELOID HYPERPLASIA/NEOPLASIA

Extramedullary Hematopoiesis

Extramedullary hematopoiesis refers to abnormal trilineage maturation of hematopoietic elements in tissues other than the bone marrow. In the skin, the process has been referred to as *dermal hematopoiesis*. Occasionally, extramedullary hematopoiesis is restricted to cells of erythroid lineage, a phenomenon termed *dermal erythropoiesis*, which may occur in neonates in association with the stress of various viral infections or in adults with myelofibrosis.

Clinical Features. Lesions typically present as macules, papules, and occasionally nodules that have a dull blue-red hue. Dermal hematopoiesis in neonates tends to affect the head and neck (so-called "blueberry muffin baby"). In adults, cutaneous extramedullary hematopoiesis frequently involves the trunk and occasionally in surgical scars after splenectomy, a procedure that in itself appears to augment the phenomenon.

Histopathology. Poorly formed micronodules of pleomorphic cells are present in the dermis, and the pattern may initially mimic leukemia cutis or an unusual dermal inflammatory reaction. Maturing erythrocytes can be identified as clustered "colonies" of cells containing round basophilic nuclei rimmed by eosinophilic cytoplasm. Admixed myeloblasts, metamyelocytes, and characteristically large megakaryocytes containing prominently multilobated nuclei are often also present. These latter cells are reactive for CD61, a helpful marker in further confirming their lineage identity.

Histogenesis. Although normal hematopoiesis occurs in the bone marrow, the occurrence of extramedullary hematopoiesis in the skin and other tissues underscores the fact that under certain conditions, extramedullary tissues contain the appropriate precursor cells and growth factors to serve as surrogates for the marrow microenvironment.

Differential Diagnosis. Extramedullary hematopoiesis in the skin must be distinguished from reactive and dysplastic

polymorphous infiltrates that may contain large atypical cells (e.g., LYP containing large Reed-Sternberg–like cells) and from forms of leukemia cutis that harbor cells with primitive myeloid features. Clinical information may be helpful in determining whether patients have predisposing factors for this phenomenon. The morphologic identification of erythropoiesis and the presence of megakaryocytes, and further confirmation of the latter via immunohistochemistry for CD61, should assist in those rare circumstances when true extramedullary hematopoiesis is detected in the skin.

Myeloid Sarcoma

Myeloid sarcoma refers to a tumor formed by myeloblasts or immature myeloid cells that affects an extramedullary site, such as the skin. The mass, also referred to as a *extramedullary myeloid tumor, granulocytic sarcoma,* or *chloroma,* may precede (aleukemic leukemia) or present simultaneously with a systemic myeloproliferative disorder, including acute and chronic myeloid leukemias (see below) and myelodysplastic syndromes, or represent a relapse of disease previously in remission. Acute monoblastic leukemia giving rise to extramedullary myeloid tumor is referred to as *monoblastic sarcoma.*

Clinical Features. Lesions may be solitary or multiple and may show clinical features indistinguishable from secondary cutaneous involvement by acute and chronic myeloid leukemia (see below).

Histopathology. Most commonly, myeloid sarcoma is composed of an admixture of myeloblasts, neutrophil precursors, and mature neutrophils (granulocytic sarcoma). Less differentiated (blastic) variants are formed primarily by myeloblasts, whereas the immature and differentiated variants are composed primarily of myeloblasts and promyelocytes, or of promyelocytes and more mature forms, respectively. Rarely, myeloid sarcomas may be composed principally of monoblasts. In situations involving transformation of chronic myeloproliferative disease, trilineage hematopoiesis may also be observed.

Histogenesis. The postulated cell of origin is a myeloid hematopoietic cell. Tumor cells stain positively for myeloperoxidase, lysozyme, and chloroacetate esterase. The myeloblastic components may express CD13, CD33, and CD117, as also would be anticipated in acute myelogenous leukemia. Tumors with monoblastic differentiation may express CD14, CD116, and CD11c as well as lysozyme and CD68. CD43 also is expressed by the majority of myeloid sarcomas.

Differential Diagnosis. Tumors containing primarily blastic and immature elements must be differentiated from various non-HLs, poorly differentiated carcinoma, melanoma, and Langerhans cell histiocytosis. In general, in any poorly differentiated malignant skin infiltrate of confirmed hematopoietic lineage, myeloid differentiation should be considered and excluded by appropriate immunohistochemical panels. Distinction from extramedullary hematopoiesis can be achieved by the identification of megakaryocytes and normoblasts.

SECONDARY MYELOID NEOPLASMS AFFECTING SKIN

Acute and Chronic Myeloid Leukemia

Leukemia cutis is an important differential consideration in the assessment of atypical hematopoietic/lymphoproliferative infiltrates of the skin. Some lymphomas may occur along a continuum with leukemic phases, and thus certain forms of leukemia have already been discussed under T- and B-cell lymphoid neoplasms. Because circulating leukemic cells may always potentially deposit in the skin, there is a wide range of disorders that come into consideration in this section. The WHO classification, for example, considers acute myeloid leukemias according to categories that relate to the presence of recurrent genetic abnormalities, association with multilineage dysplasia, and those that are of ambiguous lineage or not otherwise categorized. Chronic myeloproliferative conditions are also classed into multiple groups, as is exemplified by chronic myelogenous, neutrophilic, and eosinophilic leukemias and polycythemia vera, to name a few. Because the nuances of these classification schemes rely heavily on morphologic, immunophenotypic, and genotypic findings in the bone marrow, a detailed discussion is beyond the scope of this section, which will focus on common features of neoplastic myeloid infiltrates of skin and how to recognize them.

Clinical Features. Clinical symptoms and signs are often related to marrow replacement by malignant cells and thus tend to relate to anemia, thrombocytopenia, and alteration in normal leukocyte function (infection). Peripheral blood generally shows leukocytosis as a result of involvement by malignant cells, although occasionally, these may not be detectable despite massive marrow involvement. In such situations, involvement of solid tissues, such as skin, may be the initial presenting feature of leukemia in evolution. Chronic leukemias are more indolent neoplasms that are composed of more mature myeloid cells that slowly replace the marrow compartment and seed the blood. Acute leukemias are more aggressive neoplasms that are composed of less mature myeloid cells and that more rapidly and completely replace normal hematopoietic marrow and seed the blood. Cutaneous infiltrates may present as red to purpuric patches, plaques, papules, or nodules, with or without ulceration (392) (Fig. 31-37). Mucosae may also be affected. There exist, in addition, numerous paraneoplastic findings that may be associated with leukemia, including gingival hyperplasia, vasculitis, Sweet's and pyoderma neutrophilic dermatitis, urticaria, erythema multiforme, and erythema nodosum, to name a few.



FIGURE 31-37. Acute myeloid leukemia. Multiple erythematous to hemorrhagic plaques and nodules are observed.

Histopathology. Myeloid leukemias may recapitulate various forms of myeloid lineage, and accordingly, these neoplasms may be described as showing myeloid, myelomonocytic, monocytic, and megakaryocytic differentiation. Acute myeloid leukemia may be divided into M0 to M7 subtypes according to differentiation patterns described in Table 31-8.

Architecturally, early acute myelogenous leukemia cutis may produce an angiocentric infiltrate, although interstitial permeation among collagen bundles within the reticular dermis soon supervenes (Fig. 31-38A). Vague nodules may form as the dermis becomes progressively expanded by malignant cells, which express myeloperoxidase (Fig. 31-38B). Malignant myeloid cells forming the dominant cell type of acute myeloid leukemia cutis tend to appear monotonous and homogeneous cytologically (Fig. 31-38C). Nuclei are round to oval, chromatin may be evenly dispersed, and nucleoli are multiple but potentially inconspicuous. On rare occasion, immature eosinophils containing typical cytoplasmic granules in the absence of bilobed nuclear contours may be helpful in assigning a presumptive diagnosis (Fig. 31-38D). However, histochemistry and immunohistochemistry are generally required for confirmation as well as examination of the peripheral blood and bone marrow (Fig. 31-38E).

It is noteworthy that myeloid leukemia cutis may mimic an angiocentric inflammatory infiltrate architecturally, and cytologically immature myeloid cells, although homogeneous, may not appear overtly anaplastic. Accordingly, it is appropriate to consider the differential possibility of acute myeloid leukemia cutis in the initial histologic evaluation of any atypical or malignant nonepidermotropic lymphoid infiltrate of presumed lymphoid origin (Fig. 31-38E). In cutaneous infiltrates with similar architectural features but containing mature myeloid elements, in addition to myeloblasts, the less common possibility of chronic myeloid leukemia cutis should be considered.

Histogenesis. Both acute and chronic forms of myeloid leukemia are derived from myeloid progenitors in the bone marrow. As such, cells are histochemically positive for myeloperoxidase (Fig. 31-38B), Sudan black B, chloroacetate esterase, and Leder stains. Myeloid cells do not express B-lineage (CD19, CD20, CD22, CD19a) or T-lineage (CD2, CD3, CD5, CD7) markers but may show immunohistochemical staining for the myeloid markers CD13, CD33, CD15, CD117 or megakaryoblastic antigens C41 and CD61.

Differential Diagnosis. In addition to possible confusion with T- and B-cell leukemia/lymphoma cutis, acute myeloid leukemia cutis must be differentiated from other interstitial dermal infiltrates dominated by monotonous populations of mononuclear cells. Mastocytosis may produce an interstitial pattern, and mast cells may react positively with the Leder stain but not with more specific markers for myeloid differentiation (e.g., myeloperoxidase). Myeloblasts, along with more mature myeloid elements, may occur in skin involved by chronic myelogenous leukemia as well as by extramedullary hematopoiesis. However, in the latter, maturing cells of erythrocyte and megakaryocytic differentiation are generally detectable.

TABLE 31-8 World Health Organization Classification of Acute Myeloid Leukemias

Acute myeloid leukemia with recurrent genetic abnormalities
- Acute myeloid leukemia with t(8;21)(q22;q22);(AML1/ETO)
- Acute myeloid leukemia with abnormal bone marrow eosinophils inv(16)(P13q22) or t(16;16)(p13;q22);(CBFβ/MYH11)
- Acute promyelocytic leukemia (AML with t(15;17)(q22;q12)(PML/RARα) and variants) (M3)
- Acute myeloid leukemia with 11q23 (MLL) abnormalities

Acute myeloid leukemia with multilineage dysplasia
- Following a myelodysplastic syndrome or myelodysplastic syndrome/myeloproliferative disorder
- Without antecedent myelodysplastic syndrome

Acute myeloid leukemia and myelodysplastic syndromes, therapy related
- Alkylating agent related
- Topoisomerase type II inhibitor related (some may be lymphoid)
- Other types

Acute myeloid leukemia not otherwise categorized
- Acute myeloid leukemia minimally differentiated (M0)
- Acute myeloid leukemia without maturation (M1)
- Acute myeloid leukemia with maturation (M2)
- Acute myelomonocytic leukemia (M4)
- Acute monoblastic and monocytic leukemia (M5)
- Acute erythroid leukemia (M6)
- Acute megakaryoblastic leukemia (M7)
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

Myeloid sarcoma

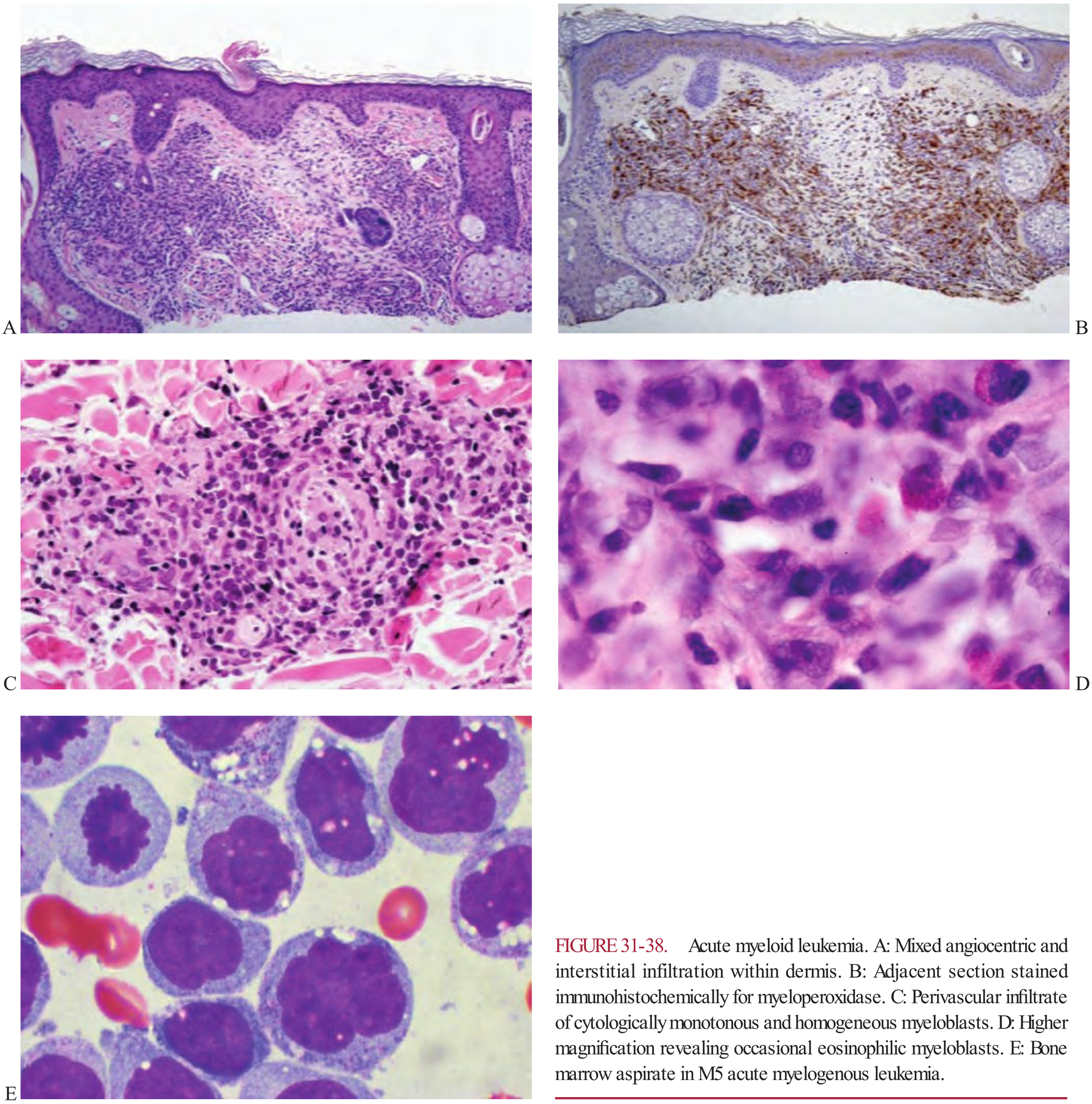


FIGURE 31-38. Acute myeloid leukemia. A: Mixed angiocentric and interstitial infiltration within dermis. B: Adjacent section stained immunohistochemically for myeloperoxidase. C: Perivascular infiltrate of cytologically monotonous and homogeneous myeloblasts. D: Higher magnification revealing occasional eosinophilic myeloblasts. E: Bone marrow aspirate in M5 acute myelogenous leukemia.

Precursor Plasmacytoid Dendritic Cell Lineage

CD4 and CD56-positive Hematodermic Neoplasm (Blastic Natural Killer–cell Lymphoma)/Plasmacytoid Dentritic Cell Leukemia/Lymphoma

$CD4^+/CD56^+$ hematodermic neoplasm/plasmacytoid dentritic cell leukemia/lymphoma is a controversial entity that was previously termed *blastic NK-cell lymphoma*, since the oncogenic origin was thought to be NK-cell precursors. More recent studies, however, have suggested a lineage derivation from a plasmacytoid (type 2) dendritic cell precursor (393). The neoplastic cells characteristically coexpress CD4 and CD56 without B-, T-, and NK-cell or myeloid lineage-specific markers. The new WHO/EORTC consensus classifies this entity as $CD4^+/CD56^+$ hematodermic neoplasm or "early" plasmacytoid dendritic cell leukemia/lymphoma (pDCL) if systemic disease is present at presentation. The condition is rare, representing $<$1.0% of acute leukemia (393) and 0.7% of cutaneous lymphomas (394).

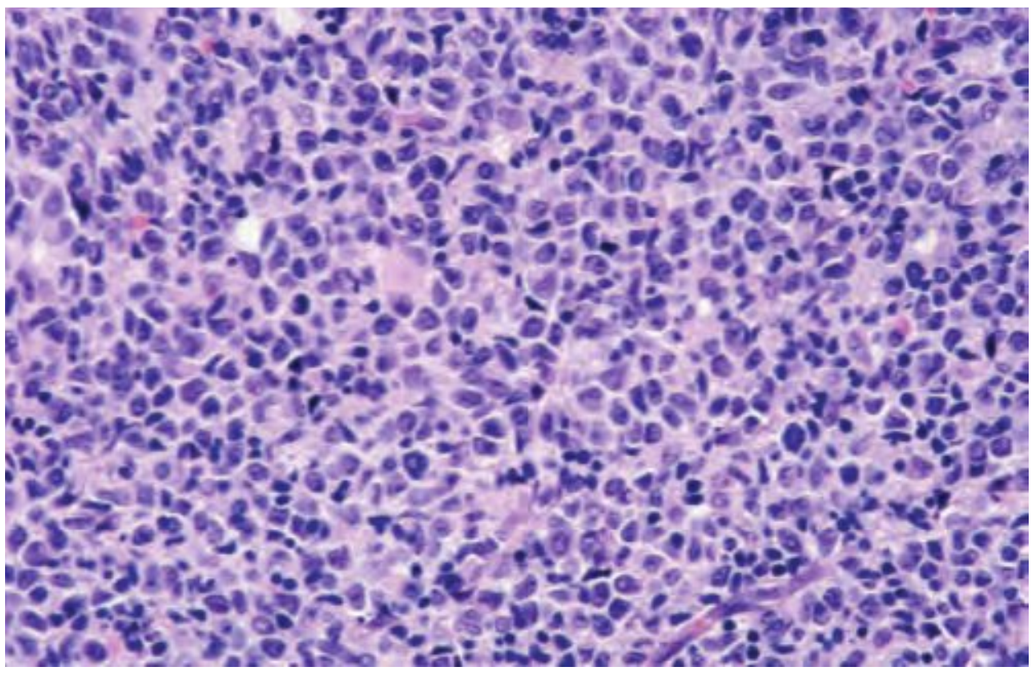


FIGURE 31-39. CD4/CD56 hematodermic neoplasm (blastic NK-cell lymphoma). The dermis is replaced by a monotonous infiltrate of intermediate-sized mononuclear cells with some morphologic overlap with myeloblasts.

Clinical Features. This lymphoma tends to affect middle-aged and elderly individuals, who at time of presentation demonstrate an isolated skin lesion that rapidly evolves to multiple sites and often with soft tissue, lymph node, bone marrow, and/or peripheral blood involvement (395). Skin involvement occurs in 87% of cases and may take the form of localized plum-colored, contusiform plaques or tumors covered by a glistening, attenuated epidermal layer. Oral mucosal lesions are common. The clinical course is aggressive, with a median survival of approximately 14 months.

Histopathology. The dermis is diffusely infiltrated by a monotonous population of intermediate-sized lymphoid cells with round or pleomorphic nuclei and a clumpy chromatin pattern that may suggest lymphoblastic or myeloblastic leukemia (Fig. 31-39; also see below). There is sparing of the epidermis and an absence of zonal necrosis or angiocentric infiltration, as may occur with extranodal NK-/T-cell lymphoma of the nasal type. On rare occasion, tumor cells may aggregate to form rosette-like structures resembling Homer-Wright rosettes (396). Azurophilic cytoplasmic granules are variably detected by Giemsa staining (397). Extravasation of erythrocytes is common, corresponding to the plum-colored bruise-like lesions clinically.

Histogenesis. Although a precursor NK-cell origin has been postulated previously, evidence now suggests that the malignant clone arises from plasmacytoid dendritic cells (pDC). The neoplastic cells tend to be $CD3^-$, $CD4^+$, $CD56^+$, TdT^+ (focal), $CD123^+$, and $TCL1^+$ (398). This disease entity is immunophenotypically somewhat ill defined, and the diagnosis should be made only in the absence of myeloid (such as myeloperoxidase, lysozyme, CD13, and CD15) and T-lineage markers other than CD4 (including TIA-1), particularly in light of the fact that both AML and T-ALL can express CD56. Distinct from NK-cell malignancies, EBV is invariably absent (1). Because of the dendritic cell lineage of the neoplastic cells, there is no clonal rearrangement of TCR genes.

Differential Diagnosis. Because of potential confusion with myeloblastic and precursor T-lymphoblastic lymphoma/leukemia, the diagnosis of $CD4^+/CD56^+$ hematodermic neoplasm is best made when neoplastic cells are negative for CD3, myeloperoxidase, and CD33 and preferably also when they fail to demonstrate TCR gene rearrangements.

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CHAPTER 32

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Tumors of Fibrous Tissue Involving the Skin

CLASSIFICATION OF FIBROUS TISSUE AND RELATED TUMORS BY CLINICAL BEHAVIOR

The main importance of correctly identifying and classifying fibrohistiocytic and soft tissue tumors lies in being able to predict their biological potential and hence appropriate treatment. Changes in our understanding of these entities have given rise to a system of classification based on expected clinical behavior (1,2). The principles of this system are used in this chapter and summarized in Table 32-1, although some lesions do not fall neatly into these recognized categories.

Although many of the tumors described in this chapter can be diagnosed on the basis of histologic features on hematoxylin-eosin–stained sections, immunohistochemistry is essential at times (Table 32-2). This should be used as an adjunct to standard histologic methods and clinical data. Additional techniques such as cytogenetics and electron microscopy can also be of value in categorizing some tumors. The possibility that a malignant lesion represents a metastasis must always be considered.

SO-CALLED FIBROHISTIOCYTIC TUMORS

Benign

Dermatofibroma (Fibrous Histiocytoma/Sclerosing Hemangioma)

Dermatofibromas (fibrous histiocytomas) are common skin tumors predominantly occurring on the extremities or trunk of young adults. They present as small, firm, solitary nodules that are red to brown in color, often due to increased intraepidermal melanin or tumoral hemosiderin. This may suggest a melanocytic lesion clinically. Dermatofibromas are seen only rarely on the palms and soles (3) and are relatively uncommon on the face, where they are more likely to recur (4). Multiple tumors have been reported associated with immunosuppressive therapy (5), pregnancy (6), HIV infection (7), and after antiretroviral therapy (8). Although most lesions are usually only a few millimeters in diameter, they occasionally measure 2 to 3 cm. The cut surface is white to yellow or brown, depending on the proportions of fibrous tissue, lipid, and hemosiderin present (Fig. 32-1A). Dermatofibromas usually persist, although spontaneous involution has been observed (9).

Histopathology. The epidermis is usually hyperplastic, with hyperpigmentation of the basal layer and elongation of the rete ridges, separated by a clear (Grenz) zone from the tumor in the dermis (Fig. 32-1B). This is composed of fibroblast-like spindle cells, histiocytes, and blood vessels in varying proportions (Fig. 32-1C–E). Foamy histiocytes and multinucleate giant cells containing lipid or hemosiderin are frequently present, sometimes in large numbers, forming xanthomatous aggregates. Prominent lipid accumulation is seen in the lipidized ("ankle type") dermatofibroma. Capillaries may be plentiful in the stroma, giving the lesion an angiomatous component. When there is also associated sclerosis, such lesions have been referred to as "sclerosing hemangioma." Some dermatofibromas may be poorly cellular and subtle, with spindle cells extending between collagen bundles associated with apparent "rounding up" of collagen fibers. More cellular forms often exhibit a storiform pattern of interwoven, fascicled spindle cells. Tumors are typically poorly demarcated.

Significant hyperplasia of the overlying epidermis occurs in more than 80% of dermatofibromas (10) and assists in making the diagnosis and distinguishing the atypical variant from atypical fibroxanthoma (11). Hyperplasia usually consists of regular rete ridge elongation, often with hyperpigmentation of the basal epidermis. In some cases the changes resemble a seborrheic keratosis, and, occasionally, downgrowths show hair matrical differentiation (12). In up to 5% of dermatofibromas the downgrowths show areas that closely resemble superficial basal cell carcinoma (13). In rare instances, genuine invasive basal cell carcinoma development has been documented (14,15).

Dermatofibroma Variants

Cellular Fibrous Histiocytoma

This is a rare, densely cellular variant with a fascicular to storiform growth pattern and frequent extension into subcutis (Fig. 32-2A, B). The tumors occur on the head and neck or trunk and may mimic dermatofibrosarcoma protuberans (DFSP) histologically. Identification of areas of more typical dermatofibroma assists in making this differentiation (16,17). Paradoxically, cellular atypia is often more pronounced in these tumors than in DFSP, and factor XIIIa staining is often negative (16). Areas of CD34 positivity may be present, but only focally at the edge of the tumor. There is an increased risk of recurrence, with rare metastases to regional nodes and the lung reported (16–19).

TABLE 32-1 Classification of Soft Tissue Tumors by Clinical Behavior

Benign

Benign behavior is the rule, but in exceptional circumstances tumors in this category may metastasize (e.g., fibrous histiocytoma, diffuse giant cell tumor of tendon sheath)

Intermediate biological potential

1. Locally aggressive

Recurrence may occur with tissue infiltration and destruction, but metastases are not expected (e.g., abdominal desmoid tumor)

2. Rarely metastasizing

A small proportion (<2%) of cases may metastasize, and these cannot be reliably predicted from histologic examination (e.g., plexiform fibrohistiocytic tumor, angiomatoid fibrous histiocytoma)

Malignant

Malignant behavior is to be anticipated

Adapted from Fletcher CDM. The evolving classification of soft tissue tumours: an update based on the new WHO classification. Histopathology 2006;48:3–12; and Fletcher CDM, Rydholm A, Singer S, et al. Soft tissue tumours: epidemiology, clinical features, histopathological typing and grading. In: Fletcher CDM, Unnik K, Mertens F, eds. World Health Organisation classification of tumours. Pathology and genetics of tumours of soft tissue and bone. Lyons: IARC Press, 2002:9–18.

Aneurysmal Fibrous Histiocytoma

In these tumors, collections of capillaries, foci of hemorrhage, siderophages, and foamy macrophages surround cleft-like and cavernous blood-filled spaces in the center of the tumor. The changes may simulate a vascular neoplasm, but other areas show more typical features of dermatofibroma (20,21) (Fig. 32-3). To avoid confusion with angiomatoid fibrous histiocytoma (a tumor of intermediate malignancy; see later discussion), it has been suggested that these tumors should be referred to as "dermatofibroma with aneurysmal change" (22).

Atypical Fibrous Histiocytoma

Atypical cells are occasionally present in dermatofibroma, which may lead to misdiagnosis as atypical fibroxanthoma (11,23), and there is some overlap with cellular fibrous histiocytoma histologically. These tumors are usually small but occasionally reach 2.5 cm or greater in diameter (24). The atypical cells show enlarged, pleomorphic nuclei, sometimes referred to as *monster cells* (24,25). Mitoses of normal morphology may be evident. Multinucleated giant cells with bizarre, large, hyperchromatic nuclei with little cytoplasm or irregular, vesicular nuclei with abundant foamy cytoplasm may also occur (Fig. 32-4A, B)(11). Extension into superficial subcutis and focal necrosis may be seen. The presence of more typical appearing dermatofibroma in the background is very helpful to enable the correct diagnosis in these lesions (26). Variable staining for smooth muscle actin and CD34 are reported, with no staining for factor XIIIa. Atypical fibrous histiocytomas may recur with very occasional metastases (26).

Epithelioid Fibrous Histiocytoma

This distinctive variant, originally described as epithelioid cell histiocytoma (27), is composed of cells showing abundant eosinophilic cytoplasm, with occasional multinucleated forms. Areas of spindle cell forms may also be present with a complement of foamy macrophages. Tumors form an exophytic nodule with an epidermal collarette resembling pyogenic granuloma or

TABLE 32-2 Selected Immunohistochemical Stains as an Aid to the Diagnosis of Spindle Cell Tumors of the Skin

	Atypical Fibroxanthoma	Dermatofibrosarcoma protuberans	Cellular Fibrous Histiocytoma (Dermatofibroma)	Spindle Cell Squamous Cell Carcinoma	Desmoplastic Melanoma	Leiomyosarcoma
S100	−	−	−	−	+	R
Desmin	−	−	−	−	−	+
CD34	V	+	V	−	−	R
Factor XIIIa	V	R	+	−	−	−
Cytokeratin	−	−	−	+	−	V
Epithelial Membrane Antigen	−	−	−	V	−	−
Smooth Muscle Actin	V	V	V	R	V	+

Note: Immunohistochemistry should be used as an adjunct to routine histologic methods and clinical data.
R, rarely positive; V, variable; −, negative; +, positive.

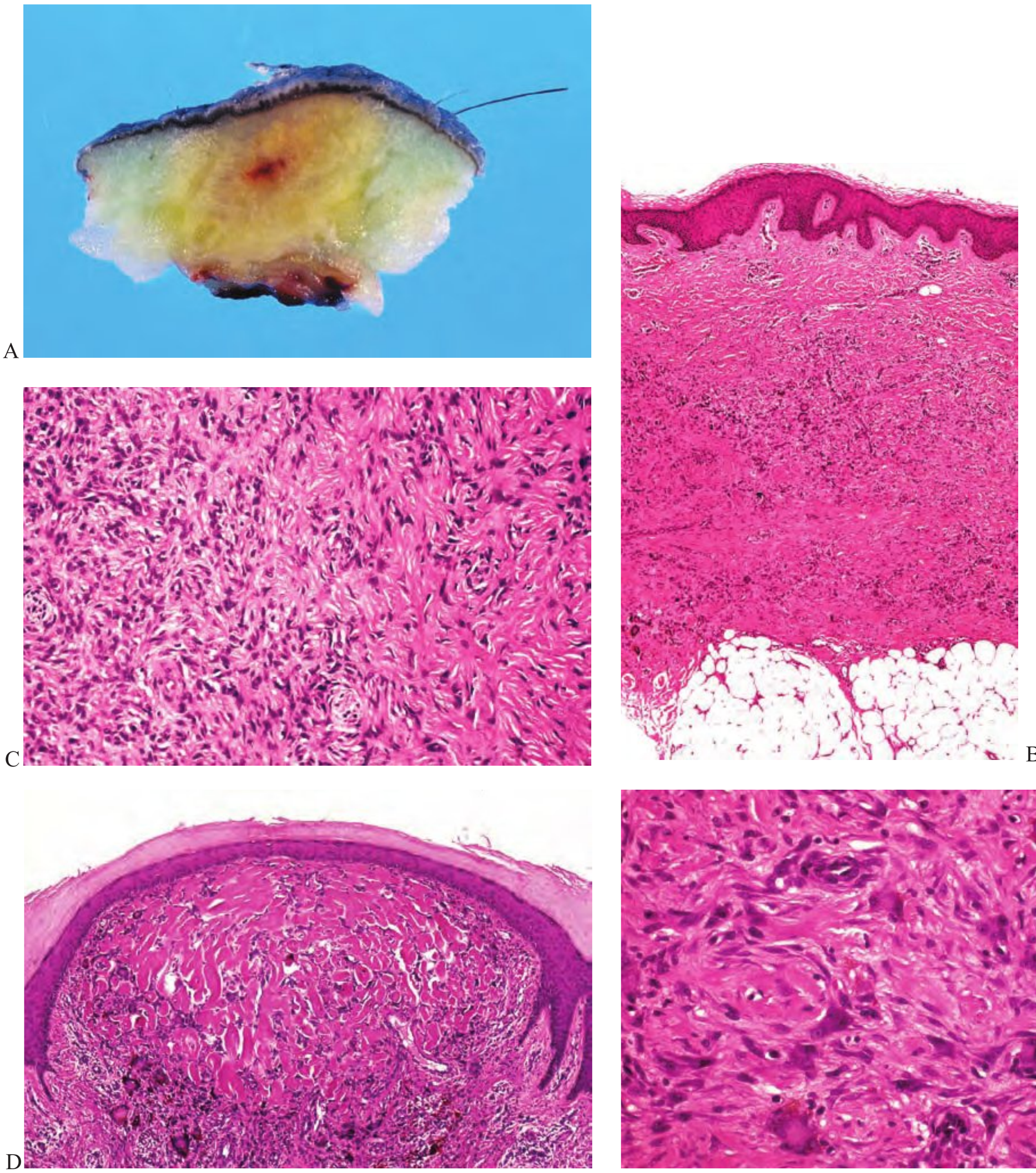
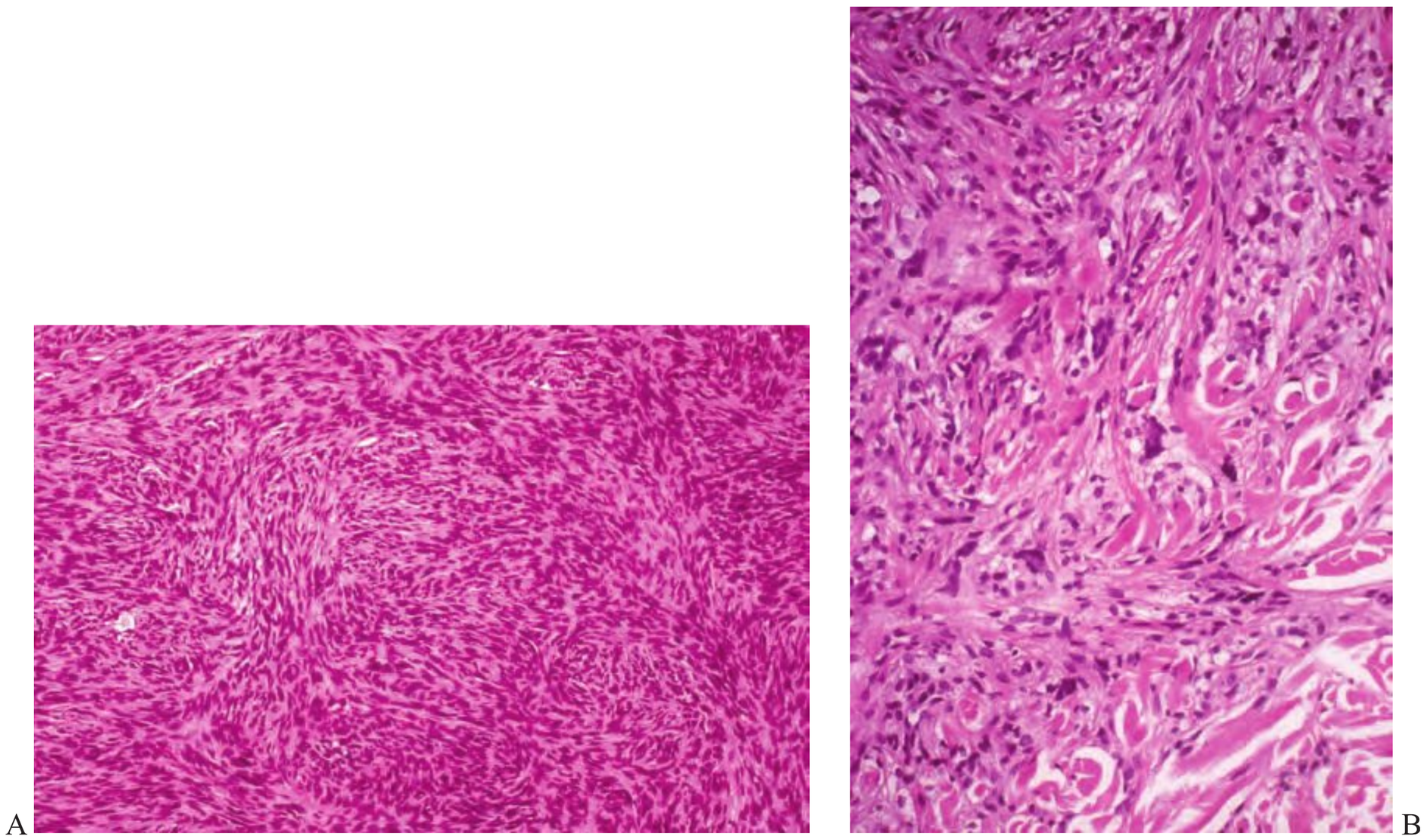


FIGURE 32-1. Dermatofibroma (fibrous histiocytoma). A: Gross specimen. A poorly circumscribed dermal lesion is present with overlying increased epidermal pigmentation and acanthosis. The tumor has a yellow cut surface with focal hemorrhage present centrally. B: The epidermis is hyperplastic and separated by a narrow clear zone from a moderately cellular spindle cell tumor extending into the deep dermis. C: The tumor is composed of variably sized spindle cells with pale eosinophilic cytoplasm in a collagenous stroma. D: This dermatofibroma shows prominent hyalinization and pigmentation. E: Hemosiderin and multinucleated giant cells dominate in this zone of another dermatofibroma.

intradermal Spitz nevus (Fig. 32-5) (28,29). The lesions are often well circumscribed. Immunohistochemistry may be required to differentiate the lesion from a melanocytic proliferation, for example. The tumor shows the expected staining pattern of a dermatofibroma.

Deep Fibrous Histiocytoma

This is a rare form that develops entirely within subcutaneous tissue, deep soft tissue, or parenchymal organs (30). Unlike typical dermatofibroma, deep fibrous histiocytoma tends to be well circumscribed, with a pseudocapsule and foci of hemorrhage



A B

FIGURE 32-2. Cellular dermatofibroma (fibrous histiocytoma). A: The tumor consists of spindle cells arranged in densely cellular fascicles with storiform areas. B: At the border of the lesion the spindle cells surround individual collagen bundles.

consisting of monomorphic spindle cells resembling the cellular variant (31).

Other less common variants include clear cell (32), granular cell (33), lipidized (34), myxoid (35), myofibroblastic (36), osteoclastic (37), keloidal (38), atrophic (39), and palisading forms (40).

Neoplasm Versus Reactive Process

It is unclear whether dermatofibromas are true neoplasms or reactive processes following minor trauma, such as an insect bite. This has given rise to the term "nodular subepidermal fibrosis" (41), with some authorities regarding the lesions as fibrosing inflammatory processes, even in the presence of "monster cells" (24,42). The demonstration of clonality in some cases of dermatofibroma (43,44) and reports of metastasizing dermatofibroma (16–19), however, suggest a neoplastic nature. Analysis of X chromosome inactivation in 31 dermatofibromas showed a variable pattern, suggesting that the lesions are heterogeneous, with some being reactive, others possibly neoplastic in nature (45–48).

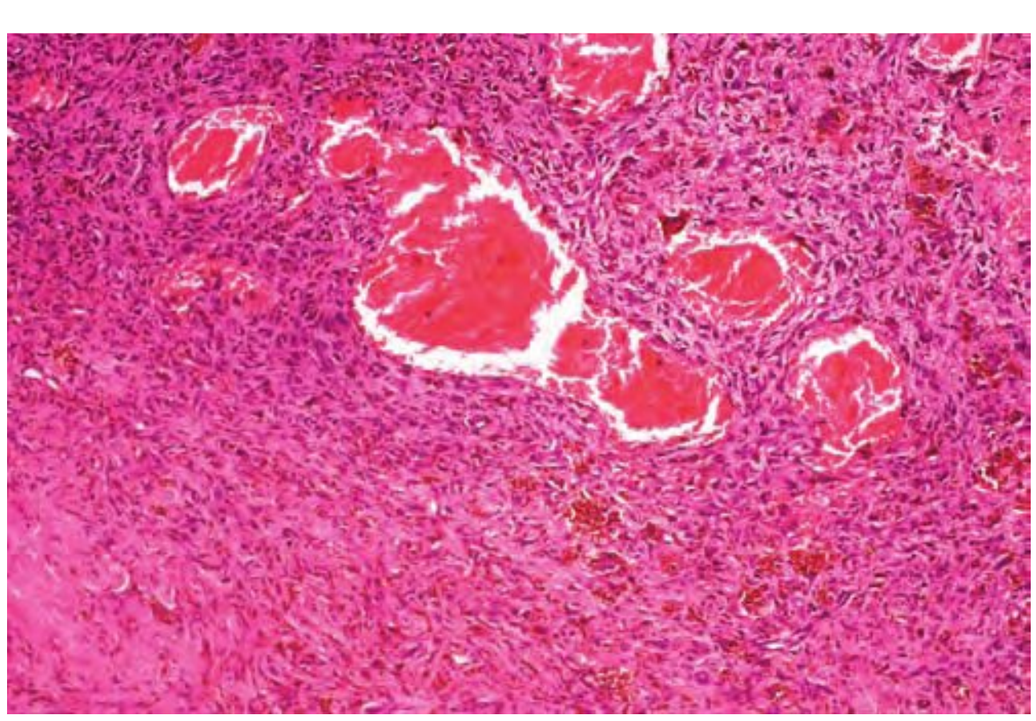


FIGURE 32-3. Aneurysmal fibrous histiocytoma (dermatofibroma). Dilated blood-filled spaces are prominent in this variant, with associated hemorrhage. Bland spindle cells and siderophages are seen in the surrounding tissue.

Histogenesis. Enzyme histochemical, electron microscopic, and immunohistochemical studies have suggested histiocytic, myofibroblastic, and fibroblastic differentiation, possibly indicating a cell of primitive mesenchymal origin (49). The term *dermal dendrocytoma* has been suggested on the basis of immunohistochemical studies using antibodies to factor XIIIa (a marker of normal dermal dendrocytes) and the histiocytic marker MAC 387 (50,51). Most cells in these tumors were found to react with factor XIIIa, whereas only a few were MAC 387 positive. Other investigators, however, believe that the factor XIIIa–positive cells seen in fibrous histiocytomas represent included reactive stromal cells rather than the true tumor cells (49,52), which often express vimentin and smooth muscle actin (52). Electron microscopic studies have variously described the cells of fibrous histiocytomas as fibroblasts, histiocytes, and myofibroblasts (53–55).

Enzyme Histochemistry. The results of enzyme studies on dermatofibromas have shown variable reactions. Positive staining

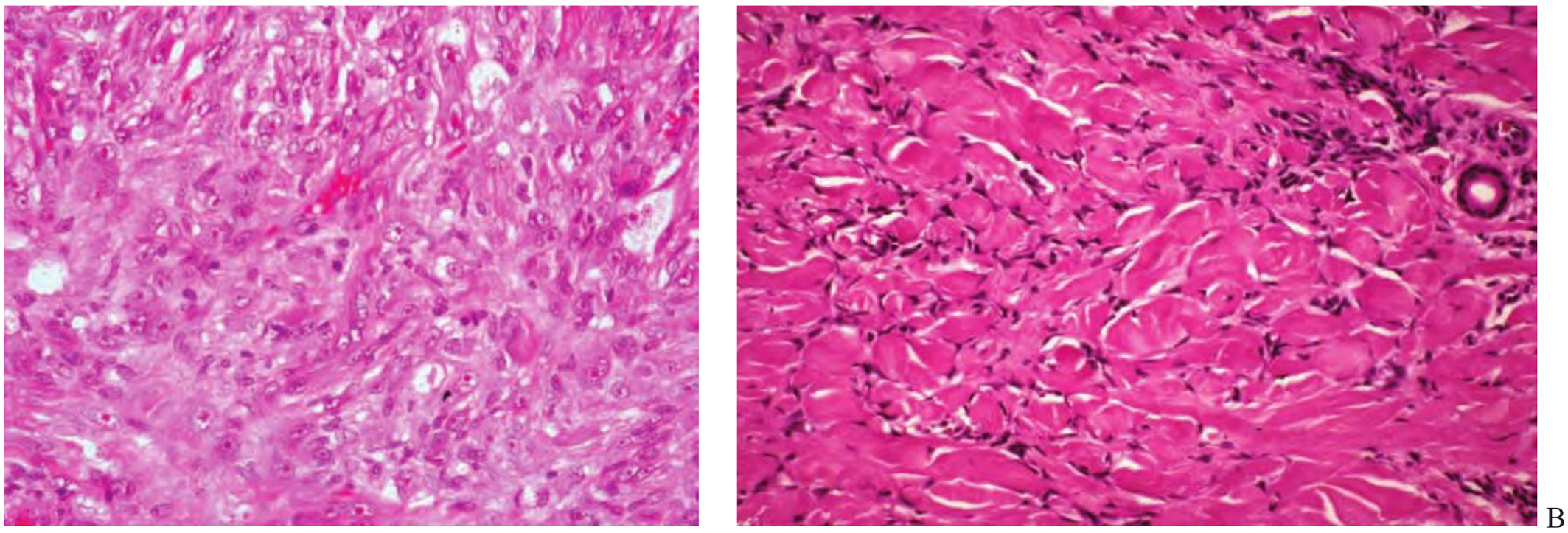


FIGURE 32-4. Atypical fibrous histiocytoma (dermatofibroma). A: This tumor shows histiocyte-like cells with enlarged and pleomorphic nuclei with prominent nucleoli. B: At the border of this tumor the cells are arranged around individual collagen bundles in the pattern typical of the more usual form of dermatofibroma.

for lysozyme and α_1-antitrypsin have been interpreted as indicating histiocytic differentiation (56,57), whereas negative results for these enzymes have led to speculation that the fibroblastic and histiocyte-like cells in these tumors arise from primitive mesenchymal cells (58). The presence of HLA-DR antigens in the majority of cells in dermatofibromas has also been regarded as evidence in favor of a histiocytic origin (59).

Differential Diagnosis. The cellular variant of dermatofibroma must be distinguished from DFSP. Points of distinction are that dermatofibromas show overlying epidermal hyperplasia, a heterogeneous population of tumor cells, often with more pleomorphism, and extension of tumor cells at the edge of the lesion around individual hyalinized collagen bundles (60). Cellular fibrous histiocytoma also extends into subcutis along the interlobular septae or in a bulging, expansile pattern rather than in the characteristic infiltrating honeycomb-like pattern of DFSP (17). DFSP is usually a larger lesion at the time of diagnosis, often consisting of multiple nodules. Cellular fibrous histiocytoma may also be confused with leiomyosarcoma, but this has plumper spindle cells, with eosinophilic cytoplasm and nuclei with rounded ends, and shows positive staining for desmin and α-smooth muscle actin (49). It should be noted that some dermatofibromas may express CD34, and some DFSP may express factor XIIIa (61). This has lead to the suggestion of a biological spectrum between fibrous histiocytoma and DFSP, with coexistence of two different cell populations in indeterminate lesions (62). Tenascin (an extracellular matrix glycoprotein) expression has been demonstrated immunohistochemically at the dermoepidermal junction overlying fibrous histiocytomas but not DFSP (63,64).

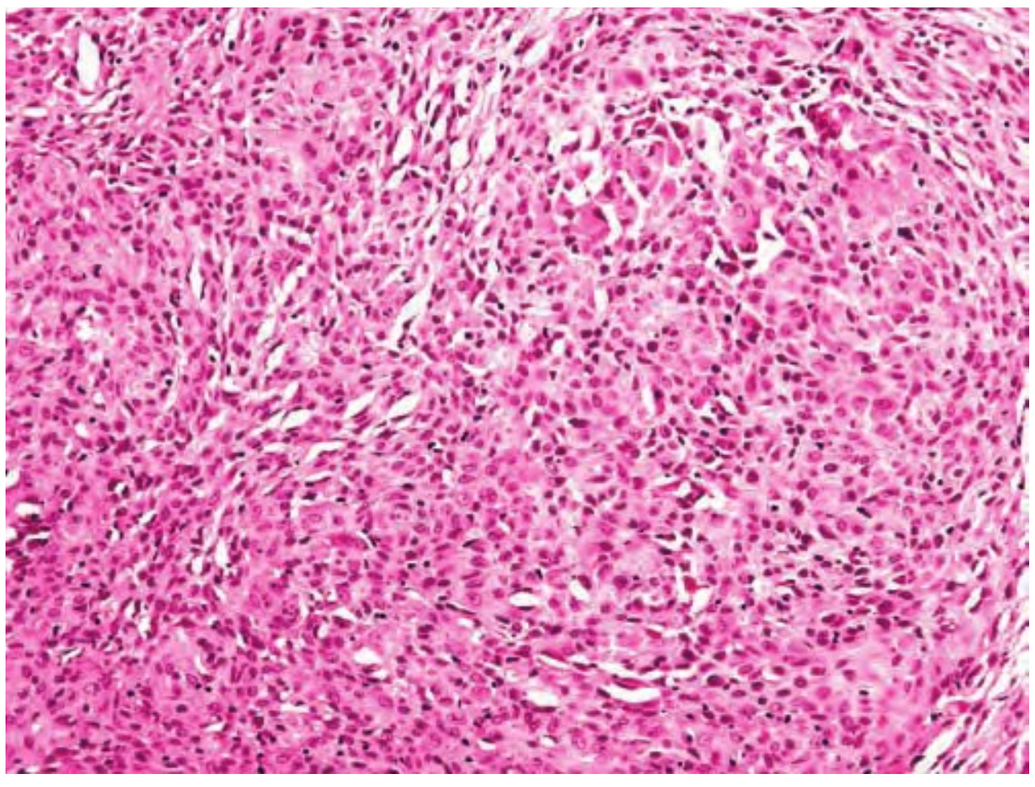


FIGURE 32-5. Epithelioid fibrous histiocytoma (dermatofibroma). The lesion shows sheets of epithelioid cells with eosinophilic cytoplasm. Differentiation from a melanocytic lesion such as a Spitz nevus may require immunohistochemistry in some cases.

Fibrous histiocytoma with aneurysmal change (aneurysmal fibrous histiocytoma) may be confused with neoplasms of vascular origin. Distinction can be made by demonstrating that factor VIII, CD31, and CD34 do not outline the apparent vascular spaces in fibrous histiocytoma, in contrast to true vascular lesions. Kaposi's sarcoma shows slit-like spaces containing erythrocytes and a monomorphic $CD34^+$ spindle cell population (49). Angiomatoid fibrous histiocytoma is distinguished by its presentation in a younger age group (sometimes with systemic symptoms), subcutaneous location and the presence of eosinophilic histiocytoid cells, a prominent lymphocytic infiltrate, and a thick pseudocapsule (65,66).

Epithelioid dermatofibroma (epithelioid cell histiocytoma) can resemble Spitz nevus and pyogenic granuloma clinically and histologically (29). The lesion differs from pyogenic granuloma by the presence of epithelioid cells between blood vessels, which are not arranged in lobules, with a less prominent inflammatory component and lack of protuberant endothelial cells. Intradermal Spitz nevus has a nested pattern superficially, spindle as well as epithelioid cells, intranuclear

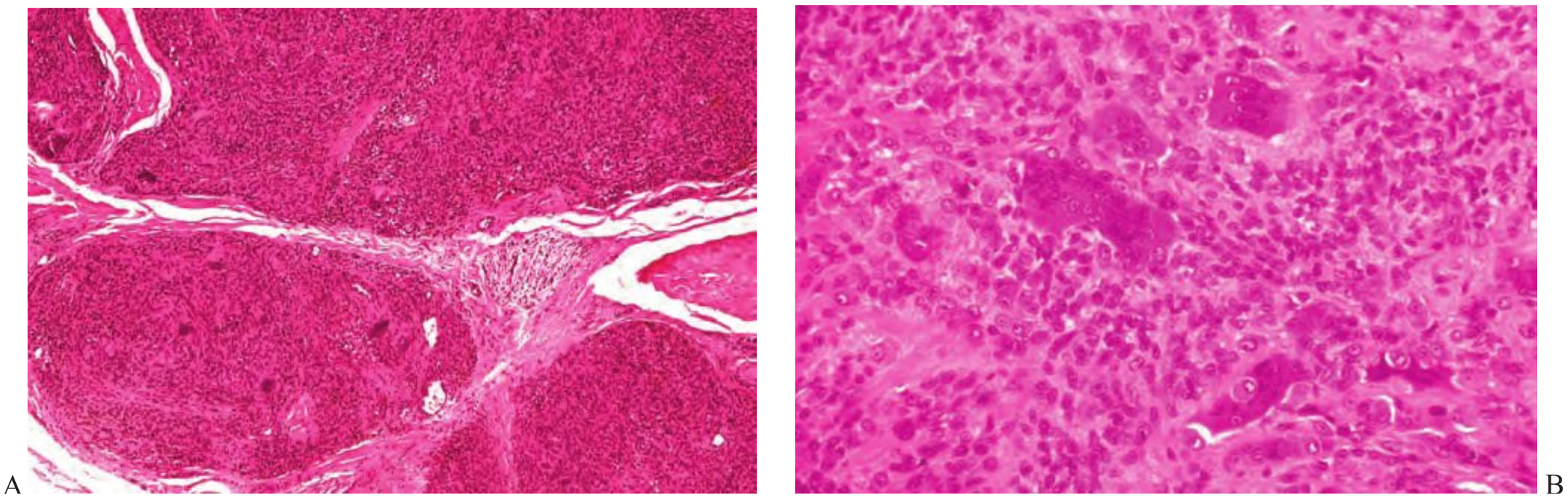


FIGURE 32-6. Giant cell tumor of tendon sheath. A: The tumor is composed of sharply circumscribed, densely cellular lobules surrounded by fibrous tissue. B: Giant cells with multiple nuclei, resembling osteoclasts, are scattered among plump epithelioid and spindle cells.

cytoplasmic inclusions, maturation with depth, and, frequently, Kamino bodies in the epidermis. Immunostaining of Spitz nevi reveals positivity for S100 and other melanocyte markers and negative staining for factor XIIIa.

Atypical fibroxanthoma differs from atypical dermatofibroma by its frequent location on sun-exposed skin of the head and neck of elderly patients, frequent ulceration, severe cellular pleomorphism, numerous mitoses, including atypical forms, and the lack of a background of more typical dermatofibroma.

Giant Cell Tumor of Tendon Sheath

Giant cell tumor of tendon sheath occurs most commonly on the tendon sheath of young and middle-aged adults on the dorsum of the fingers, hands, and wrists. They can also be found on the feet and around the ankle and knee joints. Tumors are firm in consistency, with a yellowish to tan cut surface, and are from 1 to 3 cm in diameter. There is no tendency toward spontaneous involution. The tumor may erode the adjacent bone and, on rare occasions, may even extend into the overlying skin (67,68). The lesions are benign, although they may recur. Recurrences are cured by local reexcision (69). Although it has been suggested that this tumor is an inflammatory proliferation (70), other reports indicate that the lesion is neoplastic (71).

Histopathology. The tumor consists of lobules of varied cellularity surrounded by a fibrous pseudocapsule (Fig. 32-6A). In cellular areas, most cells are macrophage-like mononuclear cells with folded, kidney-shaped or grooved, oval nuclei and abundant eosinophilic cytoplasm. There is a variable number of foamy macrophages, which may be associated with cholesterol clefts and siderophages. Less cellular areas consist of spindle cells within a fibrous or hyalinized stroma (67,72). The characteristic osteoclast-like giant cells (73) are scattered through both the cellular and fibrous areas. Their cytoplasm is deeply eosinophilic and contains a variable number of haphazardly distributed nuclei (Fig. 32-6B). Although mitotic figures are seen in a large proportion of cases and may be frequent (74), they are not atypical. There is no evidence that mitotic activity is related to metastasis, which is an extremely rare event, but it may be associated with an increased risk of recurrence (75).

Histogenesis. Ultrastructural (73,76), enzyme (72), and immunohistochemical studies (72,77–79) have indicated variously that the cells may be related to synovial cells, monocytes, and osteoclasts.

Intermediate Biological Potential (Locally Aggressive)

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans is a slowly growing dermal spindle cell neoplasm of intermediate malignancy. It typically forms an indurated plaque on which multiple congested, firm nodules subsequently arise, sometimes with ulceration (Fig. 32-7A). The trunk and proximal limbs of young adults are most commonly affected, with occasional involvement of the head and neck or other sites (80,81). Some cases have been reported in childhood and, rarely, as congenital lesions (82–84). Local recurrence is common, and transformation to fibrosarcoma can occur, but metastasis is rare (85,86).

Histopathology. DFSP is composed of fascicles of densely packed, monomorphous spindle cells arranged in a storiform (mat-like) pattern. Lesions are poorly circumscribed, with diffuse infiltration of dermis and subcutis yielding a honeycomb pattern (Fig. 32-7B–D) (17). Infiltration into the underlying fascia and muscle occurs as a late event (86). Cytologically, the cells have a deceptively bland appearance, which can result in difficulty in defining the margin of the lesion. Mitotic activity is generally limited, typically less than 5 mitoses per 10 high-power fields. Myxoid areas may occur, especially in recurrent

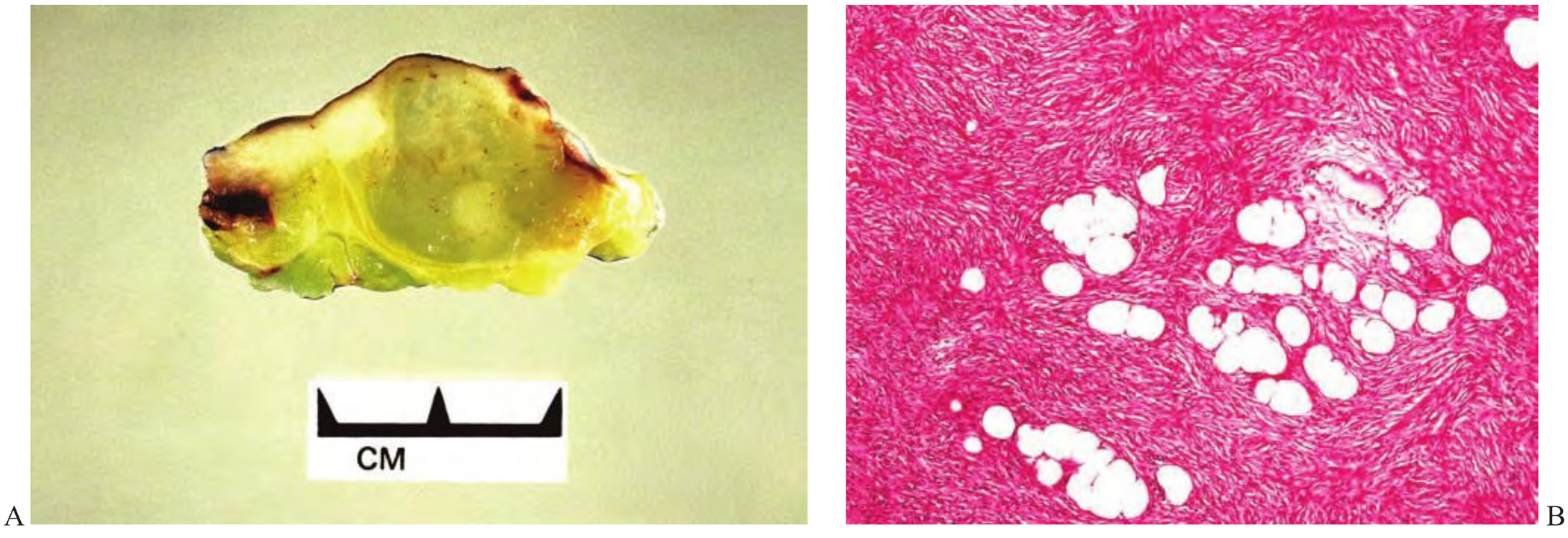


FIGURE 32-7. Dermatofibrosarcoma protuberans (DFSP). A: Gross specimen of a myxoid variant of DFSP. The lesion is better circumscribed than the more typical form of DFSP and forms a central nodule extending into subcutis, with lateral extension in the dermis showing a component of firmer white tissue. B: Densely packed spindle cells are present, arranged in a storiform pattern extending around fat cells. C: Strands of bland spindle cells infiltrate subcutis, producing a honeycomb-like pattern. D: This DFSP exhibits an area with a prominent fibrosarcoma-like pattern. This feature is not said to be of prognostic significance (see text).

tumors. Sometimes there is a vascular component of fine anastomosing blood vessels with a "chicken-wire" appearance resembling myxoid liposarcoma (Fig. 32-8) (87).

Pigmented melanosome-containing cells can be identified in the tumors on rare occasions—the *Bednar tumor* (pigmented DFSP, storiform neurofibroma) (88–90). A number of congenital presentations of this tumor have been recorded (91).

Fibrosarcomatous areas are seen in a small proportion of DFSP, characterized by a fascicular or herringbone growth pattern (92–94). This variant does not appear to have any greater propensity for local recurrence, provided that the lesion is adequately excised (94). Giant cells are rarely seen in otherwise typical DFSP but are characteristically prominent in the juvenile variant of DFSP, giant cell fibroblastoma (see next section) (95–100).

Histogenesis. Electron microscopic studies suggest that the tumor cells are fibroblasts because they show active synthesis of

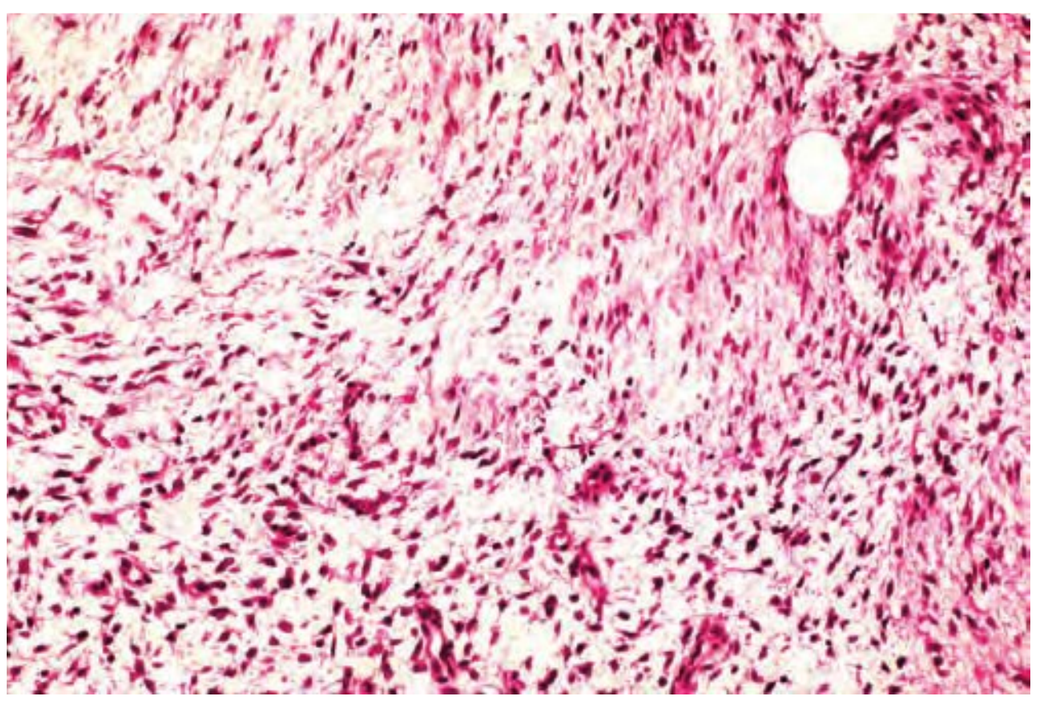


FIGURE 32-8. Myxoid dermatofibrosarcoma protuberans (DFSP). This DFSP shows a myxoid appearance as it extends into subcutis. Myxoid change is more common in recurrent tumors.

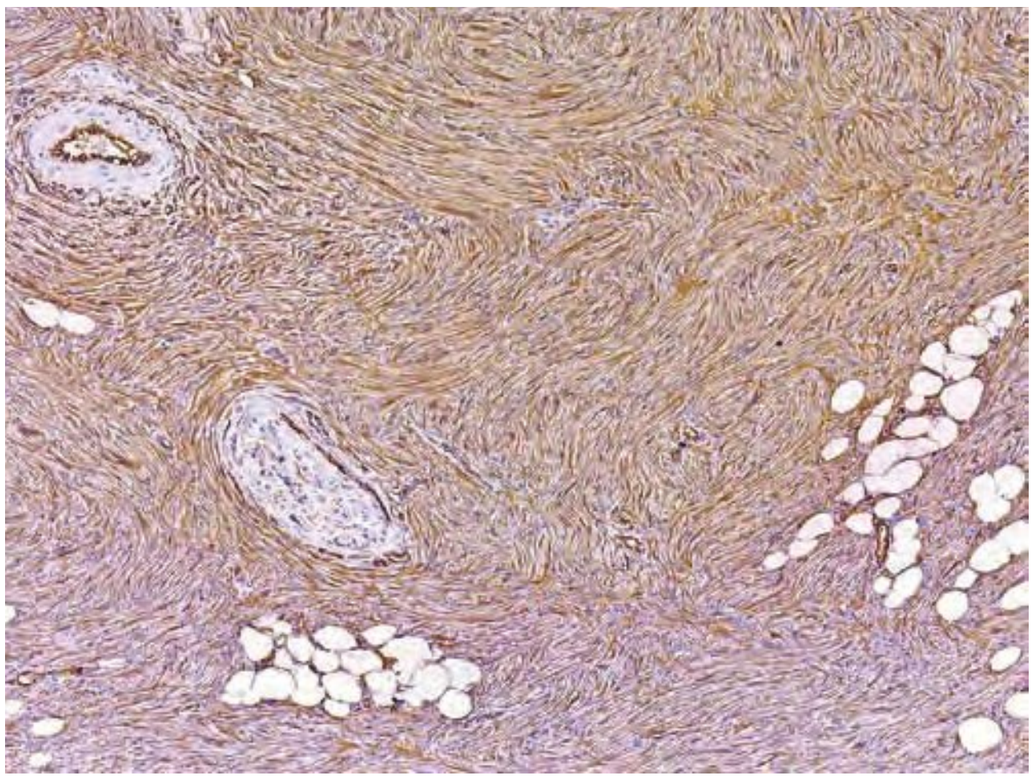


FIGURE 32-9. Dermatofibrosarcoma protuberans. Immunohistochemistry shows strong, uniform positivity for CD34 in the lesion. (Courtesy of Dr. E-C. Jung, University of California, San Francisco, California.)

collagen in a well-developed endoplasmic reticulum (101,102). In some tumors the presence of interrupted basement membrane–like material along the cell membrane suggested that the cells are modified fibroblasts with features of perineural and endoneural cells (103). Epithelial membrane antigen expression in a few cases and consistent CD34 positivity raised the possibility of a perineural origin (104). Although DFSP is commonly regarded as a fibrohistiocytic tumor, immunohistochemical and ultrastructural evidence indicates that a fibroblastic origin is most likely (87,105–107).

Cytogenetic studies have revealed a t(17;22) translocation in more than 90% of cases of DFSP, leading to formation of a ring chromosome in some tumors (108). The translocation involves the COL1A1 gene on chromosome 17 and the platelet-derived growth factor B gene on chromosome 22. Although management of this disease continues to be primarily surgical, high rates of clinical response have been achieved through the use of imatinib to inhibit platelet-derived growth factor receptors in patients with unresectable or metastatic DFSP (109).

Differential Diagnosis. DFSP is generally characterized by more uniform spindle cells and a more prominent storiform pattern than that seen in dermatofibroma. Small biopsies may make assessment of architecture impossible, so caution is required in these cases. In contrast to cellular dermatofibroma, the epidermis overlying DFSP is usually attenuated or ulcerated rather than hyperplastic, and a clear (Grenz) zone between the epidermis and tumor may be absent. DFSP has a more infiltrative pattern of growth, in contrast to the well-demarcated bulging deep margin of cellular dermatofibroma, although this tumor may also extend into subcutis, predominantly along septae (17,60). CD34 staining is usually diffusely positive in DFSP and negative in most forms of dermatofibroma (110–112) (Fig. 32-9), but there is some overlap in the expression of CD34 in these conditions (62). Demonstration of tenascin at the dermoepidermal junction overlying dermatofibroma but not DFSP may help in the differential diagnosis (63,64). It has also been shown that dermatofibromas strongly express CD44 with only faint stromal hyaluronate, whereas DFSP shows reduced or absent CD44 and strong stromal hyaluronate deposition (113). Apolipoprotein D has recently been identified immunohistochemically in the majority of cases of DFSP but not in dermatofibromas (114). Neurofibroma expresses S100 protein, which is absent in DFSP, and shows other features of neural differentiation, without the dense, uniform cellularity of DFSP.

Giant Cell Fibroblastoma

Giant cell fibroblastoma represents a juvenile variant of DFSP and was first formally reported in 1989 (95). It is a rare tumor

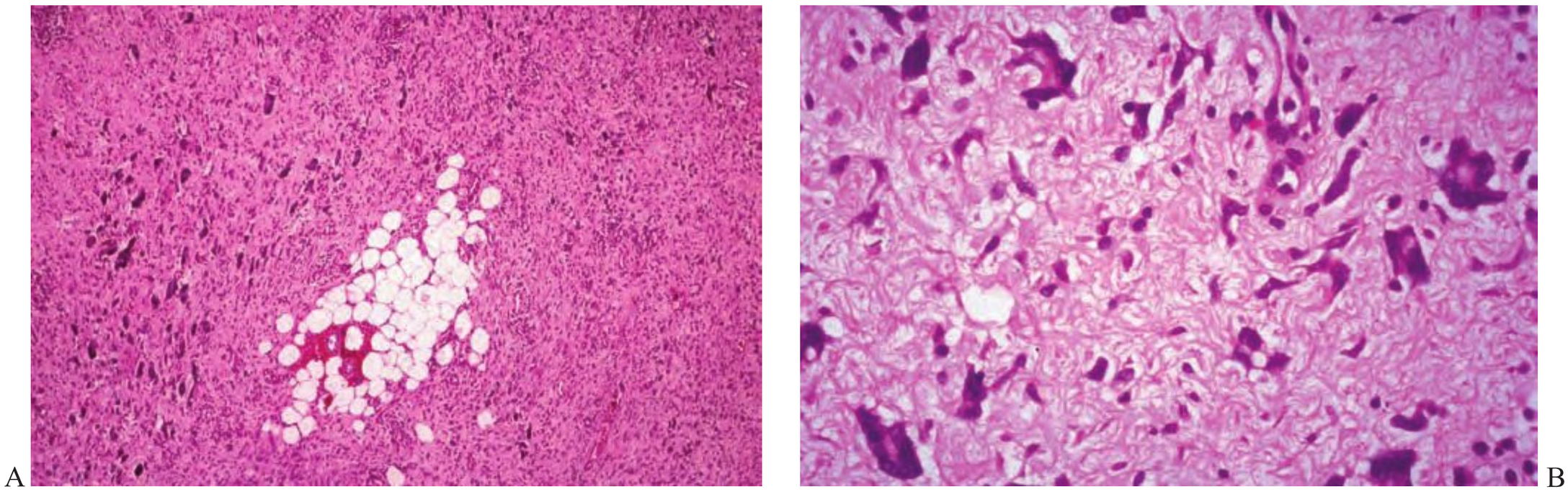


FIGURE 32-10. Giant cell fibroblastoma. A: The growth pattern resembles that of dermatofibrosarcoma protuberans with infiltration of subcutaneous fat by uniform spindle cells, with the additional feature of numerous giant cells. (Courtesy of Dr. I. Strungs, Adelaide Children's Hospital, Adelaide, Australia, and Dr. P. W. Allen, Flinders Medical Centre, Bedford Park, SA 5042, Australia.) B: Numerous multinucleated giant cells are present on high power, some with pleomorphic, multilobated nuclei.

occurring almost exclusively in children, with more than 75% of patients younger than 20 years old (115). Lesions are solitary and most often sited on the trunk or thigh. Local recurrence after incomplete excision is common (116), but no metastases have been reported (117). Fibrosarcomatous change is very rare (115).

Histopathology. The proliferation is sited in the dermis and subcutis, usually with areas showing the honeycomb pattern typical of DFSP (Fig. 32-10A). In contrast, multinucleated giant cells line small clefts in the tissue (Fig. 32-10B), and foci of hemorrhage and perivascular lymphocytes may be seen (115). Zones of myxoid to hyalinized stroma are also present and often prominent. Electron microscopy suggests that the giant cells are not in fact multinucleated, but that the appearance represents multiple lobations of a single nucleus (95).

Histogenesis. Ultrastructurally, the cells resemble fibroblasts. Immunohistochemistry shows CD34 positivity (including in the giant cells) with no staining for S100, smooth muscle actin, or desmin (115,118).

The concept that giant cell fibroblastoma is a variant of DFSP is supported by the coexistence of areas of both tumors in a single lesion in some instances, the same immunogenetic and cytogenetic profile, and the recurrence of DFSP as giant cell fibroblastoma and vice versa (95–100). As in DFSP, the translocation t(17;22), sometimes forming an extra ring chromosome, has been repeatedly identified (108,119), and responsiveness to imatinib in inoperable cases might therefore be anticipated (109).

Differential diagnosis includes fibrous hamartoma of infancy (page 986). Points of distinction are the patient's age, the presence of three "zones" in fibrous hamartoma, and its lack of multinucleated cells.

Intermediate Biological Potential (Rarely Metastasizing)

Plexiform Fibrohistiocytic Tumor

Plexiform fibrohistiocytic tumor is a rare multinodular neoplasm of the dermis and subcutis composed of histiocyte-like cells, fibroblasts, and multinucleate giant cells in a plexiform pattern (120). This distinctive lesion occurs as a slowly growing mass, usually involving the arm of the young, especially females. Infants are occasionally affected (121). The lesion is considered to be of intermediate biological potential, with local recurrence common but with only rare metastases to lymph nodes or viscera (122). No features predictive of recurrence or metastasis have been delineated.

Histopathology. A biphasic pattern is seen, with nodules of histiocytes surrounded by fascicles of spindle cells intersecting the stroma in a plexiform pattern. Osteoclast-like giant cells are seen in the majority of cases, but not all (Fig. 32-11A) (123–125). The proportion of different cellular elements varies from case to case. Mitotic activity with mild nuclear atypia and pleomorphism may be present.

Histogenesis. Ultrastructural and immunocytochemical studies have indicated histiocytic and myofibroblastic differentiation (122,126) in the different cellular components (Fig. 32-11B). No consistent genetic changes have been identified.

Differential Diagnosis. Cellular fibrous histiocytoma and dermatomyofibroma do not have the distinctive nodules of histiocytic-like cells of plexiform fibrohistiocytic tumor, whereas fibromatosis and nodular fasciitis are usually more deeply situated and lack the characteristic plexiform growth pattern. Fibrous hamartoma of infancy has no histiocytic nodules or giant cells (116).

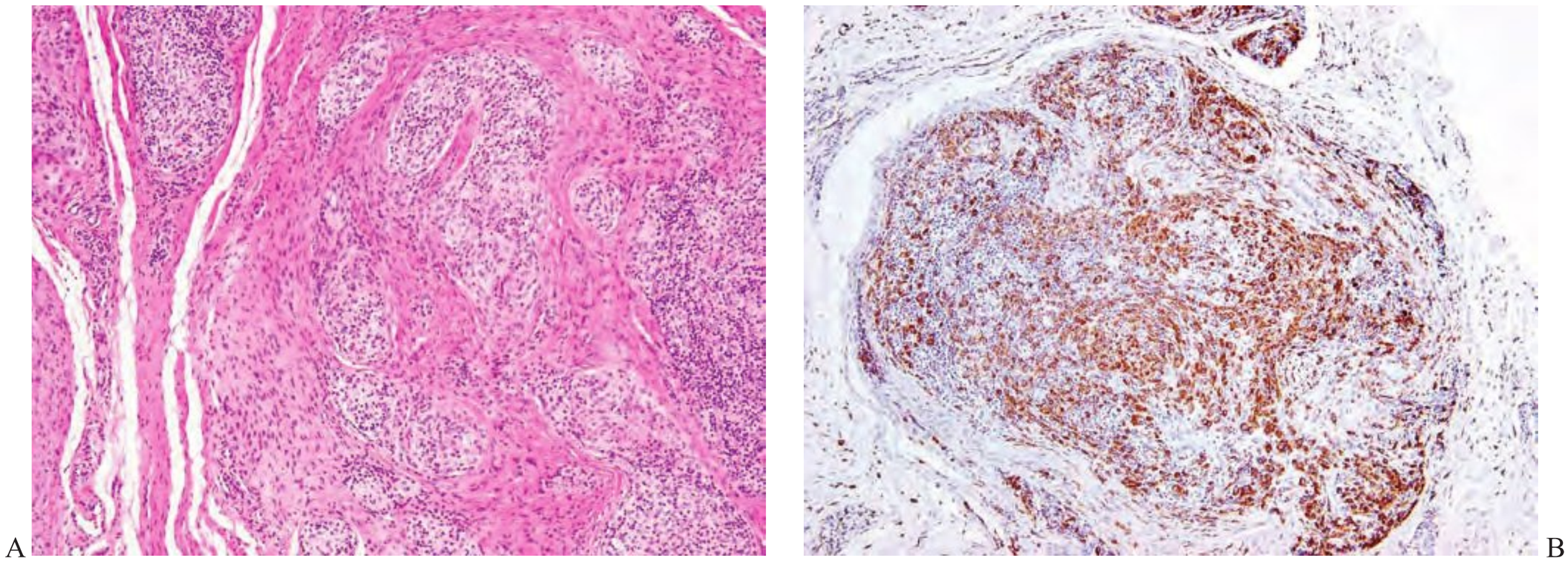


FIGURE 32-11. Plexiform fibrohistiocytic tumor. A: Pale, nodular groups of histiocyte-like cells are present between collagenous bands in the dermis and subcutis. B: Immunohistochemistry demonstrates that many of the pale cells are CD68 positive.

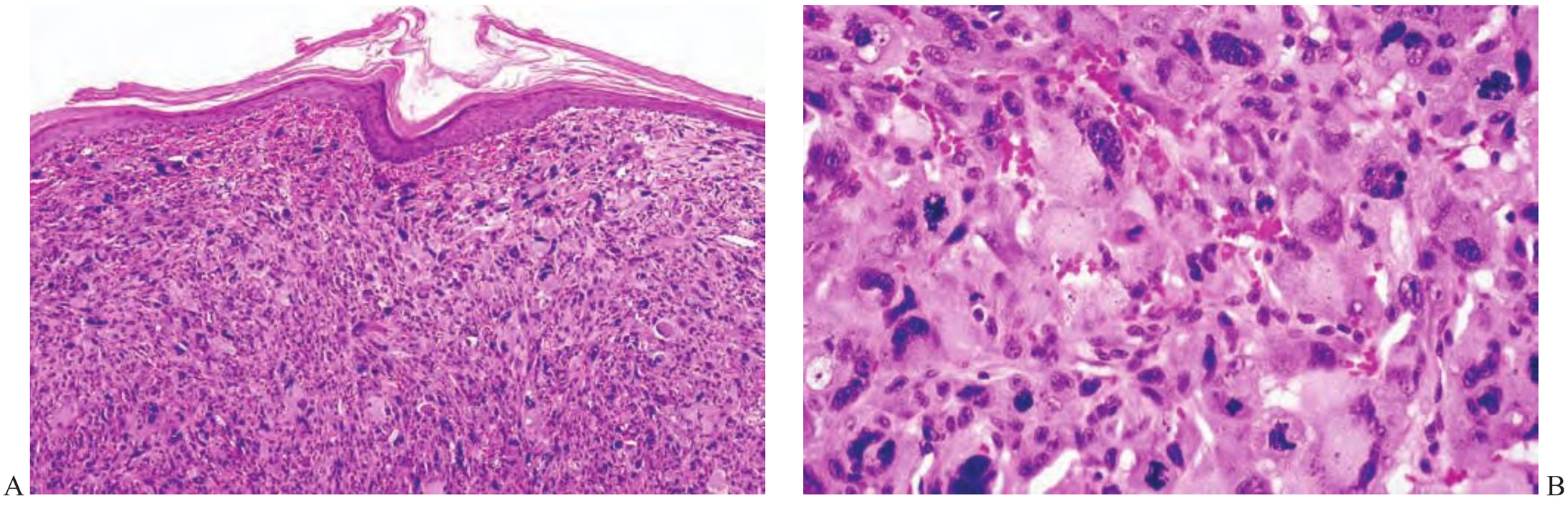


FIGURE 32-12. Atypical fibroxanthoma. A: The tumor is composed of a cellular mass of malignant cells that are unconnected to the epidermis. A lack of keratinization and pigmentation are clues to the diagnosis in these pleomorphic tumors, but immunohistochemistry is recommended in all cases for definitive diagnosis. B: Highly pleomorphic spindle cells are present with some multinucleated giant cells and scattered mitoses, including atypical forms.

Atypical Fibroxanthoma

Atypical fibroxanthoma (AFX) is characterized by a malignant histologic appearance but a generally benign course with only occasional recurrences and exceptionally rare metastases (127–136). Lesions are typically associated with actinic damage and so tend to present on the head, neck, or dorsum of the hand of elderly patients. AFX usually forms a solitary nodule up to 2 cm in diameter, often with a short history of rapid growth.

Histopathology. AFX is a dermal tumor with no or only limited involvement of the subcutis. Lesions are cellular, with marked and often striking pleomorphism and atypia of the constituent cells. Mitoses are readily identified with some atypical forms (Fig. 32-12A, B) (130,133,137). Most tumors are predominately composed of spindle cells, with areas of more epithelioid and histiocyte-like appearing forms also present. The cells are arranged in disordered fascicles, surrounding but not destroying adnexal structures. An epidermal collarette is often seen, with ulceration frequently present. Scattered inflammatory cells are present, often with focal hemorrhage.

The *spindle cell variant* of AFX consists exclusively of spindle cells with eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli arranged in fascicles. Some examples of this subtype have a somewhat more regular and bland cytologic appearance, and a plaquelike pattern of growth may be evident (Fig. 32-13A, B) (129,134,138). *Clear cell AFX* is a

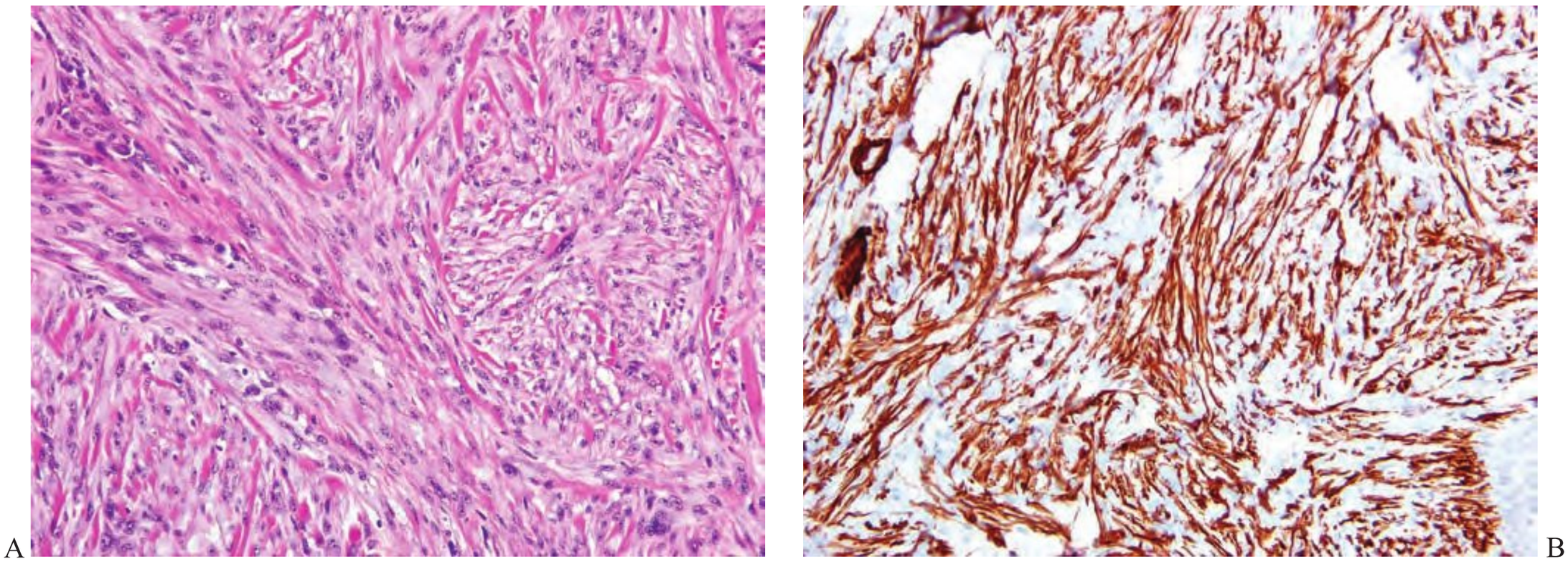


FIGURE 32-13. Spindle cell atypical fibroxanthoma. A: Swathes of pleomorphic spindle cells are present, with some background collagen. Some tumors of this type show relatively monomorphic cytologic features. B: Immunohistochemistry demonstrates strong positivity in the cytoplasm of the spindle cells for smooth muscle actin. Desmin was negative (not shown).

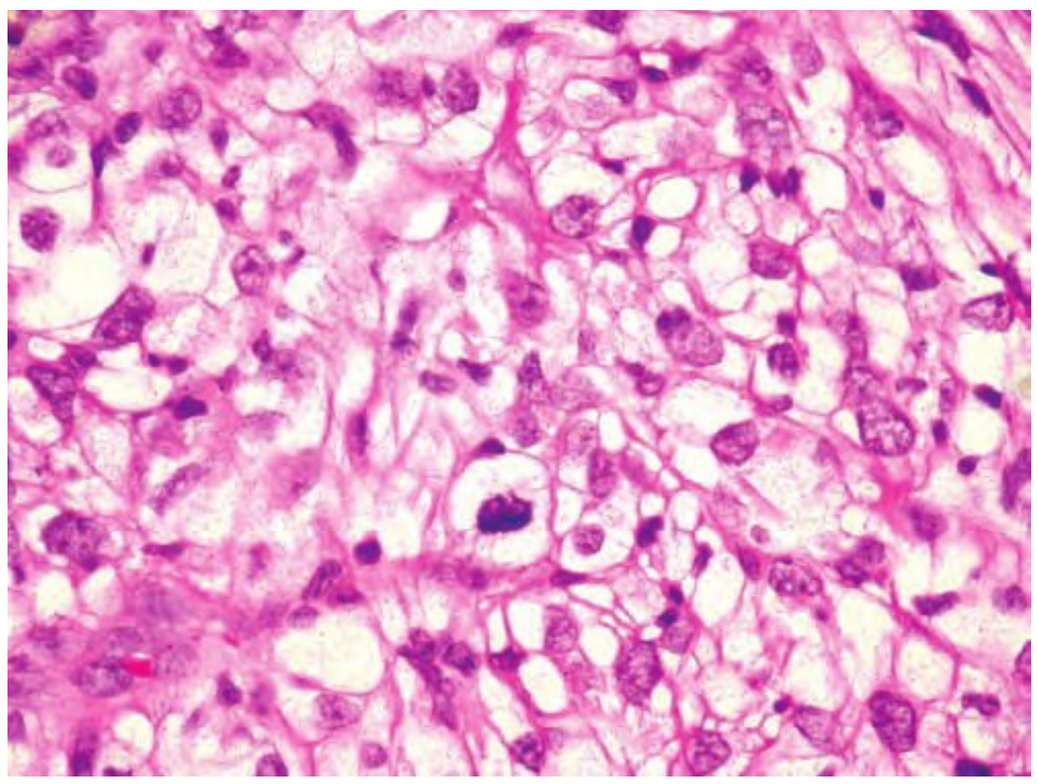


FIGURE 32-14. Clear cell atypical fibroxanthoma. The atypical cells exhibit abundant clear cytoplasm in this variant.

rare variant composed of sheets of large cells with foamy cytoplasm and hyperchromatic, pleomorphic nuclei (Fig. 32-14) (139,140). Occasional tumors are pigmented due to hemosiderin deposition (141). *Granular cell* and *sclerotic* variants have also been reported (142,143).

Histogenesis. Electron microscopic (130,144) and immunohistochemical (106,145) studies suggest that the progenitor cell is an undifferentiated mesenchymal cell capable of showing histiocytic, fibroblastic, and myofibroblastic differentiation.

Differential Diagnosis. Although the features of this tumor are often characteristic, it is important to perform immunohistochemistry to exclude other malignancies, in particular melanoma, leiomyosarcoma, and poorly differentiated squamous cell carcinoma. The possibility of a metastasis should always be considered. In our laboratory, a broad panel of markers is applied, with an expected profile of negative staining for desmin, epithelial, and melanoma markers. Positivity with CD68 is generally present (Fig. 32-15), with quite frequent smooth muscle actin positivity; a negative desmin stain helps to exclude leiomyosarcoma in cases of actin positivity. Desmin positivity has been reported in some cases of AFX, but lesions might be better regarded as leiomyosarcoma if staining is extensive or intense (146). Vimentin, although expected to be positive, has little discriminatory value. Recently CD10 has been shown to be expressed in many cases of AFX (134,147). h-Caldesmon has been reported as negative in AFX but positive in leiomyosarcoma (146), and CD99 is frequently expressed by AFX (134,148).

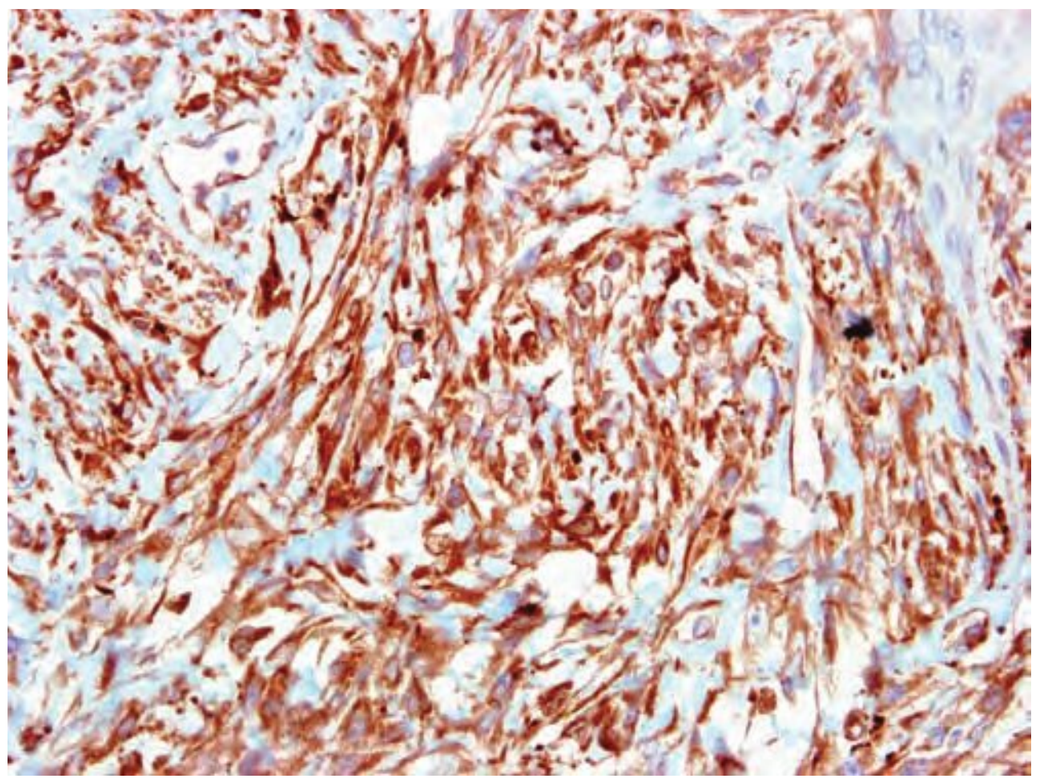


FIGURE 32-15. Clear cell atypical fibroxanthoma (AFX). CD68 is typically positive in all forms of AFX.

Malignant

Malignant Fibrous Histiocytoma

The concept of malignant fibrous histiocytoma (MFH) (149–151) has generally fallen into disrepute, with many authorities considering that the tumor is neither of histiocytic origin nor a specific entity. Based on the use of techniques such as immunohistochemistry, cytogenetics, and electron microscopy, most MFH can be recategorized as other types of sarcoma, melanoma, carcinoma, or even lymphoma (1,128,152–154). The majority of tumors in these categories arise in deep soft tissue, only occasionally reaching the skin by direct growth or metastasis; as such, presentation in the skin is uncommon (155,156).

Despite the best techniques available, a small group of such tumors apparently show no definable line of differentiation, and these are probably best classified for the most part as *undifferentiated pleomorphic sarcomas* (128,153,157). *Myxoid MFH* is generally considered to be a myxoid fibrosarcoma (myxofibrosarcoma), and *giant cell MFH* (158,159) probably often represents a form of osteosarcoma or, perhaps, malignant giant cell tumor of soft tissue (160).

Angiomatoid fibrous histiocytoma was formerly regarded as a subtype of MFH (161) but has been reclassified as a fibrohistiocytic tumor of intermediate grade on the basis of its excellent prognosis (see page 994) (66,162).

FIBROBLASTIC/MYOFIBROBLASTIC TUMORS

Benign

Hypertrophic Scar and Keloid

Excessive fibrous tissue deposited in association with scar formation may lead to a hypertrophic scar or keloid. There are important clinical and pathologic differences between these processes, although it has been suggested that they may form a spectrum of changes (163–165). Keloids become much more prominent than hypertrophic scars and extend beyond the original site of injury, with a high rate of recurrence following

surgical treatment. However, contractures are not a feature of keloid scars, tending to occur mostly in postburn hypertrophic scars. Keloids occur mainly on the upper chest and arms, head and neck, and especially on the ear. They are uncommon in the periocular region and on the palms, soles, penis, and scrotum (166,167). Keloids mostly affect people in the second and third decades of life, and they are more common in wounds that have been infected or under excess tension.

There is frequently a history of prior trauma (such as ear piercing), but some keloids arise spontaneously, especially in the presternal region. Dark-skinned individuals are much more susceptible to keloids, and occasional familial cases have been recorded (167).

Histopathology. Hypertrophic scars and keloids both exhibit excess collagen formation with varying numbers of fibroblastic cells. These tend to form nodular, whorled masses, with vertically aligned vessels in hypertrophic scars and reduced vascularity in keloids (167,168). In keloids, characteristic hypocellular zones of fibrous tissue contain thickened, glassy, eosinophilic collagen bundles, in contrast to the more cellular nodules in hypertrophic scars (Fig. 32-16A, B).

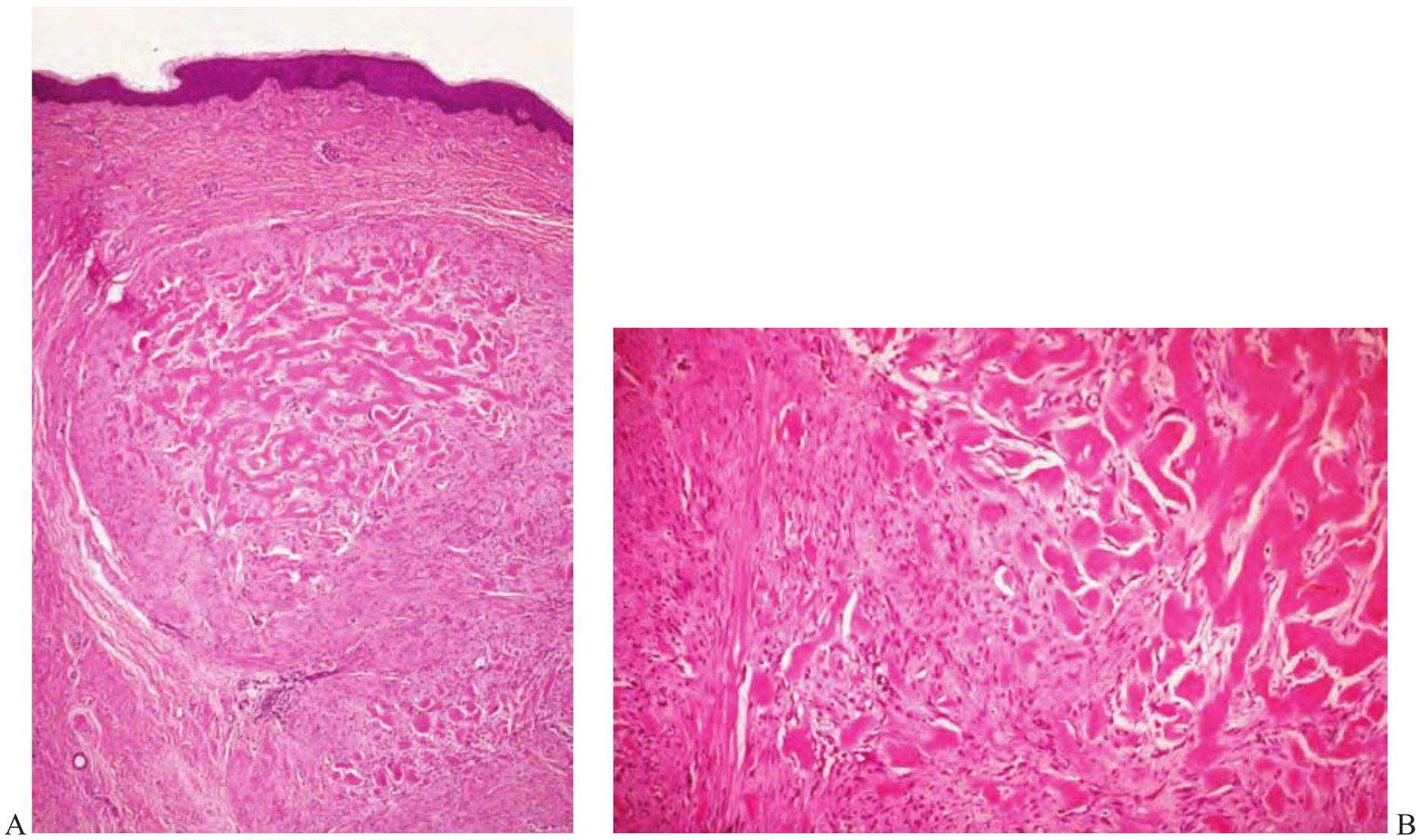
Histogenesis. Keloids have been shown to exhibit abnormal fibroblast activity, with increased hyaluronic acid production and increased levels of transforming growth factor β and other cytokines (169). Decreased apoptosis may also play a role, allowing the keloidal fibroblasts to proliferate and produce more collagen (169). Reduced vascular density in keloids compared to hypertrophic scars and normally healing scars suggests that hypoxia may also play an important role (167).

Dermatomyofibroma

Dermatomyofibroma is an uncommon plaque-like proliferation of fibroblasts and myofibroblasts in the dermis, occurring mainly in young females. The lesions are typically small, with a variety of sites involved, although the shoulder region and neck are most commonly affected (170–172).

Histopathology. Uniform spindle cells in elongated and intersecting fascicles are arranged mainly parallel to the epidermis to form a well-circumscribed plaque. There is occasional involvement to the level of upper subcutis, with sparing of adnexae (Fig. 32-17A, B) (170,173). Overlying epidermal hyperplasia and pigmentation may be seen with increased and fragmented elastin within the lesion. Three cases have recently been reported in adult males on the thigh and trunk that showed red blood cell extravasation associated with dilated capillaries and slit-like spaces giving a resemblance to Kaposi's sarcoma (174).

Histogenesis. Immunohistochemical reactivity for nonspecific muscle actin, variably for α-smooth muscle actin, and the ultrastructural features suggest myofibroblastic differentiation (170,173,175,176).



A B

FIGURE 32-16. Keloid scar. A: Nodules of spindle cells with abundant collagen are present in the dermis with prominent hyalinization. B: Glassy eosinophilic and hyalinized collagen fibers are interspersed with swathes of fibroblasts.

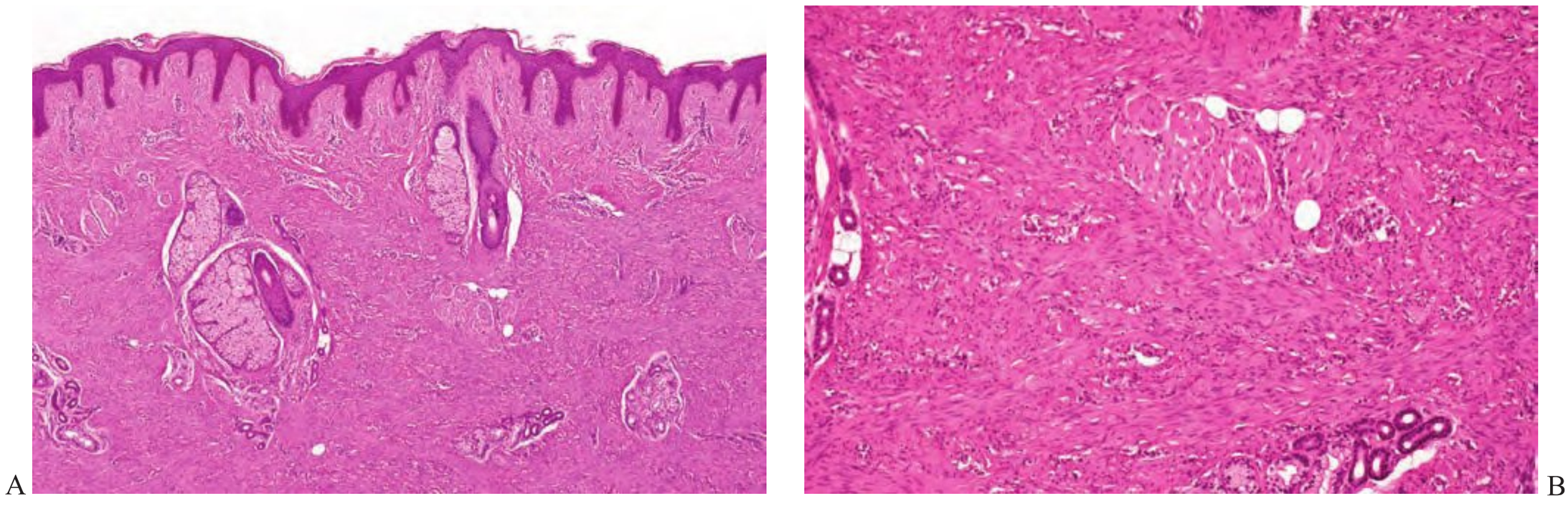


FIGURE 32-17. Dermatomyofibroma. A: The epidermis shows elongated rete ridges overlying a plaque of increased cellularity that surrounds but does not replace appendages. B: At higher power, the lesion is seen to be composed of uniform spindle cells with eosinophilic cytoplasm that efface the dermis, sparing adnexae.

Differential Diagnosis. The orientation parallel to the epidermis of monomorphic spindle cells and their location primarily in the reticular dermis are points of distinction from fibrous histiocytoma. Dermatomyofibroma does not express factor XIIIa, CD34, or h-caldesmon (173,175). Desmin and S100 are also negative.

Soft Fibroma (Fibroepithelial Polyp)

Soft fibromas, also called fibroepithelial polyps, acrochordons, or skin tags, occur as three types: (a) multiple, 1- to 2-mm, furrowed papules, especially on the neck and axillae; (b) single or multiple filiform, smooth growths in varying locations, up to 5 mm long; and (c) solitary, pedunculated or "baglike" growths, usually about 10 mm diameter but occasionally much larger, most often on the lower trunk (177,178).

Several reports have suggested an association between the presence of soft fibroma and colonic polyps (178–181), diabetes (182–184), and acromegaly (185). The association with colonic polyps, however, has not been confirmed by subsequent reports (186–191).

Histopathology. The multiple small furrowed papules usually show papillomatosis, hyperkeratosis, and regular acanthosis. Occasionally horn cysts are also present, giving a resemblance to a pedunculated seborrheic keratosis. The epidermis of the filiform, smooth growths shows slight to moderate acanthosis and occasionally mild papillomatosis. The connective tissue stalk is composed of loose collagen fibers and often contains numerous dilated capillaries filled with erythrocytes. Nevus cells are found in as many as 30% of the filiform growths, indicating that some of them represent involuting melanocytic nevi (192). The larger pedunculated growths generally show a flattened epidermis overlying loose collagen fibers and mature fat cells in the center (187). In some instances, the fat is prominent, indicating lipofibroma formation (193).

Pleomorphic Fibroma

Pleomorphic fibroma typically presents as a slow-growing exophytic nodule most commonly on the trunk or extremities and rarely at other sites, such as the face and subungual location, of middle-aged to older adults (194–196).

Histopathology. The epidermis is flattened, overlying a circumscribed nodule in the dermis composed of plump mononucleate and multinucleate, spindle-shaped or stellate cells with atypical nuclei and occasional mitoses, distributed sparsely in a fibrous stroma (Fig. 32-18A, B).

Histogenesis. The tumor cells are variably smooth muscle actin and CD34 positive, suggesting either myofibroblastic or dermal dendritic cell origin (190,194,195,197).

Differential Diagnosis. Dermatofibromas with monster cells are more cellular, and have areas with typical histologic features of dermatofibroma and often acanthotic pigmented epidermis overlying the lesion. In contrast to dermatofibroma, pleomorphic fibroma expresses CD34 (197). Atypical fibroxanthomas present as rapidly growing, highly cellular lesions composed of pleomorphic, spindle-shaped to epithelioid cells with numerous mitotic figures, which may be atypical.

Sclerotic Fibroma (Storiform Collagenoma or Plywood Fibroma)

This is an uncommon lesion occurring as a small, solitary nodule occasionally as large as 3 cm diameter (199). Multiple lesions are a marker for Cowden's disease (200).

Histopathology. The tumors are circumscribed and composed of interwoven fascicles of laminated eosinophilic collagen with prominent clefting (Fig. 32-19A, B). Cellularity is low, with inconspicuous nuclei. Occasional cases have been reported containing pleomorphic cells, suggesting a relationship to pleomorphic fibroma (198). Giant cells may be conspicuous in

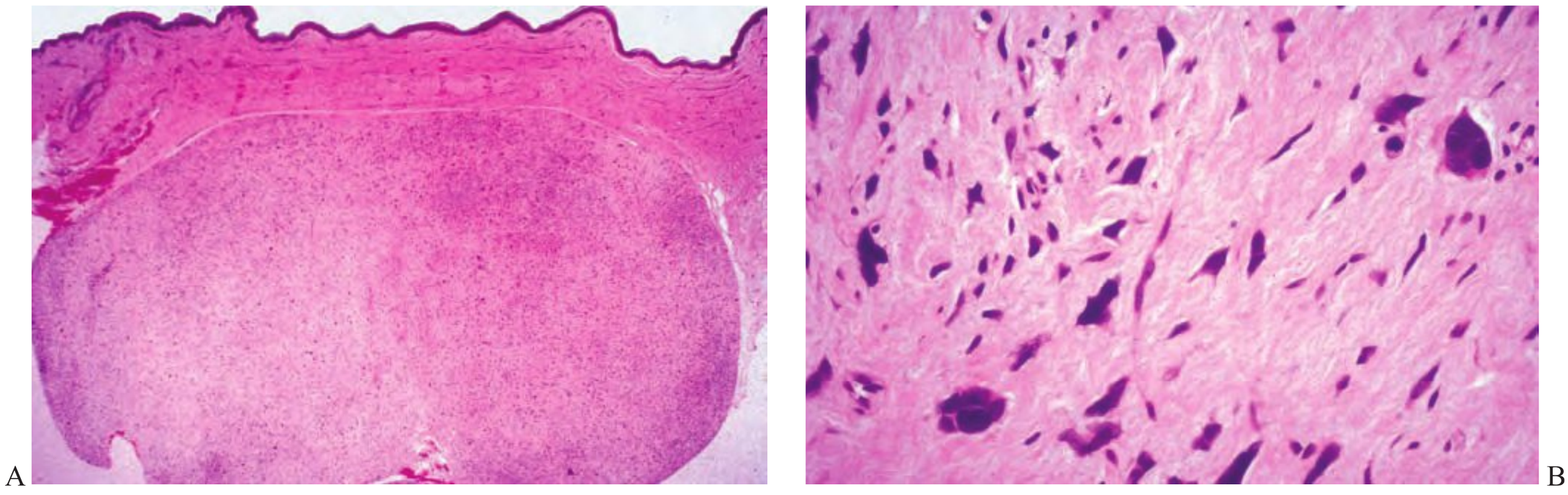


FIGURE 32-18. Pleomorphic fibroma. A: A sharply circumscribed nodule in the dermis and subcutis. B: Spindle cells and giant cells with marked nuclear pleomorphism and hyperchromatism in a pale, hyalinized stroma.

some examples (201). Immunostaining is positive for factor XIIIa, with focal positivity for CD34 (202).

Histogenesis. On the basis of similar fibrotic changes seen in dermatofibroma and in inflammatory lesions, it has been suggested that sclerotic fibromas may have diverse origins (204,205). The demonstration of ongoing collagen synthesis, rare recurrence, and detection of proliferative activity with immunohistochemistry, however, suggests that the lesions are benign fibroblastic neoplasms (202,206,207).

Fibroma of Tendon Sheath

Fibroma of tendon sheath presents as a slow-growing nodule near tendinous structures, most frequently in the hands and wrists. Other less common sites include feet, elbows, and knees. It is uncertain whether fibroma of tendon sheath is a neoplasm or a reactive process. A clonal chromosomal abnormality, t(2;11) (q31-32;q12), has been demonstrated (208). The identical translocation has been described in collagenous fibroma, raising the possibility of a genetic link (209). Treatment is by local excision, with a recurrence rate of 24% (210).

Histopathology. The lesion is characterized by nodules largely composed of interlacing bundles of hyalinized, hypocellular fibrous tissue, with occasional more cellular areas of spindle-shaped, fibroblast-like cells (Fig. 32-20A, B). The more cellular areas may show some degree of pleomorphism, with mitotic figures (211). A characteristic feature is the presence of slit-like vascular channels (212). No foam cells are seen, and multinucleated giant cells are very rare (211).

Histogenesis. The cells of fibroma of tendon sheath express smooth muscle actin. Ultrastructural studies show features of myofibroblastic differentiation (213).

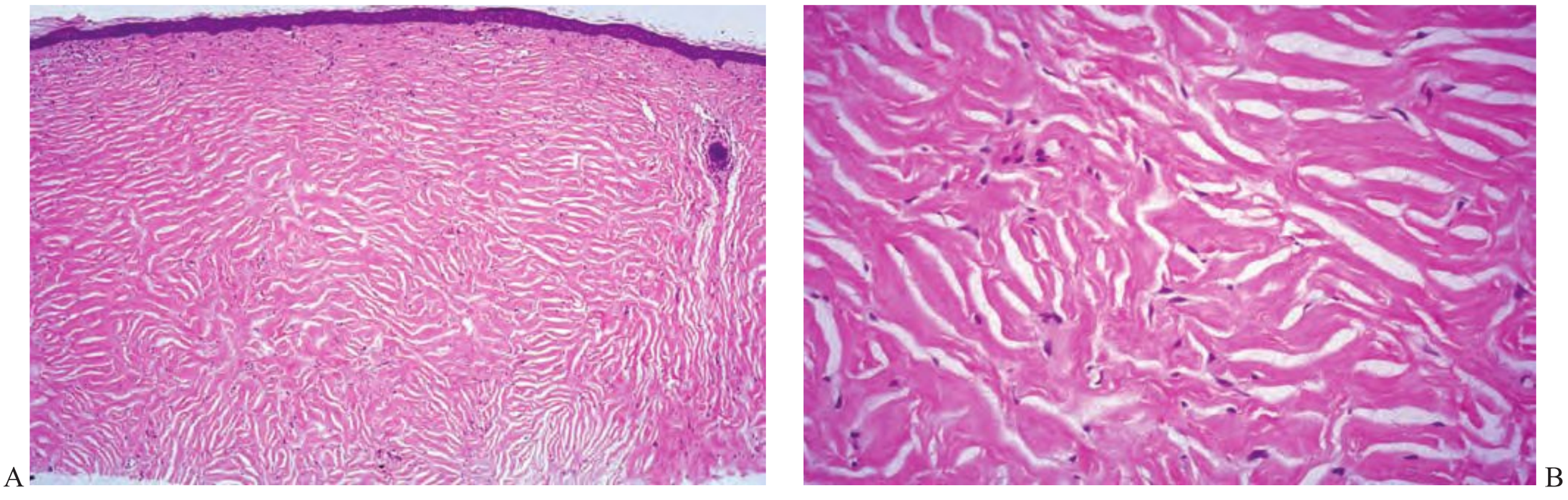


FIGURE 32-19. Sclerotic fibroma. A: A pale, poorly cellular lesion replaces the dermis with some flattening of overlying rete ridges. B: Clefts are prominent between laminated, hyaline, and highly eosinophilic collagen.

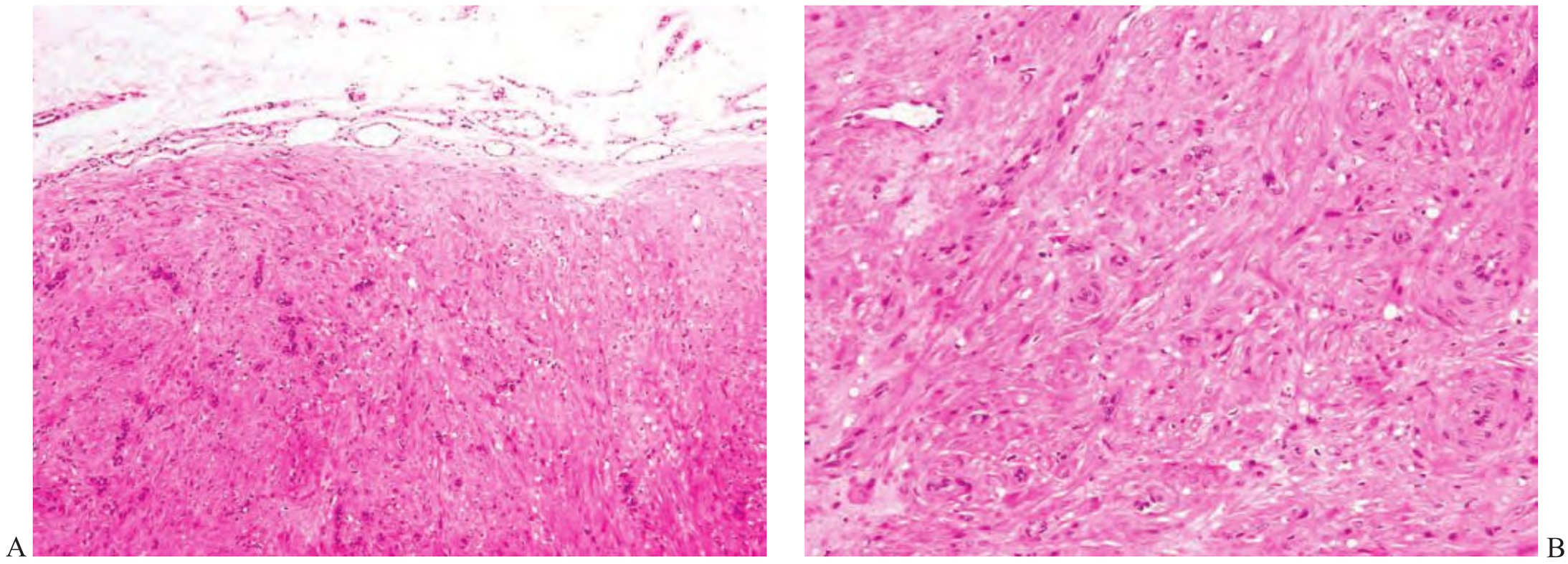


FIGURE 32-20. Fibroma of tendon sheath. A: These lesions are poorly cellular, with ill-defined fascicles of bland, myofibroblast-type cells. B: The spindle cells show a smooth muscle–like appearance and are typically actin positive.

Collagenous Fibroma (Desmoplastic Fibroblastoma)

Collagenous fibroma is a rare benign tumor mainly affecting men. It typically involves subcutis or skeletal muscle, but occasionally it primarily involves the dermis (214–216). Tumors are usually small (1 to 4 cm diameter), but examples up to 20 cm in diameter have been reported (217).

Histopathology. Tumors are circumscribed, ovoid masses that may be lobulated and are composed of dense, paucicellular collagenous tissue with scattered spindle cells without mitotic activity. These show features of myofibroblasts ultrastructurally (218–220). A fascicular growth pattern is absent, and areas reminiscent of a keloid may be seen (Fig. 32-21). Focal myxoid change may be present with inconspicuous blood vessels (217). The tumor cells variably express α-smooth muscle actin and, rarely, keratins AE1/AE3. The cells are negative for desmin, epithelial membrane antigen (EMA), S100 protein, and CD34 (217). Cytogenetic studies performed in a small number of cases have shown a t(2;11) translocation, suggesting a relationship to fibroma of tendon sheath, which shows the same abnormality (221,222).

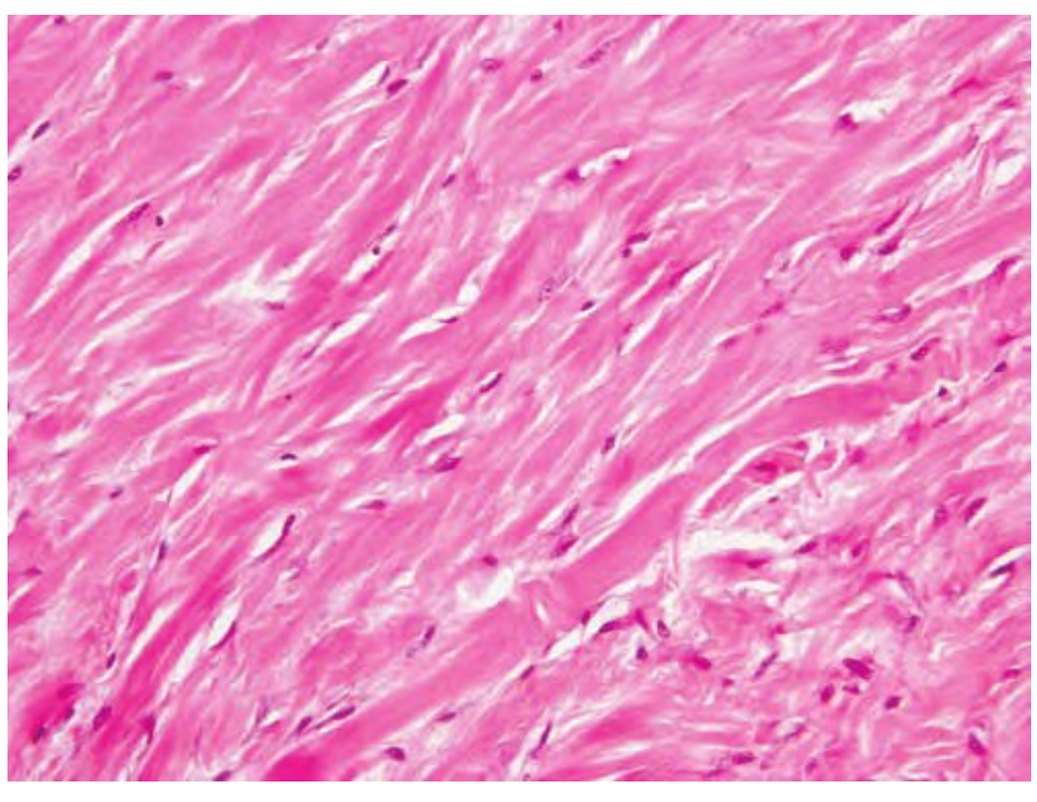


FIGURE 32-21. Desmoplastic fibroblastoma/collagenous fibroma. Thick bands of hyalinized, eosinophilic collagen are present, giving an appearance resembling a keloid.

Nodular Fasciitis

Nodular fasciitis is a rapidly growing benign soft tissue lesion. It usually presents as a solitary, sometimes tender subcutaneous nodule that reaches its ultimate size of 1 to 5 cm within a few weeks. The lesions tend to regress, even if incompletely excised, usually within a few months (223). Although the arm is the most common site, lesions may occur in any subcutaneous area. Nodular fasciitis occurs in all age groups but is more common in young adults, with an equal sex distribution. The cause is unknown. Although trauma does not seem to play a role, the general view is that nodular fasciitis represents a reactive fibroblastic and vascular proliferation.

Histopathology. Nodular fasciitis usually occurs in the subcutis, less often in muscle, and rarely in the dermis. A prominent feature is the infiltrative growth pattern along fibrous septa of the subcutis, resulting in poor demarcation. The nodule consists of immature spindly myofibroblasts and fibroblasts growing haphazardly in vascular, myxoid stroma, presenting a "tissue culture–like" pattern (Fig. 32-22A, B). The vascular component includes well-formed capillaries and slit-like spaces with extravasation of red blood cells. The fibroblasts may show numerous mitoses, which are not atypical. Multinucleate, osteoclast-like giant cells are frequently present. In some instances, degenerate muscle fibers simulate multinucleate

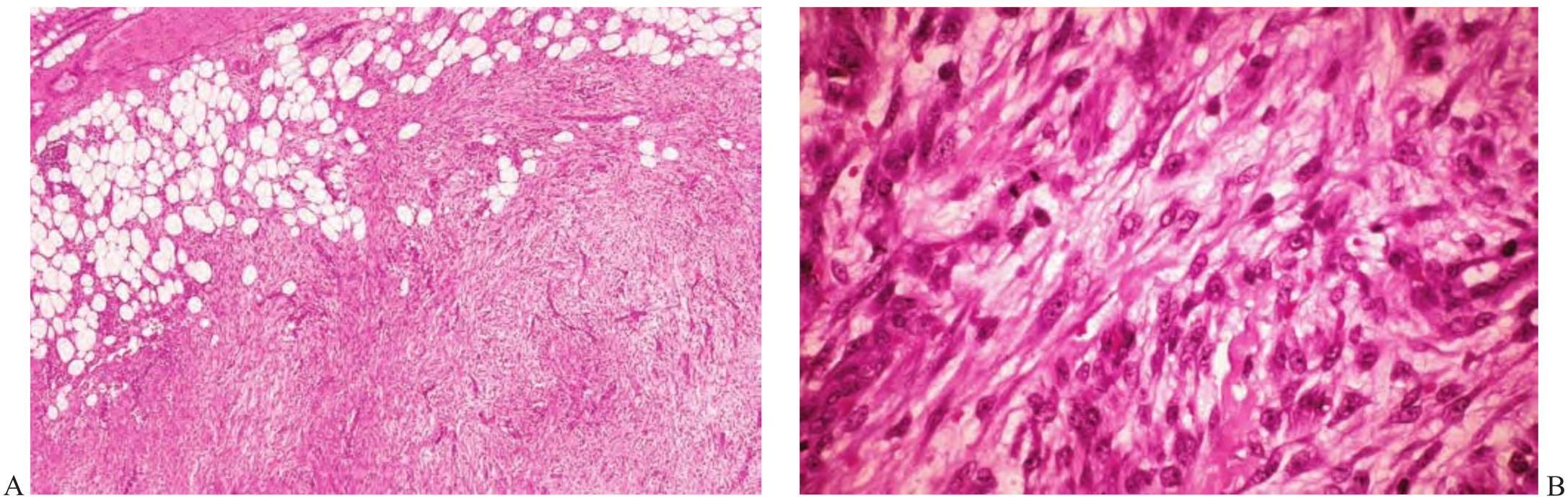


FIGURE 32-22. Nodular fasciitis. A: Plump spindle cells are arranged in varied cellularity in a loosely structured, vascular stroma. B: Plump spindle cells with ovoid, vesicular nuclei and scattered mitoses are embedded in a loosely structured stroma with capillaries and scattered erythrocytes.

giant cells (224). A lymphocytic infiltrate is often present, mainly at the periphery of the nodule (225). In older lesions, the fibroblasts appear more mature, showing a more compact arrangement of spindle cells with increased production of collagen (226).

Dermal fasciitis is a rare variant arising within the dermis, usually occurring in the head and neck region (227–231). *Postoperative/posttraumatic spindle cell nodule* has also been described as the dermal analog of nodular fasciitis (232). Another variant, *intravascular fasciitis* (233), occurs within vessel walls. *Proliferative fasciitis* appears to be related to nodular fasciitis but includes giant cells resembling ganglion cells, similar to those of proliferative myositis. These show abundant, irregularly outlined, basophilic cytoplasm with one or two large vesicular nuclei and a prominent nucleolus (234,235).

Histogenesis. The spindle cells in nodular fasciitis have the ultrastructural features of myofibroblasts (236). As in other myofibroblastic lesions, the cells are immunoreactant for smooth muscle actin and muscle-specific actin but not for desmin (237).

Differential Diagnosis. The presence of numerous large, pleomorphic fibroblasts and the infiltrative type of growth may suggest a malignancy such as sarcoma. In addition to rapid growth and tenderness, however, the combination of fibroblastic and vascular proliferation is the most helpful diagnostic feature of nodular fasciitis. Other findings suggesting the diagnosis are the presence of a mucoid ground substance and an inflammatory infiltrate, especially near the margin of the lesion. Recurrence of a lesion originally diagnosed as nodular fasciitis should spur a careful reappraisal of the clinical and histologic findings (224).

Cranial fasciitis of childhood is considered an unusual variant of nodular fasciitis of uncertain etiology. It occurs in infants and children as a rapidly growing mass in the subcutaneous tissue of the scalp that extends into the underlying cranium. In some cases, the lesion extends through the cranium to involve the dura (238). No recurrence has been reported after excision of the mass with resection or curettage of the underlying bone (238,239). The histologic features closely resemble those of nodular fasciitis. An origin in one of the deep fascial layers of the scalp appears likely (238). Immunohistochemical studies and electron microscopy of the spindle cells demonstrate features of myofibroblasts (238,240).

Ischemic Fasciitis

This condition is also known as atypical decubital fibroplasia and occurs at sites of longstanding pressure, typically in the elderly (241,242). The resultant ischemia is believed to induce formation of a reactive fibroblastic proliferation that may mimic nodular fasciitis or even a sarcoma. The process extends through dermis and into subcutis and underlying tissue, often abutting bony prominences.

Histopathology. Reactive fibroblastic tissue is present associated with foci of necrosis and repair. Atypical reactive fibroblasts are seen with a proliferation of fine vessels, and ulceration may be present (Fig. 32-23A, B) (242).

Myofibroma/Myofibromatosis

Myofibroma is a benign neoplasm that can present as solitary or multiple lesions. The majority of tumors are solitary, measuring between 0.5 and 7.0 cm in size. The nodules are most commonly confined to the dermis, subcutis, and skeletal muscle of the head, neck, and trunk, but any site may be affected. In *infantile myofibromatosis*, multiple tumors may also develop in bones and viscera in addition to skin involvement, causing death in rare cases (243–245). Death may occur in the first few months of life, usually from cardiopulmonary or gastrointestinal complications, but in survivors and in those with superficial

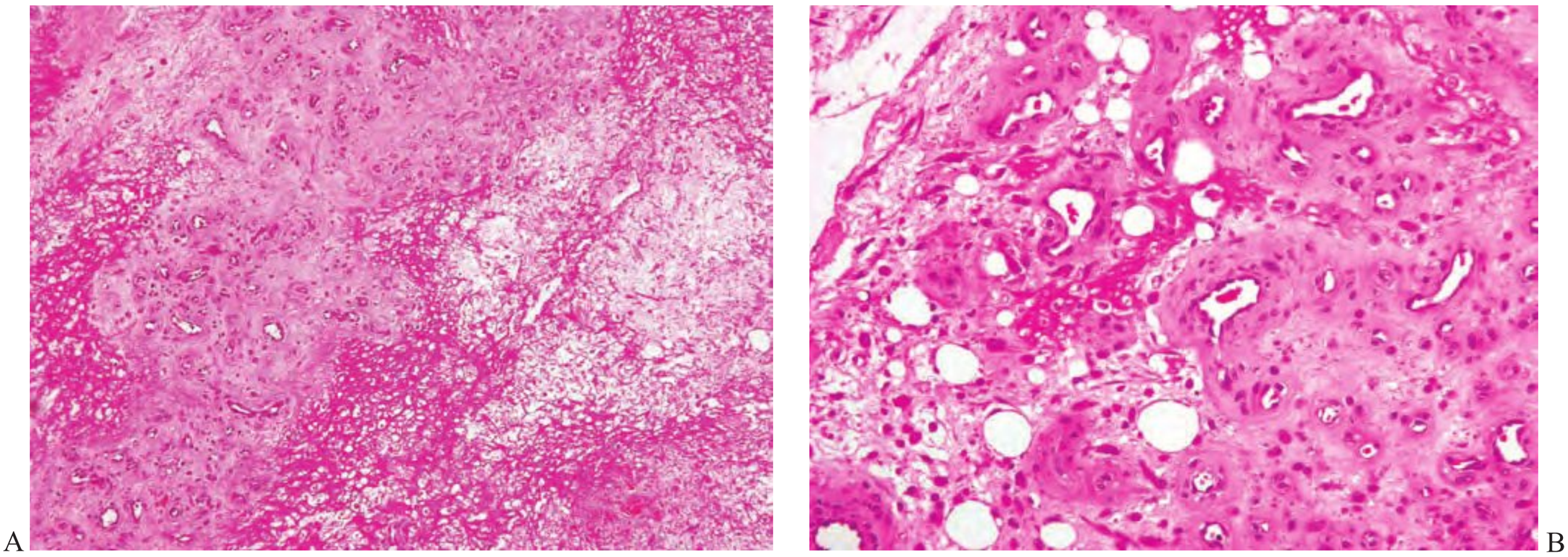


FIGURE 32-23. Ischemic fasciitis. A: Fibrin deposition and granulation tissue are present in this lesion excised from the greater trochanter of an elderly, bed-ridden man. B: Dilated vessels and reactive stromal cells are seen at high power. The degree of atypia may raise the possibility of a sarcoma at times.

myofibromatosis, spontaneous involution of the lesions usually takes place, often within the first year of life. Involution may be mediated by apoptosis or overgrowth of its own vascular supply (246,247). In adults, the tumors are solitary, superficial, and show no tendency to regress (248,249). Familial cases of infantile myofibromatosis are believed to be inherited in an autosomal dominant manner (250).

Histopathology: Most tumors have a characteristic biphasic growth pattern. The lesions consist of nodular dermal aggregates of plump spindle cells resembling smooth muscle cells with pale eosinophilic cytoplasm arranged in short fascicles, sometimes with areas of hyalinization (251) (Fig. 32-24A, B) surrounding a central, hemangiopericytoma-like component where less-differentiated rounded cells with scant cytoplasm

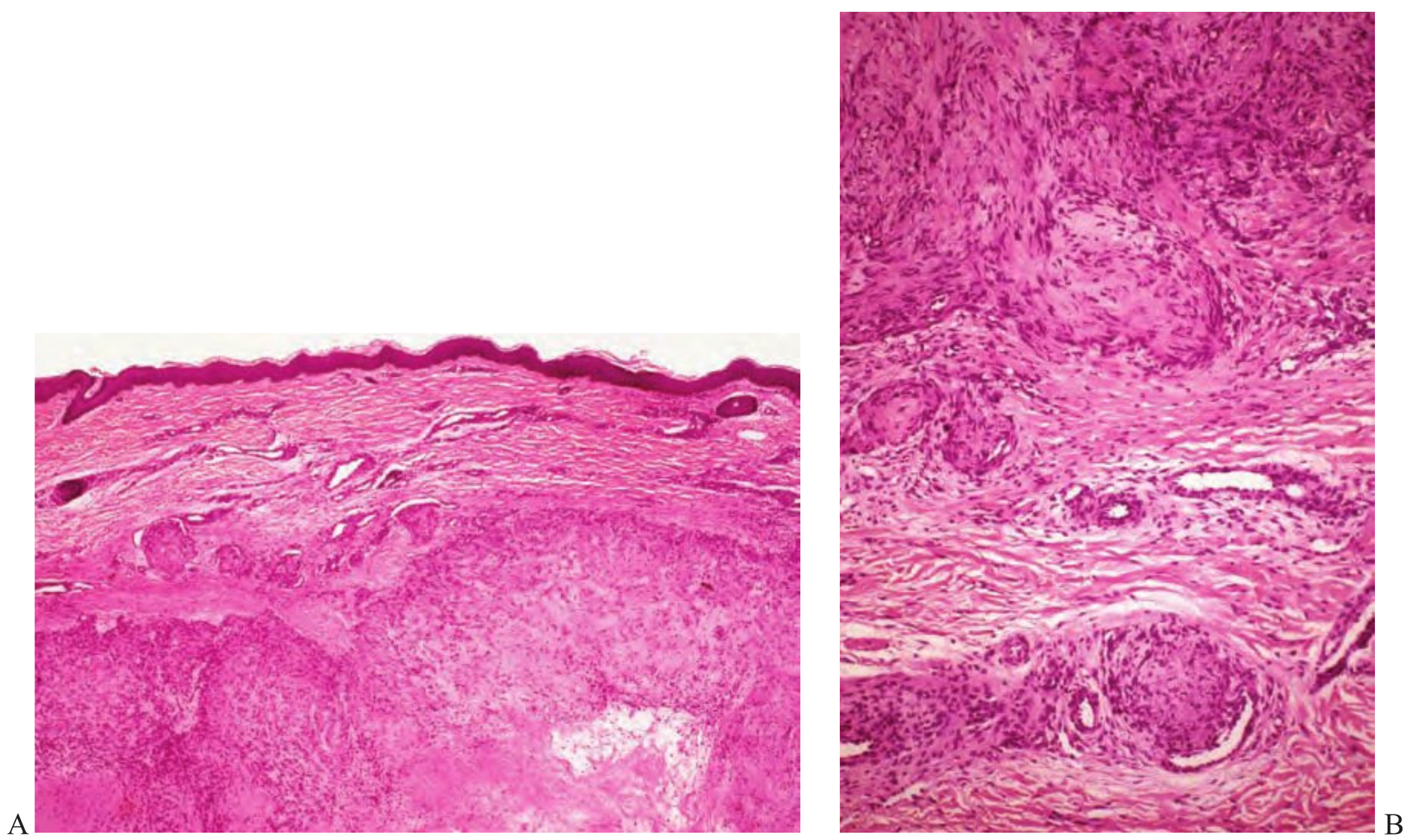


FIGURE 32-24. Myofibroma. A: Circumscribed dermal nodules of varied size, with hyalinization in the center of the largest nodule. B: The nodules consist of fascicles of plump spindle cells with pale eosinophilic cytoplasm, some of which indent the walls of blood vessels.

are arranged around irregularly shaped, thin-walled blood vessels. There is no atypia or pleomorphism. The stroma may appear mucoid in the less cellular areas (252). Foci of necrosis and calcification may be present centrally. In some cases, the distribution of the two components is reversed, that is, the hemangiopericytoma-like areas are situated peripherally. Other lesions may show a predominance of myoid or hemangiopericytomatous elements.

Histogenesis. The spindle cells are immunoreactive for actin but are negative for desmin (248,253,254). The cells are believed to be myopericytic in origin (249,255).

Fibrous Hamartoma of Infancy

Fibrous hamartoma of infancy usually occurs as one or, rarely, two subcutaneous nodules that may be present at birth or develop during the first 2 years of life (256–259). After an initial period of growth, there is no further increase in the size of the nodule. There is a predilection for boys, with male-to-female ratio of up to 2.6:1 (259,260). These lesions present in a wide range of locations, most commonly the axilla, upper arm, upper trunk, inguinal region, and external genitalia (259). Complete local excision is usually curative, and the recurrence rate is low (261). A case with t(2;3) (q31;q21) chromosomal translocation was described (262).

Histopathology. The nodule consists of three distinct tissue components: fibrocollagenous trabeculae composed of bland spindle cells, whorls of immature-appearing spindle mesenchymal cells with scant cytoplasm cells in a mucoid matrix, and mature fat (Fig. 32-25A, B) (256,257). The fibrous component varies in cellularity, pattern, and amount and may resemble granulation tissue, deep fibrous histiocytoma, or fibromatosis in some areas (260). The spindle cells in the fibrous trabeculae express actin (259).

Juvenile Hyaline Fibromatosis

This is a rare, autosomal recessively inherited disorder. It starts in early infancy with flexural contractures and innumerable skin papules and nodules that gradually increase in size, with osteolytic bone lesions and gingival hyperplasia. Wart-like papillomatous lesions may occur in the perianal region. The largest nodules are usually seen on the scalp and around the neck. Juvenile hyaline fibromatosis has been reported in association with skull and encephalic abnormalities and in the hand of an adult (263). *Infantile systemic hyalinosis* is believed to be a severe form of the disease, with widespread visceral involvement and an invariably fatal outcome (264).

Histopathology. The nodules are composed of spindle-shaped or round stromal cells and homogeneous, amorphous eosinophilic ground substance to varying degrees. Small, newly developed tumors are more cellular, whereas larger, older tumors contain more ground substance (265,266). The spindle-shaped cells tend to be arranged in interlacing cords, and the ground substance is periodic acid-Schiff positive and diastase resistant. In paraffin-embedded, formalin-fixed material, empty spaces are seen around the nuclei of stromal cells, giving these cells a chondroid appearance (267,268).

Histogenesis. The stromal cells have the ultrastructural features of fibroblasts (268–270). The perinuclear vacuoles are intracytoplasmic, membrane-bound vesicles filled with fibrillogranular material identical in appearance to the ground substance (268,271).

Infantile Digital Fibromatosis (Inclusion Body Fibromatosis)

Infantile digital fibromatosis occurs as single or multiple nodules on the fingers or toes, excluding the great toe and the thumb. Lesions may be present at birth, but they usually

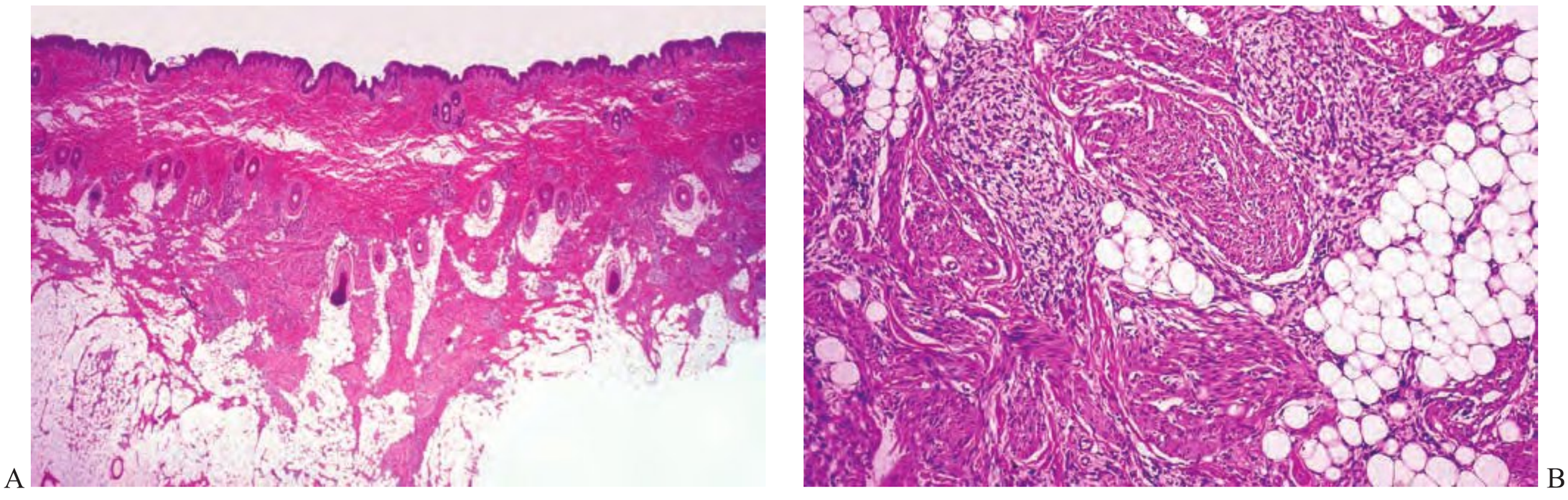


FIGURE 32-25. Fibrous hamartoma of infancy. A: Trabeculae of varied thickness intersect lobules of fat in the subcutis. B: The trabeculae are composed of immature spindle cells arranged in loosely structured myxoid areas and more densely collagenous tissue.

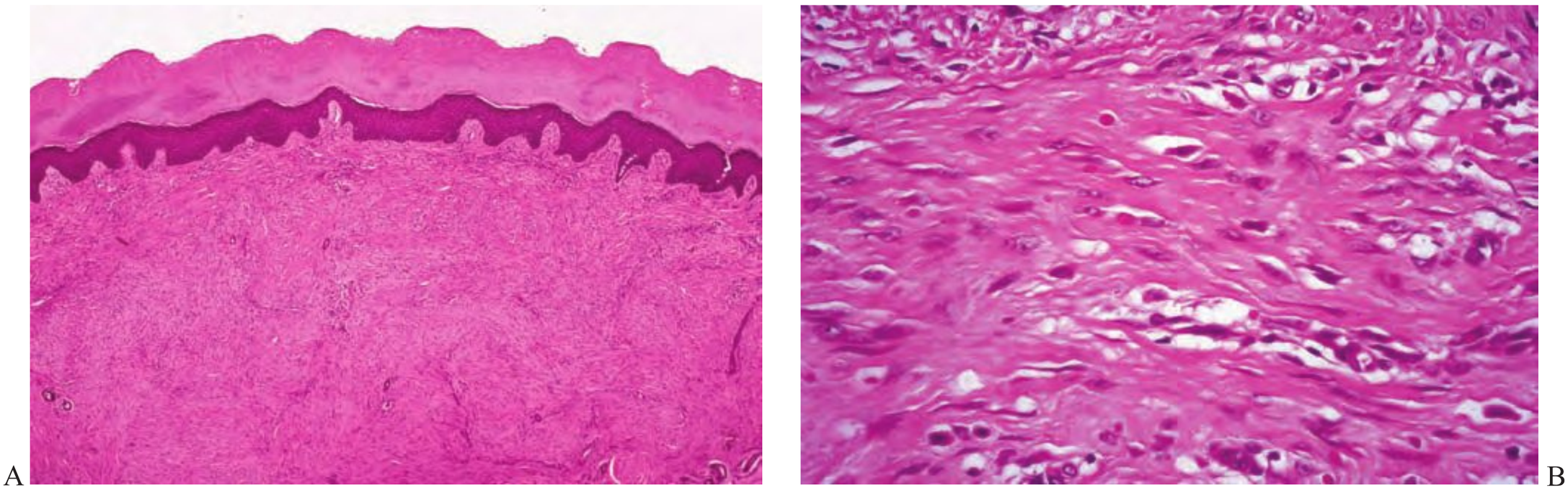


FIGURE 32-26. Infantile digital fibromatosis. A: Intersecting fascicles extend from the papillary dermis into the subcutis. B: Fascicles of spindle cells, some of which contain small round, eosinophilic, cytoplasmic inclusions.

appear during the first year of life and occasionally later in childhood. The nodules rarely exceed 2 cm in diameter and involute spontaneously. In about 75% of the cases, recurrences are observed during early childhood (272).

Histopathology. The dermis is infiltrated by uniform spindle cells and collagen bundles arranged in interlacing fascicles, extending from just below the epidermis into the subcutis (Fig. 32-26A). A characteristic feature is the presence of eosinophilic cytoplasmic inclusions 3 to 10 μm in diameter resembling erythrocytes, often indenting the nucleus (Fig. 32-26B). These inclusions stain deep red with Masson trichrome and purple with phosphotungstic acid–hematoxylin. They express vimentin and actin (203).

Histogenesis. The lesional cells are vimentin and muscle actin positive. Ultrastructurally, the spindle cells show the features of myofibroblasts and contain actin filaments, which extend into and are continuous with the granular intracytoplasmic inclusions.

Elastofibroma Dorsi (Elastofibroma)

This condition appears to be degenerative and occurs most often in older women beneath the scapula. Lesions form a poorly circumscribed connective tissue mass, which may be as large as 15 cm in diameter. Rare cases have been recorded away from the scapula, and some lesions are multiple (273–275). The behavior is benign, with recurrence exceptional.

Histopathology. Irregular zones of poorly cellular collagen extend into the soft tissues with prominent, abnormally formed elastin bundles (Fig. 32-27). Elastin stains show these to have a globular and beaded morphology. CD34 staining is present in some of the spindle cells in the tumors that are negative for S100 and actin (276,277).

Histogenesis. Repeated mild trauma has been suggested as an etiologic factor leading to elastin degeneration. Abnormal elastin production is also a possible cause, with evidence of various chromosomal changes in lesions in a few patients and some genetic predisposition (278,279).

Differential Diagnosis. Once the presence of abnormal elastin is appreciated, the diagnosis is straightforward. Fibromatoses are more-cellular lesions, and nuchal-type fibromas, although occurring in a similar site, typically occur in males and show more dense collagen with only fine elastin bands and sometimes a proliferation of fine nerve twigs.

Angiofibromas

The histologic features of angiofibroma occur in a number of different clinical contexts. Multiple lesions on the face may occur in association with several clinical syndromes, including tuberous sclerosis and multiple endocrine neoplasia type 1 (280).

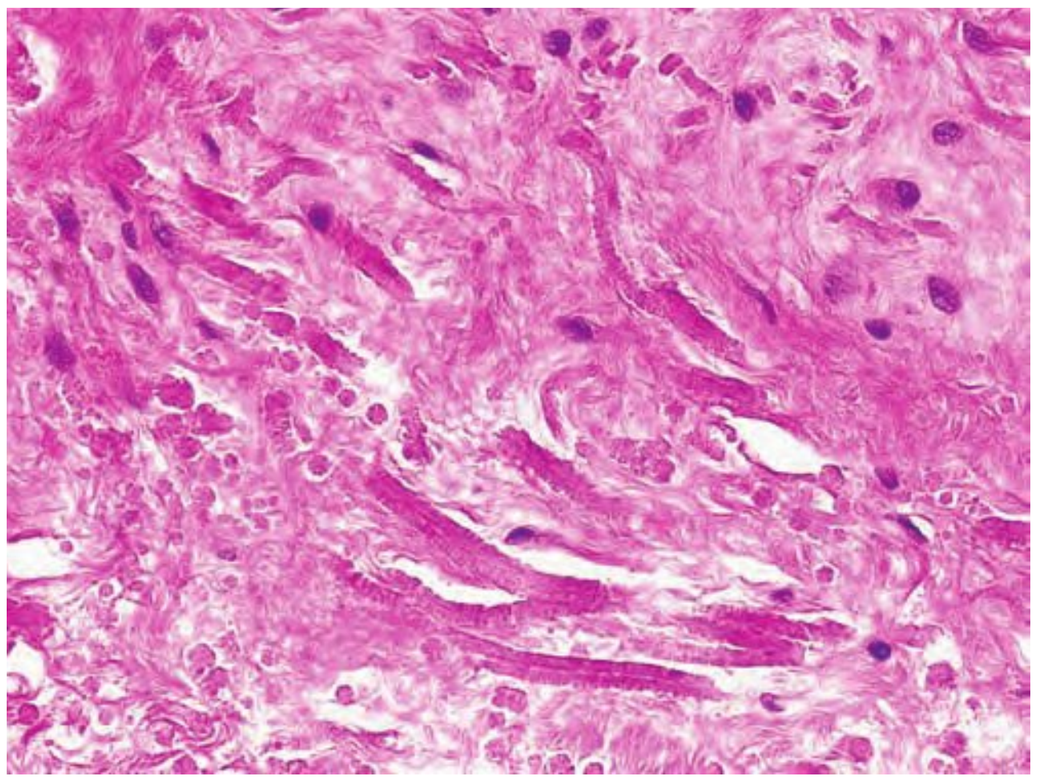


FIGURE 32-27. Elastofibroma. Coarse elastin fibers are prominent in the lesion, with small globular excrescences. (Courtesy of Dr. E.-C Jung, University of California, San Francisco, California.)

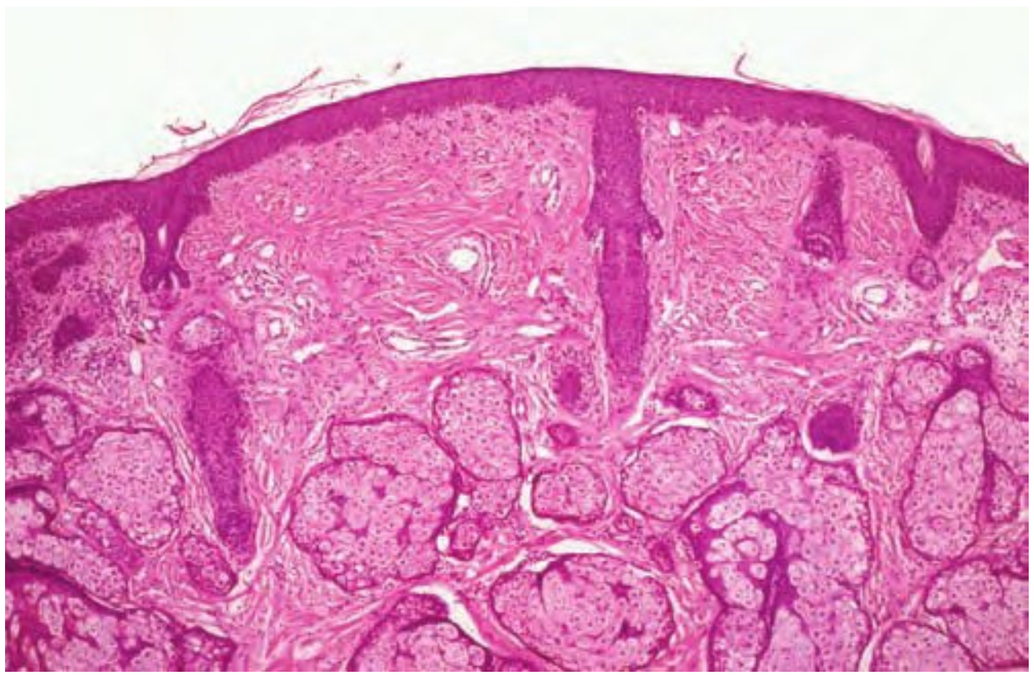


FIGURE 32-28. Angiofibroma (fibrous papule of the face). The epidermis is elevated over a zone of vascular fibroplasia in the superficial dermis.

Fibrous Papule of the Face

These common lesions typically occur on the nose or adjacent skin of adults. They present as small, firm, dome-shaped nodules up to 5 mm in diameter. Although originally believed to represent involuting melanocytic nevi (281,282), they are now considered to be a discrete entity (283).

Histopathology. The epidermis is raised, overlying a localized area of fibroplasia and fine vascular proliferation in the upper dermis (Fig. 32-28). There are scattered associated enlarged triangulate or stellate cells, which may be multinucleated (282,284). Atypia may be evident in these cells, with nuclear hyperchromasia, enlargement, and pleomorphism (Fig. 32-29A, B). In some cases, increased melanocytes are seen at the dermoepidermal junction. *Clear cell fibrous papule* appears to be a variant in which the cells show cytoplasmic clearing that is not due to glycogen accumulation (285,286).

Histogenesis. Electron microscopic and immunohistochemical studies indicate that the stromal cells are of fibroblastic or dermal dendrocytic origin rather than melanocytic (287,288). They express factor XIIIa but not S100 protein (289–293).

Cellular angiofibroma appears to be a separate entity that occurs almost exclusively on the vulva. It is a condition of superficial soft tissue origin rather than dermal location and may be related to angiomyofibroblastoma (294). Similarly, *giant cell angiofibroma* appears to be unrelated to dermal angiofibromas, showing features more in common with solitary fibrous tumor (295).

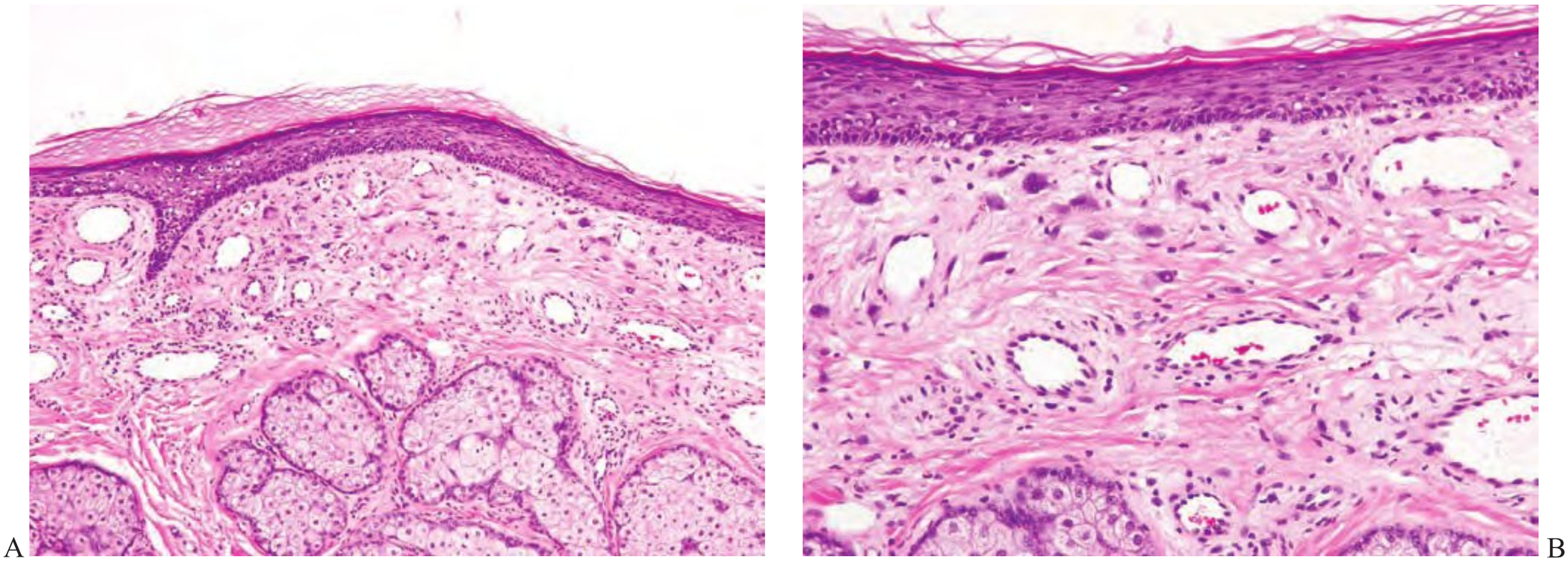
Pearly Penile Papules

These small (1 to 3 mm in diameter), persistent white papules occur mainly on the coronal margin and sulcus of the penis and rarely on the glans in groups or rows in about 10% of young men. They do not appear to be related to human papillomavirus infection (296).

Histopathology. The features are typical of an angiofibroma, without associated hair follicles (297).

Tuberous Sclerosis

Tuberous sclerosis is a rare genetic disorder that may be inherited in an autosomal dominant pattern or present as a new spontaneous mutation (298,299). A variety of cutaneous lesions occur with systemic defects in wide-ranging body systems, including the brain, kidney, eye, and lung (300). The majority of patients develop multiple facial angiofibromas (previously misleadingly termed adenoma sebaceum). These tumors consist of numerous small, red papules in symmetric distribution over the nose, cheeks, and chin. Soft fibromas may also develop on the face and the scalp, with skin tags and subungual and periungual fibromas a frequent finding. Shagreen patches are usually found in the lumbosacral region and consist



A B

FIGURE 32-29. Angiofibroma. This angiofibroma shows prominent atypical stromal cells—a not uncommon finding of no sinister significance.

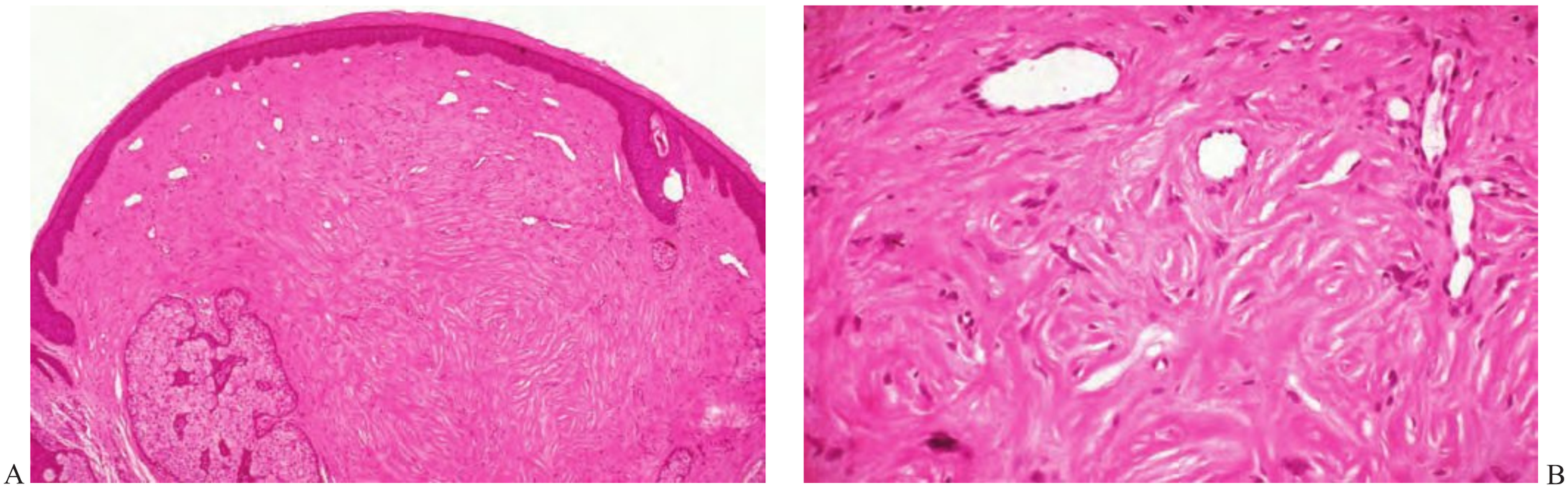


FIGURE 32-30. Angiofibroma arising in tuberous sclerosis. A: The epidermis is raised in a dome-shaped pattern overlying a zone of compact fibroplasia with prominent blood vessels in the upper half. B: The typical features of an angiofibroma are seen with sclerotic, hyalinized stroma, with scattered spindle and stellate cells and telangiectatic blood vessels.

of slightly raised, yellowish, leathery areas of skin. Various hypopigmented skin lesions are present in more than half of patients with tuberous sclerosis; significantly, they may be present at birth or appear at an early age and are often the earliest indication of tuberous sclerosis (301).

Genetic studies show linkage to chromosome 9q34 (TSC1) or to chromosome 16p31 (TSC 2) in many patients with TSC (298,299,302–304). Two thirds of cases are sporadic and are assumed to result from new mutations, many of which are in TSC 2 (304). TSC 2 patients tend to have more severe disease with greater numbers of hypopigmented lesions (298).

Systemic Lesions. Multiple tumors are commonly found in the brain (gliomas, often calcified) (305), retina (gliomas) (306), heart (rhabdomyomas) (307), and kidneys (angiomyolipomas) (308).

Histopathology. The angiofibromas show a fine vascular proliferation in the dermis with associated fibrosis and occasional reactive stromal cells (309). Elastic tissue is absent in these lesions, and compression of adnexae may be seen (Fig. 32-30A, B).

The soft fibromas on the face and scalp show markedly sclerotic collagen arranged in thick, concentric layers around atrophic pilosebaceous follicles. In contrast to the angiofibromas, dilated capillaries are usually absent. Giant angiofibroma (310) and a cluster growth of large nodules (311) have also been reported.

The ungual fibromas show fibrosis, occasionally with capillary dilation. The shagreen patches have the histologic features of connective tissue nevi, with either a dense, sclerotic mass of broad collagen bundles in the dermis, mimicking morphea, or normal collagen bundles interwoven throughout the dermis. The elastic tissue in some instances shows fragmentation and clumping (309) but is generally reduced in amount (312).

The hypopigmented areas show a normal number of melanocytes, with decreased pigmentation. On electron microscopy, the melanosomes within the melanocytes and keratinocytes are smaller and show reduced melanization (301,312).

Differential Diagnosis. The angiofibromas seen in tuberous sclerosis are often histologically identical to solitary angiofibromas (fibrous papules of the face). The shagreen patches of tuberous sclerosis differ from other connective tissue nevi by the reduced amount of elastin present.

Acral Fibrokeratoma (Acquired Digital Fibrokeratoma, Periungual Fibroma)

Acral fibrokeratoma is considered by some authors to fall within the spectrum of angiofibromatous proliferations, although the vascular component may be limited. Lesions normally present as solitary firm, hyperkeratotic projections from the finger or toe but are occasionally sited on the palm or sole (312–314). Some appear to originate from the nail bed (315,316), and there are isolated examples of large size (314,317). Tumors arise in adults, with rare cases of familial multiple acral mucinous fibrokeratoma and multiple acral fibromas associated with familial retinoblastoma, which may represent cutaneous markers of tumor suppressor gene germline mutation (318,319). Some lesions are associated with tuberous sclerosis.

Histopathology. There is hyperkeratosis and acanthosis with broad, often branching rete ridges. In the core are prominent interwoven collagen bundles mostly vertically oriented (Fig. 32-31). Elastic fibers are present but are normally thin and sparse. Many tumors show abundant fine vessels. Recently, a *cellular variant* has been described that shows features similar to DFSP, including CD34 positivity (320). Some authors consider that this may in fact represent a form of superficial acral fibromyxoma (321).

Differential Diagnosis. Rudimentary supernumerary digits may appear similar clinically and histologically. However,



FIGURE 32-31. Digital fibrokeratoma. A polypoid lesion with acanthotic epidermis overlying dense bundles of collagen in the dermis.

rudimentary polydactyly almost always occurs at the base of the fifth finger, is present from birth, and is often bilateral. Histologically, numerous nerve bundles are present, especially at the base of the lesions.

Nuchal-Type Fibroma (Nuchal Fibroma)

Nuchal fibroma is an uncommon lesion typically arising on the posterior neck of adult men (322,323). Similar changes have also been seen at a number of nonnuchal sites, leading to the inclusion of the qualifier "type" into the name. A large proportion of patients have diabetes mellitus, and consideration should be given to the possibility of Gardner's syndrome (see discussion below) (322). Lesions occasionally recur but do not metastasize.

Histopathology. In the dermis and subcutis there is a poorly circumscribed mass containing haphazardly arranged collagen bundles with sparse, bland, spindle-shaped cells (Fig. 32-32). There is frequently entrapment of fat and a proliferation of fine nerves resembling a traumatic neuroma. Inflammation is not a feature, and elastin fibers may be reduced in number (324).

Histogenesis. A fibroblastic origin is proposed, with immunohistochemical staining showing CD34 positivity in the spindle cells in some cases (324).

Differential Diagnosis. *Gardner's fibroma* is considered to be similar, if not identical, histologically, but it occurs in the context of Gardner's syndrome (322,324–326). It may be the presenting feature of that syndrome, which represents a form of familial adenomatous polyposis coli with osteomas and epidermoid cysts (325). Some authors recognize fibromatous proliferations in patients with Gardner's syndrome that have a more diverse appearance than typical nuchal fibroma (326,327). Recurrence of Gardner's fibromas as desmoid tumors has been recorded (325). Elastin fibers are decreased in number, in contrast to elastofibroma (324).

Superficial Acral Fibromyxoma

This uncommon tumor was first described in a series of 37 cases in 2001 (328). The lesions are almost always sited on the toes or fingers, often close to the nail, and average about 2 cm in size (328–331). A few have been reported on the palm (328), and lesions may be of long duration at presentation. A broad range of ages may be affected, but many patients are young adults. The course is benign, with recurrence uncommon.

Histopathology. Tumors are sited in the dermis or subcutis and show a partly circumscribed proliferation of spindle to stellate cells in loose fascicles. There may be mild nuclear atypia and occasional multinucleated stromal cells, but mitoses are sparse. A myxocollagenous matrix bears fine vessels, with mast cells often conspicuous (Fig. 32-33A, B).

Histogenesis. The majority of tumors stain prominently with CD34 and frequently with epithelial membrane antigen and CD99 (328,330). S100, actin, desmin, keratins, and HMB-45 are typically negative.

Differential Diagnosis. The appearances have features in common with a variety of other connective tissue lesions, especially those with a tendency to become myxoid. However, correlating the clinical setting, histology, and immunostaining pattern should lead to the correct diagnosis.

Angiomyofibroblastoma of the Vulva

Angiomyofibroblastoma is a benign tumor that occurs mainly in the vulvovaginal region of middle-aged premenopausal women (332) but has also been rarely described in the inguinoscrotal region of males. It presents as a circumscribed tumor 0.5 to 12 cm in size and is often mistaken clinically for a Bartholin's gland cyst. The tumors do not recur when treated with local excision (333–335).

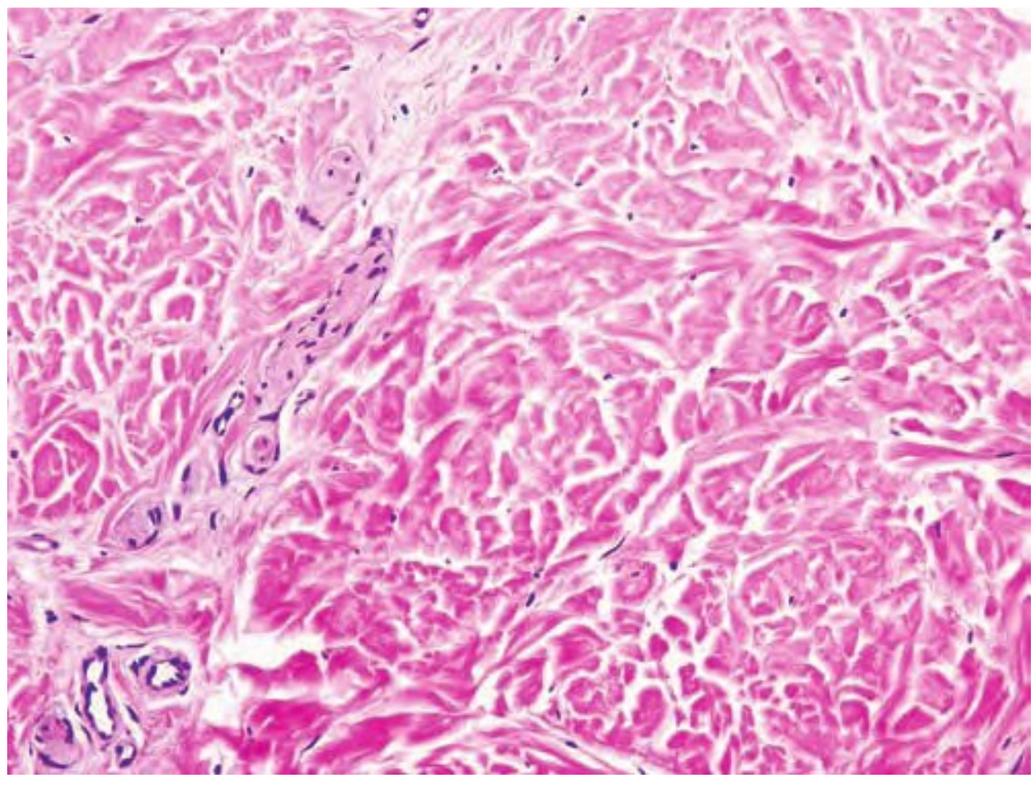


FIGURE 32-32. Nuchal-type fibroma. The tumor is hyalinized and poorly cellular. Note the small nerve twigs within the lesion.

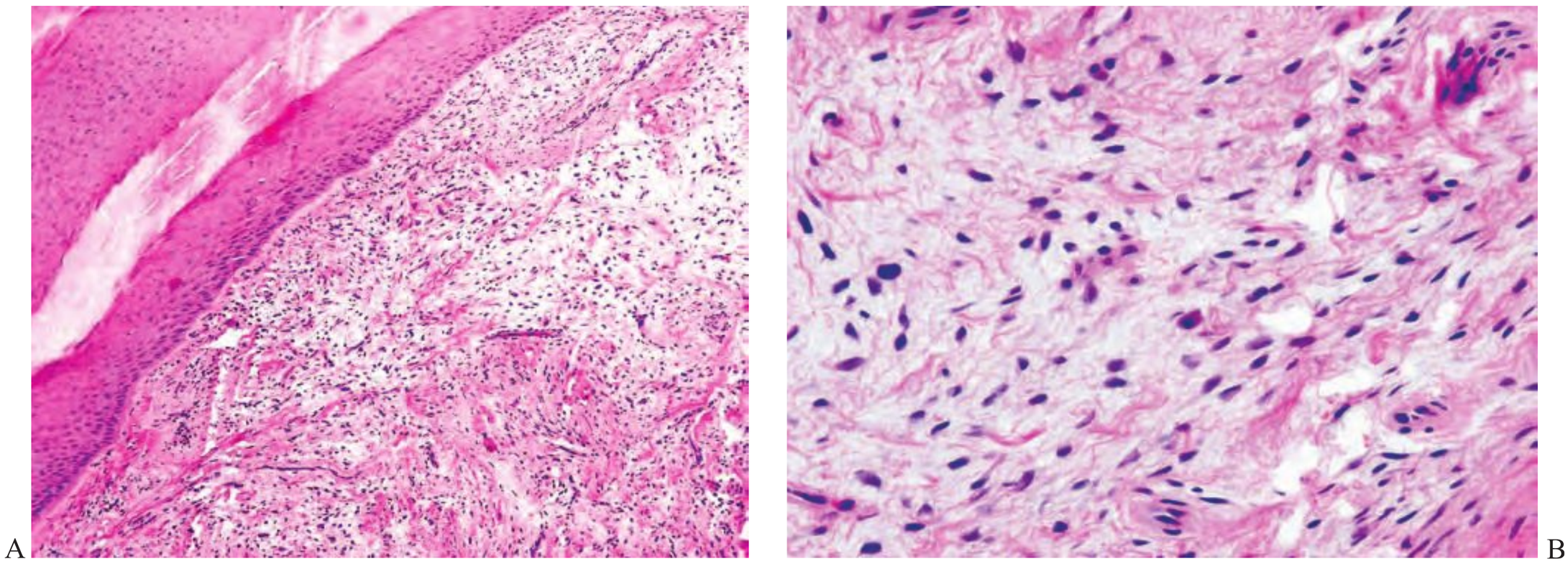


FIGURE 32-33. Superficial acral fibromyxoma. A: This lesion was from under the big toe nail, seen in the upper left of the photograph, a common site of origin. B: Myxoid stroma is present with nondescript, bland, spindle-shaped cells. These were CD34 and epithelial membrane antigen positive on immunohistochemistry.

Histopathology. Angiomyofibroblastomas are well-circumscribed tumors composed of hypercellular and hypocellular areas. There are plump epithelioid or spindle cells with moderate amounts of eosinophilic cytoplasm arranged singly, in clusters, or forming linear arrays around numerous small to medium-sized dilated capillaries within an edematous stroma. Some of the cells may have eccentric nuclei, imparting a plasmacytoid appearance. Multinucleated cells are not uncommon. There is minimal cytologic atypia, and mitoses are generally difficult to find (333–337). An adipose tissue component is present in some cases (338).

Histogenesis. The tumor cells of angiomyofibroblastoma are desmin positive and actin negative in most cases. Occasional cases are smooth muscle actin positive (333–337). The cells also express estrogen and progesterone receptors (33,338,339).

Differential Diagnosis. In contrast to angiomyofibroblastoma, aggressive angiomyxoma has an infiltrating growth pattern, prominent hyalinized vessels, and mucin within the stroma. The cells of aggressive angiomyxoma are actin positive and desmin negative.

Angiofibroblastoma of the Skin

Angiofibroblastoma of the skin is a benign neoplasm that occurs as small, solitary dermal nodules on the extremities of adults (340,341).

Histopathology. There are dome-shaped, circumscribed nodules in the upper dermis composed of stellate and spindle fibroblasts embedded in a fibromyxoid and fibrous matrix. There are focal collections of stellate cells arranged in a whorled pattern with numerous capillary-sized vessels present throughout the lesion. Mitotic figures are not a feature.

Histogenesis. Immunohistochemical and ultrastructural studies of the tumor cells support fibroblastic differentiation. Both stellate and spindle cells show focal positivity for muscle-specific actin but are negative for smooth muscle actin. Factor XIIIa is present only in associated dendritic cells (341).

Differential Diagnosis. Angiofibroblastoma is more cellular than sclerotic fibroma and does not express CD34. Giant cell fibroblastomas develop in infants and consist of cells that express CD34, pseudovascular spaces, and large, multinucleated cells. Myxoid neurofibromas contain S100-positive Schwann cells with wavy nuclei. Angiomyofibroblastomas present in the vulva and are characterized by desmin-positive cells clustered around vessels within edematous stroma. Although perineuriomas also possess spindle cells arranged in a whorled pattern, they are generally EMA positive (341).

Fibromatosis Colli

Fibromatosis colli presents 2 to 4 weeks after birth as a hard, immobile, fusiform swelling in the mid or lower portions of the sternocleidomastoid muscle, causing the head to tilt toward the side of the affected muscle (342). There is a high associated incidence of preceding breech and forceps delivery. However, the lesion develops *in utero* and not as a consequence of birth trauma as was once believed (343). Some cases are associated with congenital musculoskeletal abnormalities, including congenital dysplasia of the hip and rib cage anomalies (344–346). Most cases respond well to conservative treatment (344). Less than 20% require surgical therapy (342). Fine-needle-aspiration cytology has been reported to be a reliable method of diagnosing these tumors (347,348).

Histopathology. There are proliferating fibroblasts of varying cellularity in a collagenous stroma partially replacing the skeletal muscle. There is little or no pleomorphism and a lack of mitotic activity. Atrophic and degenerate skeletal muscle fibers are entrapped with the lesion.

Intermediate Biological Potential (Locally Aggressive)

Desmoid-Type Fibromatosis (Aggressive Fibromatosis, Desmoid Tumor, Musculoaponeurotic Fibromatosis)

Desmoid-type fibromatoses are benign clonal fibroblastic proliferations that arise as firm, nontender masses from muscular aponeuroses and tend to invade the muscle. This infiltrative growth pattern predisposes to local invasiveness and recurrence, but the lesions do not metastasize. Their rate of growth is slow, but the lesions may attain considerable size, as large as 25 cm in diameter (349). Although usually solitary, they may be multiple (350). Desmoid fibromatoses may occur in children, but they are seen mainly in young adults, particularly in women, the most common type arising from the rectus abdominis muscle after pregnancy. The lesions also occur as extraabdominal masses in older adults in equal gender distribution (351).

The association of desmoid fibromatoses with familial adenomatous polyposis and Gardner's syndrome is well documented. The prevalence in familial adenomatous polyposis is between 10% and 25% (352). Adenomatous polyposis coli gene mutation occurs in desmoid-type fibromatosis in patients with familial polyposis and less commonly in sporadic lesions (352–354). Trisomies for chromosomes 8 and 20 also have been demonstrated in some cell subpopulations (355,356).

Histopathology. Desmoid fibromatoses are composed of poorly circumscribed bundles of uniform spindle cells surrounded by abundant collagen with extensive hyalinization, whereas some cases have abundant mucoid matrix. The nuclei are small, regular, and pale staining, with a variable mitotic rate. The lesions frequently infiltrate adjacent striated muscle, entrapping atrophic muscle fibers (Fig. 32-34A, B) (349).

Histogenesis. Ultrastructurally, the spindle cells of desmoid fibromatosis show features of fibroblasts or myofibroblasts (350,357,358). Immunostaining shows variable smooth muscle actin and muscle-specific actin positivity (359).

Palmar Fibromatosis (Dupuytren's Contracture)

Palmar fibromatosis presents as a benign, slow-growing nodule or cordlike thickening on the volar surface of the hands accompanied by flexion contracture of the digits. The incidence rises with increasing age, and bilateral disease is common. There is a higher incidence among patients with epilepsy, diabetes, or alcoholic liver disease and heavy smokers. There is a genetic predisposition, and some studies show an association with manual labor (360–366). *Plantar fibromatosis* is a similar lesion that arises from the plantar aponeurosis and rarely causes flexion contractures of the toes. Palmar and plantar fibromatoses and knuckle pads can develop in the same patient (367,368).

Histopathology. Early lesions consist of multinodular cellular proliferations of uniform plump, spindle-shaped fibroblastic cells within a collagenous stroma (Fig. 32-35). Mitotic figures may be present but are usually infrequent. Longstanding lesions are less cellular and contain increased amounts of dense collagen.

Histogenesis. The cells variably express smooth muscle and muscle-specific actin (369). Ultrastructural studies show features of fibroblasts and myofibroblasts (370,371).

Knuckle Pads

Knuckle pads are uncommon, entirely benign fibroblastic tumors that present as persistent, slow-growing lesions over the extensor surfaces of the proximal interphalangeal and metacarpophalangeal joints (372). The lesions are flesh colored, flat or dome shaped, and freely mobile and mostly arise in men

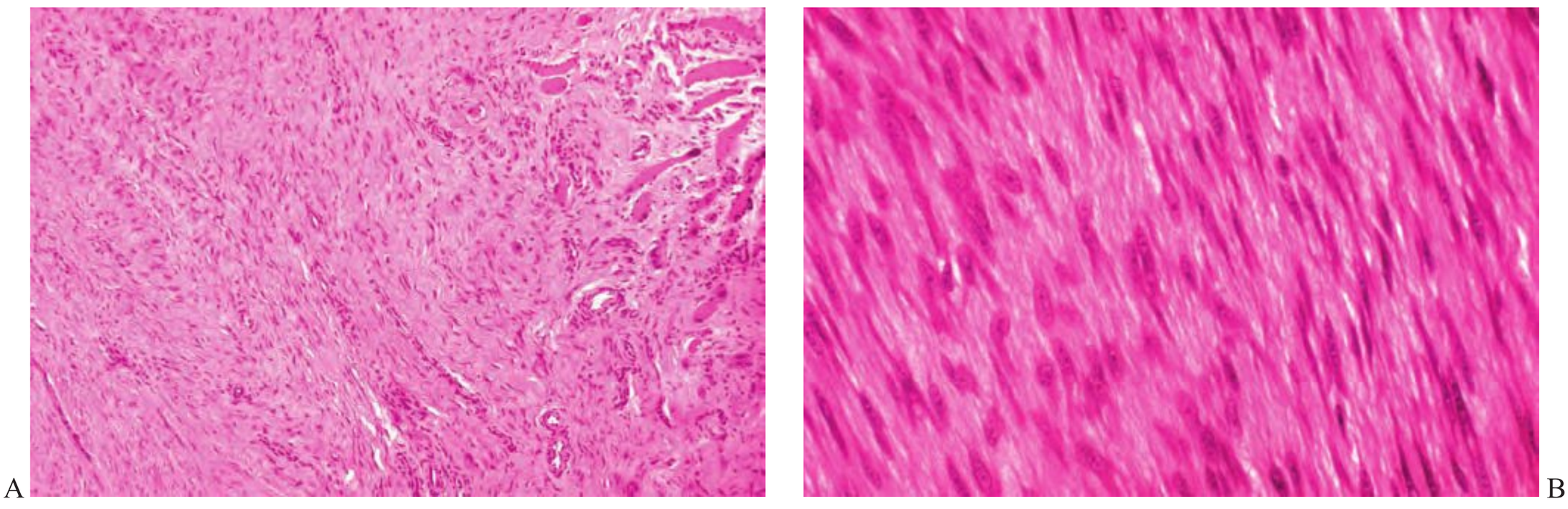


FIGURE 32-34. Desmoid type fibromatosis (desmoid tumor). A: A mass composed of dense bundles of eosinophilic spindle cells is present within striated muscle (right). B: The tumor cells are monomorphic, with regular nuclei and pale eosinophilic cytoplasm.

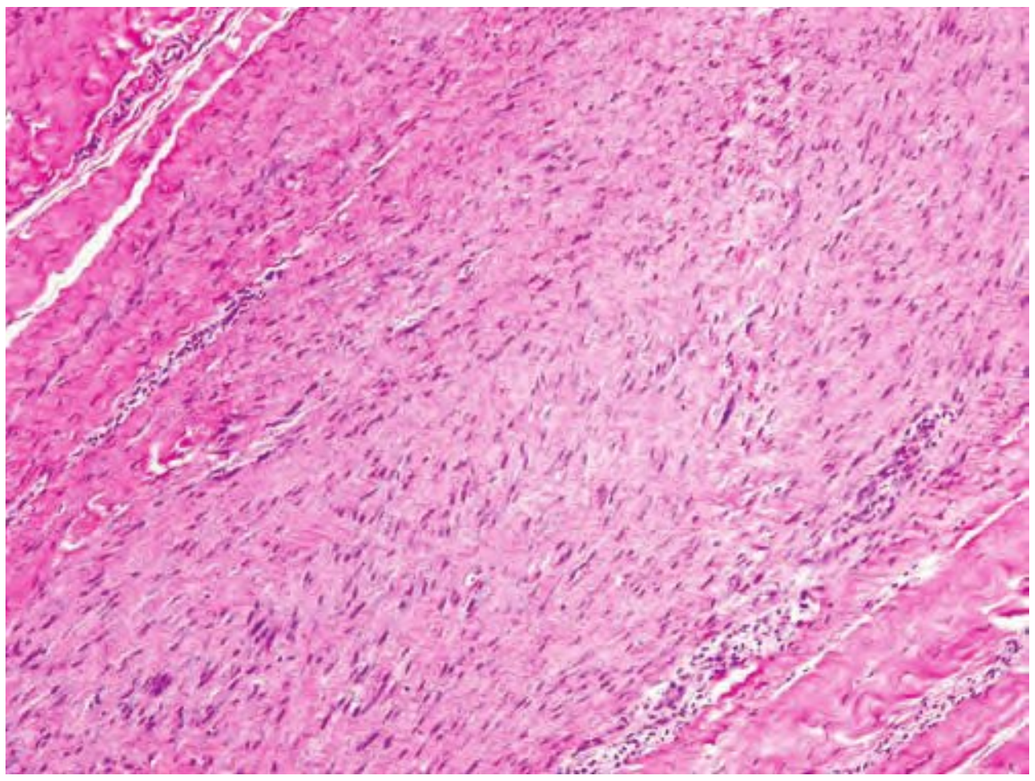


FIGURE 32-35. Palmar fibromatosis (Dupuytren's contracture). Proliferation of uniform fibroblastic cells within a collagenous stroma.

(372). Some patients have coexisting Dupuytren's contractures, and these entities may be related (367).

Histopathology: The histologic features are similar to those of Dupuytren's contracture. There is fibroblastic proliferation, with thickened irregular collagen bundles. The overlying epidermis may show hyperkeratosis and acanthosis (372,373).

Intermediate Biological Potential (Rarely Metastasizing)

Solitary Fibrous Tumor

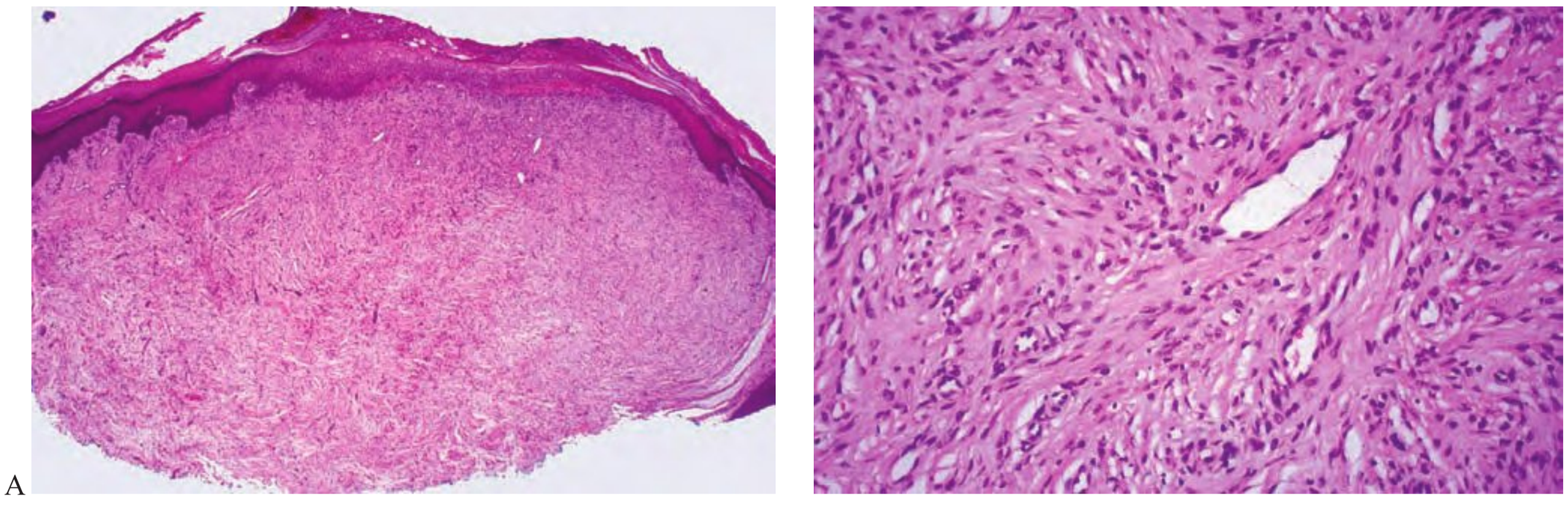
Solitary fibrous tumor is a rare mesenchymal neoplasm that most commonly involves the pleura but has also been reported in numerous extrapleural locations, including rare cases in the skin (374–377). In the skin, lesions present as a circumscribed nodule, mainly on the head and neck (377,378). Rare metastases from pleural solitary fibrous tumors have been reported, but all documented cutaneous tumors appear to be benign and cured by complete excision (374).

Histopathology: The tumors are circumscribed, unencapsulated nodules involving the dermis, subcutis, and fascia. Lesions are typically described as having a "patternless pattern" with hypercellular and hypocellular areas composed of bland spindle cells with pale vesicular nuclei, inconspicuous nucleoli, and indistinct cell borders. The spindle cells form fascicles or storiform patterns similar to dermatofibrosarcoma protuberans, alternating with a vascular component of ectatic vessels and slit-like staghorn vessels presenting a hemangiopericytoma-like appearance. Abundant hyalinized collagen makes up the less cellular areas (Fig. 32-36A, B), and mitotic activity is inconspicuous. The cells express CD34, CD99, bcl-2, and, focally, factor XIIIa, but they are negative for smooth muscle, neural, and epithelial markers (376,377,379).

Inflammatory Pseudotumor

Inflammatory pseudotumor encompasses a heterogeneous group of lesions also known as inflammatory myofibroblastic tumor and plasma cell granuloma. The tumor was originally described in the lung but has since been reported in other organs, including rare cases in the skin. The exact pathogenesis of inflammatory pseudotumor is unclear. Some lesions probably represent an exaggerated response to an antigenic stimulus such as an infectious agent, whereas others are true neoplasms (380–383). Although tumors in extracutaneous sites can recur and occasionally metastasize, all cases reported in the skin have behaved in an indolent manner, with no reports of recurrence after complete excision (384).

Histopathology: Inflammatory pseudotumors present as circumscribed, unencapsulated lesions confined to the dermis or involving both dermis and subcutaneous fat. Two histologic patterns have been described in the skin (381–386). The first consists of bland spindle cells arranged in fascicle or storiform



A B

FIGURE 32-36. Solitary fibrous tumor. A: A circumscribed dermal nodule is present with some overlying reactive epidermal hyperplasia. B: Prominent vascularity is seen extending between bland "patternless" spindle cells.

pattern admixed with variable numbers of inflammatory cells within myxoid and collagenous stroma. Although mitotic figures are usually present, there is no nuclear pleomorphism. The predominant inflammatory cells are plasma cells and small lymphocytes. Lymphoid follicles with germinal centers, eosinophils, and neutrophils may also be present. The second pattern is characterized by nodules composed of lymphocytes and plasma cells in a background of thick, hyaline collagen bundles arranged in intersecting or onion skin-like pattern without spindle cells. Giant histiocyte-like cells and Reed-Sternberg–like cells were described in one case report (381).

Histogenesis. The spindle cells are smooth muscle actin positive (381,383,384). Ultrastructural studies demonstrate features of myofibroblastic and fibroblastic differentiation (385). Immunoreaction to anaplastic lymphoma kinase (ALK) has been reported in up to 60% of extracutaneous cases, mostly in lesions from the pediatric population and young adults (380,387,388). There have been no reports of ALK in cutaneous lesions. ALK protein is a product of t(2;5) chromosomal translocation, adding support to the belief that some of these tumors are genuine neoplasms of myofibroblasts.

Differential Diagnosis. Nodular fasciitis typically presents as a rapidly developing tumor consisting of plump myofibroblasts within myxoid stroma imparting a "tissue culture" appearance accompanied by a sparse inflammatory infiltrate and red blood cell extravasation. Dermatofibromas are less well circumscribed, are usually associated with epidermal hyperplasia, and lack the prominent lymphoplasmacytic infiltrate.

TUMORS OF UNCERTAIN DIFFERENTIATION

Benign

Multinucleated Cell Angiohistiocytoma

Multinucleated cell angiohistiocytoma is an uncommon lesion that presents in middle-aged to elderly women as grouped red-to-brown or violaceous, circumscribed, dome-shaped tumors. Lesions occur in acral regions, most commonly the lower legs, wrists, and back of the hands and on the face. The tumors have a smooth surface and range from 2 to 10 mm in size. Some of the papules may coalesce to form larger annular lesions. They are benign lesions that progress slowly and persist, although spontaneous regression has been reported in some cases (389–394). One case of generalized multinucleated cell angiohistiocytoma was described (395). The pathogenesis of multinucleated cell angiohistiocytoma is uncertain.

Histopathology. The lesions are characterized by fine vessels with prominent endothelium in a fibrous stroma. There are sparse perivascular lymphocytes, with neutrophils and plasma cells present in some cases. Characteristically, there are increased numbers of large, irregular, bizarre mononuclear or multinucleated cells with hyperchromatic nuclei and scalloped basophilic cytoplasm in the interstitium. The epidermis may be hyperplastic (389–394).

Histogenesis. The mononuclear interstitial cells express lysozyme and factor XIIIa. The multinucleated cells are immunoreactive only for vimentin (389,391,393,394).

Intermediate Biological Potential (Rarely Metastasizing)

Angiomatoid Fibrous Histiocytoma

This tumor is now considered to be of intermediate biological potential (rarely metastasizing) and was previously known as "angiomatoid malignant fibrous histiocytoma" (161,162). The prognosis is generally good, with recurrence seen in some cases, primarily related to incomplete excision (66). Metastases arise in 5% or less of patients and are usually confined to local lymph nodes only, but fatalities occasionally occur (66,161,162,396). This tumor should not be confused with aneurysmal fibrous histiocytoma, which might be better described as dermatofibroma with aneurysmal change (22) (see page 970).

The tumor occurs most often on the extremities of children and young adults as a slowly growing nodular or cystic mass of the dermis or subcutis (66,397). There may be associated pain and systemic symptoms such as anemia, pyrexia, and weight loss.

Histopathology. The tumors show hemorrhagic cystic areas lined by flattened, attenuated tumor cells that are not endothelial. Associated multinodular groups of eosinophilic histiocytoid or myoid cells are present in varying patterns with an infiltrate of lymphocytes and plasma cells (Fig. 32-37A, B) (162). Mitotic activity and atypia are not usually prominent. Stromal desmoplasia may efface much of the tumor in some instances. The overall pattern may suggest a lymph node, with lymphoid tissue with follicles and germinal centers and a thick pseudocapsule.

Histogenesis. The cell of origin of this entity is unclear, with varying results using immunohistochemistry (65,398). Many cases are CD68 positive, but the expression of desmin in some cases has been interpreted as evidence of myoid or myofibroblastic differentiation (65,162). Vascular markers such as CD31 and CD34 are negative in the tumor cells. It should be noted that myogenin and MyoD1 are negative in these cases, in contrast to rhabdomyosarcoma (22). Some cases are epithelial membrane antigen positive (399). Cytogenetic studies have been performed in a few cases, revealing t(12;16) and t(12;22) translocations (400).

Malignant

Synovial Sarcoma

Synovial sarcoma most commonly occurs on the limbs, particularly the thigh, of young and middle-aged adults. Superficial lesions adjacent to the joints of the hand, foot, or knee sometimes present with dermal involvement (401,402). The chromosomal translocation t(X;18) (p11;q11) has been

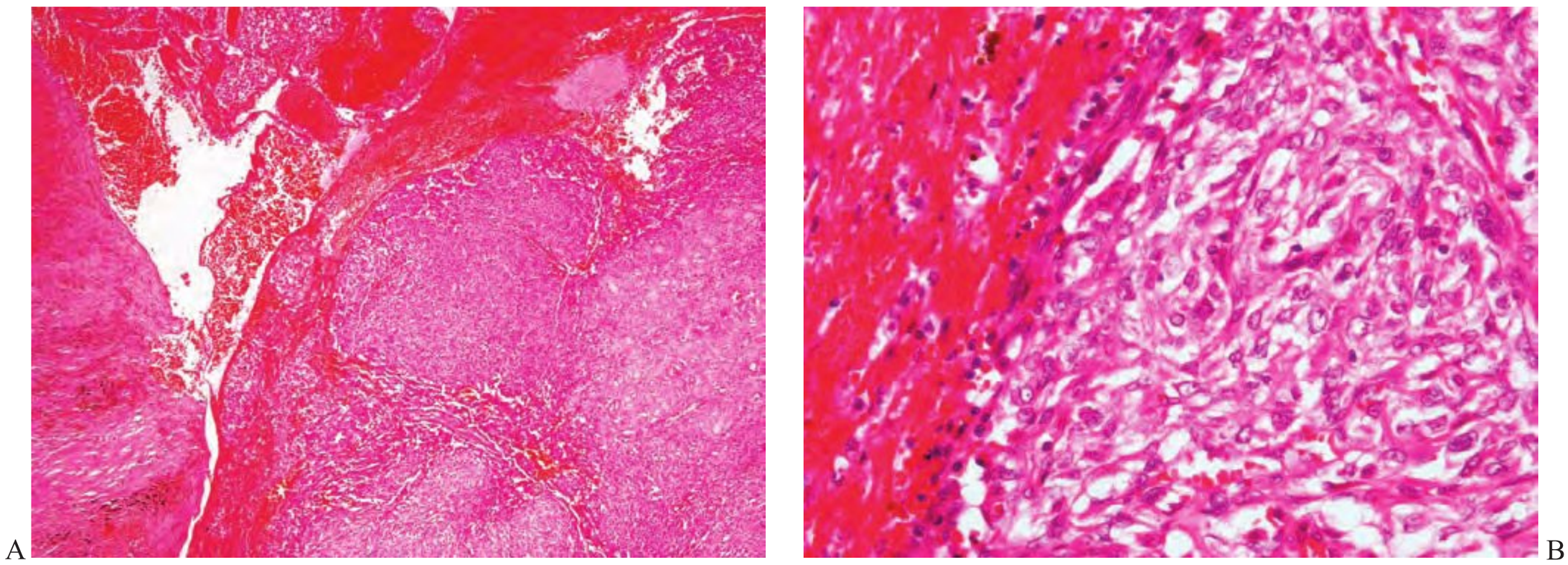


FIGURE 32-37. Angiomatoid fibrous histiocytoma. A: This 20-year-old man had severe anemia associated with this lesion, which was sited on the shoulder. Blood-filled spaces are prominent, with surrounding pale zones of tissue. B: Pale histiocytoid cells are present in the wall of the blood-filled spaces that do not show an endothelial lining.

described in the majority of cases of synovial sarcoma (403,404), but cytogenetic analysis is not considered mandatory for diagnosis (405).

Histopathology. The tumor typically presents a biphasic pattern, including an epithelioid cell component forming glandular spaces and a uniform small, spindle cell component resembling fibrosarcoma (Fig. 32-38). Monophasic synovial sarcoma is composed usually only of spindle cells. Purely glandular monophasic synovial sarcoma theoretically exists but without cytogenetic analysis would be indistinguishable from adenocarcinoma (406). Most tumors express EMA and low and high molecular-weight cytokeratins, including cytokeratins 7 and 19. It is of note that the latter are not found in malignant peripheral nerve sheath tumor or Ewing's sarcoma (406). S100 is stainable in 30% of cases (407).

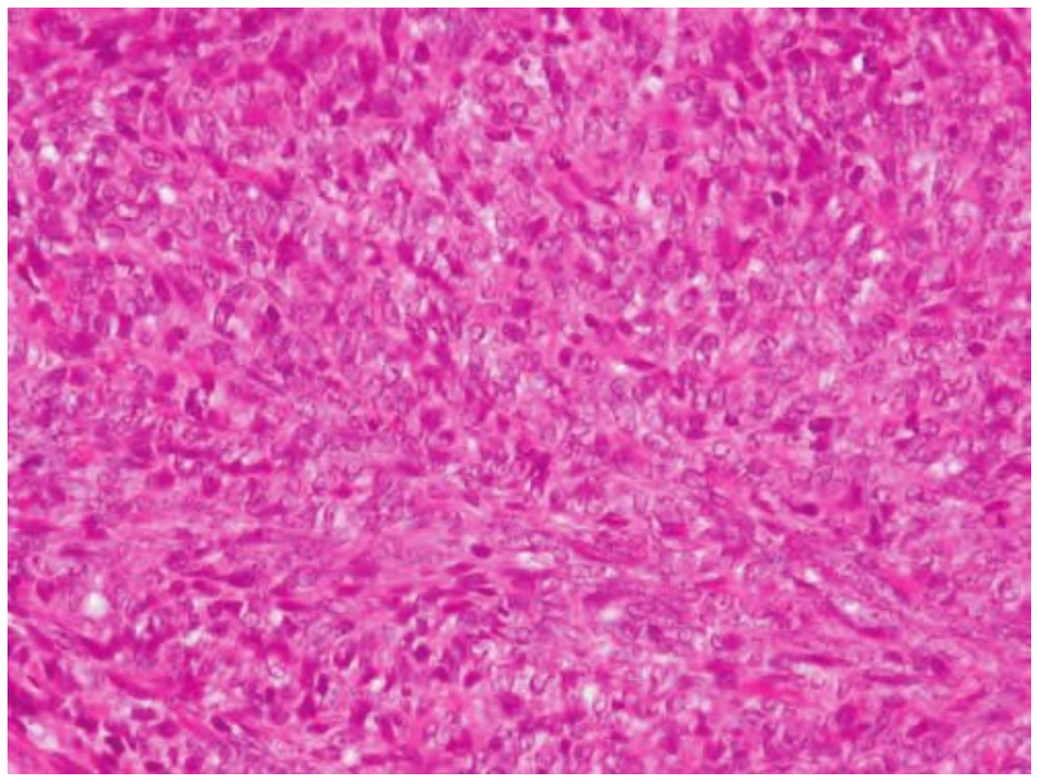


FIGURE 32-38. Synovial sarcoma. A cellular proliferation of fairly monomorphic, ovoid to spindle-shaped cells is seen in this monophasic tumor. Immunohistochemistry showed cytokeratin positivity in these cells.

Histogenesis. Immunohistochemical and ultrastructural features indicate that the tumor is not derived from synovium, leading to suggestions of alternative terms such as connective tissue carcinosarcoma and soft tissue carcinoma (408,409). The distribution of collagens, fibronectin, laminin, and tenascin in synovial sarcoma suggests similarities with the embryonic development of epithelia from mesenchymal cells, supporting the concept that synovial sarcoma is a soft tissue carcinosarcoma (410).

Prognostic factors include tumor size, differentiation, and patient age, with younger patients faring more favorably (411–413).

Epithelioid Sarcoma

Epithelioid sarcoma is a rare, highly malignant soft tissue neoplasm of uncertain histogenesis. It occurs most commonly on the distal limbs of young men as a slowly growing nodule or plaque (Fig. 32-39) (414,415). Occasionally, it also arises at a variety of other sites, including the head, neck, pelvis, and genital region (416–421). Most lesions are sited in subcutis or soft tissue, but occasional examples present primarily in the dermis and upper subcutis. Recurrence and metastasis are frequent, usually to lymph nodes and lung (415). Prognosis is related to tumor size and is more favorable in females (423).

Histopathology. Tumors are composed of nodules of atypical epithelioid cells with pleomorphic nuclei and variable amounts



FIGURE 32-39. Epithelioid sarcoma. Ulcerated nodules on the back of the hand of a 32-year-old. The patient died from systemic metastases 18 months later.

of eosinophilic cytoplasm. These merge with spindle cells and an associated fibrous stroma, in which there may be hemorrhage, hemosiderin, and mucin deposition with a patchy peripheral lymphocytic infiltrate. Variable mitotic activity is seen, with frequent vascular and perineural invasion. Necrosis is characteristically present in the center of tumor nodules, contributing to the granulomatous appearance. Foci of calcification and ossification may be present. The lesions are diffusely invasive and may show overlying ulceration (Fig. 32-40A–C).

Positive immunostaining is seen for cytokeratin, vimentin, EMA, and, frequently, CD34 and actin (424).

A *spindle cell (fibroma-like) variant* of epithelioid sarcoma also occurs, in which the spindle cell pattern predominates without the characteristic epithelioid cells and nodularity (425,426).

Proximal-type epithelioid sarcoma is an aggressive variant occurring predominantly in the pelvis, perineum, and genital tract of older adults. It frequently shows rhabdoid features microscopically, simulating extrarenal rhabdoid tumor (427,428).

Histogenesis. The histogenesis of epithelioid sarcoma is uncertain, but the ultrastructural features of desmosome-like intercellular junctions, numerous microvilli, and whorled arrangements of intermediate filaments (416,429), allied with immunoreactivity for EMA, cytokeratin, vimentin, and, in many cases, CD34 and actin, suggest an origin from primitive mesenchymal cells with the capacity for epithelial differentiation (424). Cytogenetic studies have shown various chromosomal aberrations, including frequent loss of 22q (430). However, no specific, reproducible changes have been identified.

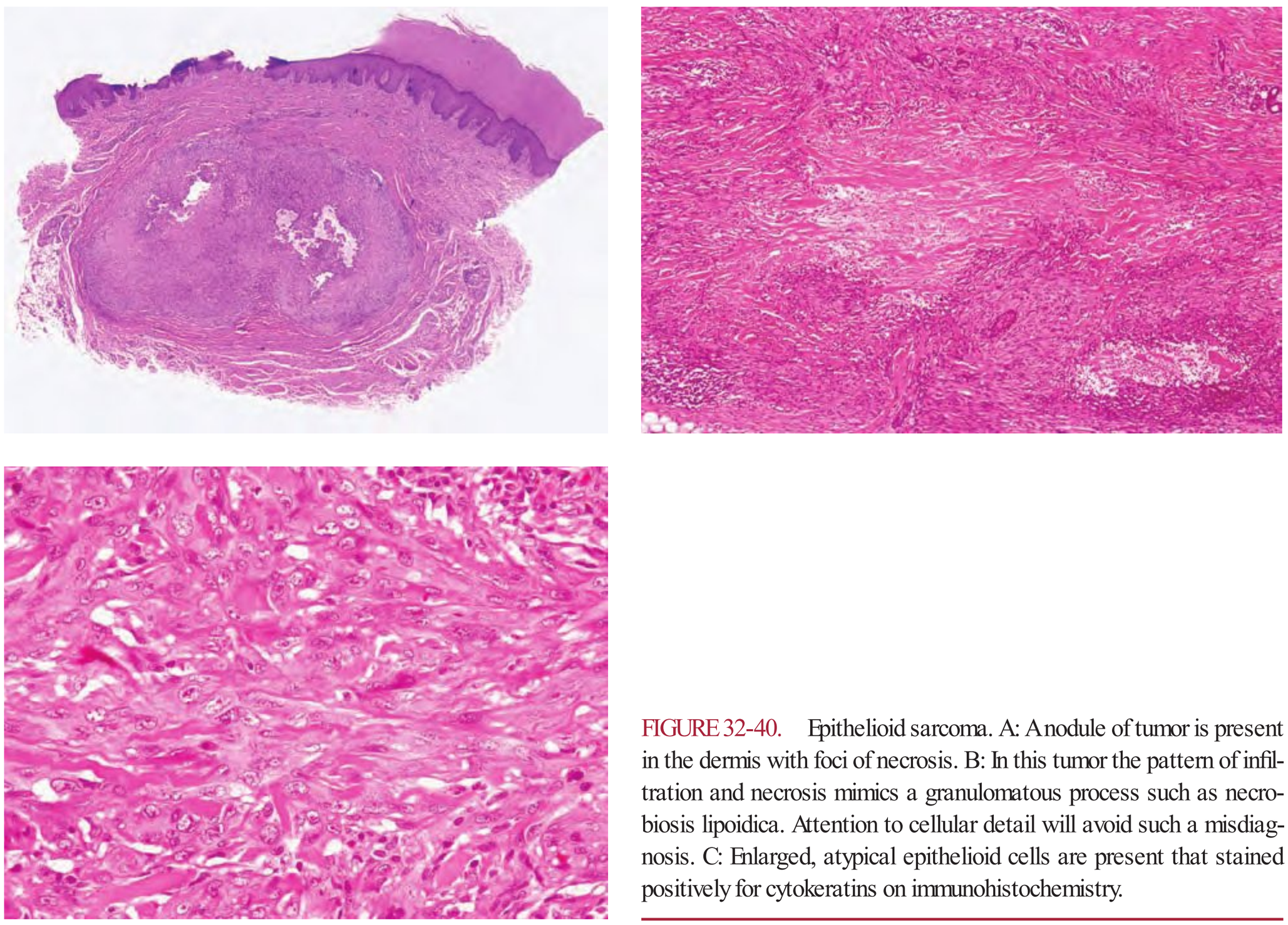


FIGURE 32-40. Epithelioid sarcoma. A: A nodule of tumor is present in the dermis with foci of necrosis. B: In this tumor the pattern of infiltration and necrosis mimics a granulomatous process such as necrobiosis lipoidica. Attention to cellular detail will avoid such a misdiagnosis. C: Enlarged, atypical epithelioid cells are present that stained positively for cytokeratins on immunohistochemistry.

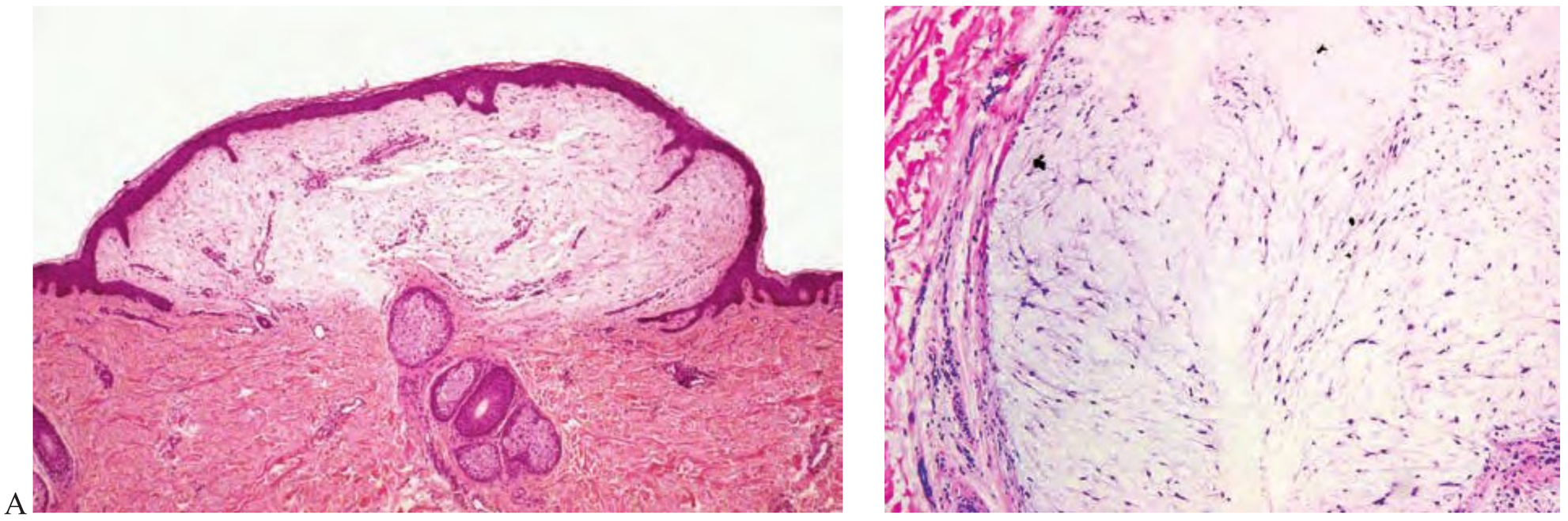


FIGURE 32-41. (A-B) Cutaneous myxoma. The lesion is a sharply circumscribed nodule composed of a vascular mucinous matrix in which spindle cells are scattered.

Differential Diagnosis. At low power, the features often suggest a granulomatous process such as granuloma annulare or rheumatoid nodule. However, cellular atypia, a general lack of mucin, and foci of tumor cell necrosis assist in making the correct diagnosis, even before immunohistochemical stains have been performed (429,431). Although epithelioid sarcoma shows both mesenchymal and epithelial differentiation, it lacks the characteristic biphasic pattern of synovial sarcoma, which does not usually express CD34 (406). Epithelioid sarcoma is negative for cytokeratins 5/6 in most cases, which helps to distinguish it from squamous cell carcinoma, which is consistently positive (432).

MISCELLANEOUS LESIONS

Cutaneous Myxoma

Cutaneous myxomas are sharply demarcated nodules in the dermis or subcutis. They may occur as multiple lesions in association with cardiac and breast myxomas, spotty pigmentation, and endocrine overactivity in Carney's complex (433) or as solitary lesions, usually on the head and neck, trunk, or digits (434–437).

Histopathology. Lesions are sharply circumscribed and sparsely cellular, composed of stellate and spindle-shaped fibroblasts, abundant small, thin-walled vessels, and myxoid matrix (Fig. 32-41A, B). An epithelial component is sometimes present, taking the form of linear strands of epithelium with basaloid features, small keratinous cysts, or follicular induction resembling superficial basal cell carcinoma (433,436,438). *Superficial angiomyxoma* describes tumors with a more prominent associated vascular pattern (436,439).

Differential Diagnosis. Cutaneous myxoma is more sharply circumscribed and more vascular than focal mucinosis (440). The tumor cells in myxomas express vimentin, with variable positivity for CD34 and actin. The cells are usually negative for S100 protein, which is helpful in the distinction from neuroid tumors such as neurothekeoma and myxoid neurofibroma. (441). Neurothekeomas display a multilobular pattern, and the cells in myxoid neurofibromas have wavy nuclei.

Digital Mucous Cyst

It has been suggested that two types of digital mucous cyst exist (442,443). One type is analogous to focal mucinosis. It differs from focal mucinosis only by its location near the proximal nail fold and by its greater tendency to fluctuation. The other type is located on the dorsum of a finger near the distal interphalangeal joint and is due to a herniation of the joint lining, thus representing a ganglion (442). Another view is that digital mucous cyst and digital myxoma are identical and that there is no anatomic connection with the interphalangeal joint (441).

Histopathology. According to the first concept, digital mucous cyst in its early stage has the same histologic appearance as that seen in focal mucinosis, namely, an ill-defined area of mucinous material. Subsequently, multiple clefts form and then coalesce into one large cystic space containing mucin composed largely of hyaluronic acid, which stains with Alcian blue and colloidal iron (444). The cystic space in early lesions is separated from the epidermis by mucinous stroma, but in older lesions it is found in a subepidermal location with thinning of the overlying epidermis. The collagen at the periphery of the cyst appears compressed. No lining of the cyst wall is apparent (Fig. 32-42) (444,445).

Histogenesis. The type analogous to focal mucinosis results from overproduction of hyaluronic acid by fibroblasts (444). In the ganglion type of digital mucous cyst, hyaluronic acid is derived from the joint fluid. This concept is supported by the observation that methylene blue injected into the distal interphalangeal joint can be identified in the cyst (445,446).

Mucous Cyst of the Oral Mucosa/Mucocele

Mucoceles present as solitary asymptomatic lesions, usually on the mucous surface of the lower lip and only rarely elsewhere

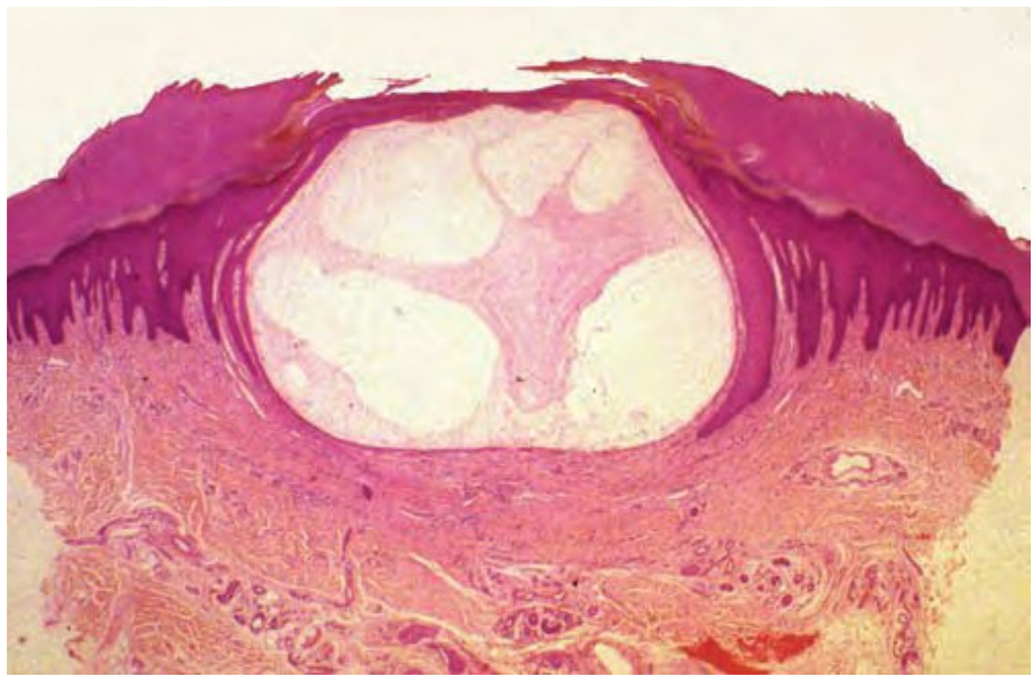


FIGURE 32-42. Digital mucous cyst. The epidermis is raised and attenuated and overlies a circumscribed mucinous cystic nodule, with an epidermal collarette.

on the oral mucosa (447). The cysts usually typically measure less than 10 mm in diameter, appear dome shaped, are translucent, and contain a clear, viscous fluid. Minor trauma causing rupture of a mucous duct appears to initiate the lesion, releasing sialomucin into the tissue. Although most patients with an oral mucous cyst have no preexisting abnormality, mucous cysts of the lower lip may occur in patients with cheilitis glandularis, a condition in which the labial mucous glands and ducts are hyperplastic (448).



FIGURE 32-43. Mucous cyst of the oral mucosa. The squamous epithelium is raised and overlies a cyst containing mucin and inflammatory cells. A segment of salivary gland duct opens into the base of the cyst.

Histopathology. Early lesions consist of multiple small spaces filled with sialomucin surrounded by or intermixed with granulation tissue in the submucosa. Older lesions show either a solitary large cystic space or several large spaces lined by a thick layer of granulation tissue composed of neutrophils, lymphocytes, fibroblasts, muciphages, and capillaries (447). The wall of some cysts shows a ruptured salivary duct opening into the cavity. The sialomucin within the cysts appears as amorphous, slightly eosinophilic material that is periodic acid-Schiff positive and diastase resistant and also stains with Alcian blue and colloidal iron. Minor salivary gland ducts in the underlying stroma provide a clue to the diagnosis (Fig. 32-43) (449).

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CHAPTER 33

Eduardo Calonje

Vascular Tumors: Tumors and Tumor-like Conditions of Blood Vessels and Lymphatics

The classification of vascular lesions and in particular benign vascular tumors is far from satisfactory. The division between developmental, reactive, benign (neoplastic), and occasionally malignant vascular tumors is often blurred, and many conditions cannot be neatly classified into a specific category. This often reflects either limited knowledge about the pathogenesis or the presence of overlapping features among different entities. While advances in knowledge and research have undoubtedly led to the improvement of this situation, the classification of many vascular tumors still remains controversial. A few examples include pyogenic granuloma and angiolymphoid hyperplasia with eosinophilia (reactive vs. neoplastic) and, more importantly, Kaposi's sarcoma (neoplastic vs. infectious). The classification of cutaneous vascular tumors proposed in this chapter and in Table 33-1 is partially based on the recent World Health Organization (WHO) classification of vascular tumors (1) and intends only to provide a framework to define and present different vascular tumors in a coherent manner based on recent developments. It does not intend to be definitive, because future changes in our understanding of vascular tumors will undoubtely give way to further modifications.

REACTIVE CONDITIONS

Intravascular Papillary Endothelial Hyperplasia (Masson's Tumor)

Not an uncommon condition, intravascular papillary endothelial hyperplasia, or Masson's tumor, represents an unusual endothelial proliferation in an organizing thrombus that can be misdiagnosed as angiosarcoma (2). Intravascular papillary endothelial hyperplasia arises primarily within a venous channel or secondarily within a preceding angioma or some type of vascular anomaly, including hemorrhoids, as in Masson's original description. Secondary Masson's tumor often occurs in deep-seated hemangiomas. An exceptional case of an extravascular location in association with a hematoma has been reported (3). The lesions are almost always solitary, arising in the skin, subcutaneous tissue, or even muscle with the head and neck region and the upper extremities. The fingers especially are the most common sites. A rare instance of multiple lesions of the lower extremities simulating Kaposi's sarcoma has also been described (4). All ages can be affected, although there is a slight female predominance (5). Primary lesions are usually tender nodules <2 cm in size, whereas secondary lesions occur because some preceding vascular abnormality increases in size.

Histopathology. Often, low-power examination allows recognition of the intravascular nature of the process in a single thin-walled vein (Fig. 33-1) or as part of a preceding angiomatous condition. Extravascular lesions fail to reveal a blood vessel wall despite serial sectioning. The main lesion consists of a mass of anastomosing vascular channels with a variable degree of intraluminal papillary projections (Fig. 33-2). The stroma consists of hyalinized eosinophilic material that may merge with uncanalized thrombus remnants. The infiltrating vascular channels show enlarged and prominent endothelial cells that may be "heaped up" to give rise to intraluminal prominences, but atypia and mitotic activity are slight.

Differential Diagnosis. The occurrence of areas of somewhat atypical endothelial-lined channels apparently showing a "dissection of collagen" appearance can closely simulate a well-differentiated angiosarcoma. However, the stroma is not collagen and thus is not refractile on polarization, and the changes are localized and occur within a preceding vessel or a vascular anomaly. Usually, angiosarcoma shows a much greater degree of nuclear atypia, multilayering, and mitotic activity.

Angioendotheliomatosis

Until the last decade, two distinctive forms of angioendotheliomatosis were recognized: an aggressive variant with systemic involvement and poor prognosis as well as a reactive self-limited form with a benign course usually restricted to the skin. However, with the advent of immunohistochemistry, many studies in recent years have demonstrated that malignant angioendotheliomatosis shows no endothelial differentiation but represents a form of angiotropic lymphoma that has been renamed *intravascular lymphomatosis* (see Chapter 31).

TABLE 33-1 Classification of Cutaneous Vascular Tumors

BENIGN VASCULAR TUMORS
Benign Tumors and Tumor-like Conditions
Papillary endothelial hyperplasia (Masson's tumor)
Reactive angioendotheliomatosis
Glomeruloid hemangioma
Bacillary angiomatosis
Vascular ectasias
Nevus flammeus (salmon patch and port-wine stain)
Angiokeratoma
Generalized essential telangiectasia
Cutaneous collagenous vasculopathy
Unilateral naevoid telangiectasia
Angioma serpiginosum
Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu)
Nevus araneus
Venous lake
Congenital hemangiomas
RICH
NICH
Capillary hemangioma
Variants:
Infantile hemangioma
Cherry angioma
Tufted angioma (angioblastoma)
Lobular capillary hemangioma (pyogenic granuloma)
Cavernous hemangioma
Variant: Sinusoidal hemangioma
Verrucous hemangioma
Microvenular hemangioma
Hobnail hemangioma
Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia)
Cutaneous epithelioid angiomatous nodule
Acquired elastotic hemangioma
Arteriovenous hemangioma
Variants:
Superficial (cirsoid aneurysm)
Deep
Angiomatosis
Spindle cell hemangioma
Symplastic hemangioma
INTERMEDIATE VASCULAR TUMORS
Locally Aggressive
Kaposi-like hemangioendothelioma
Giant cell angioblastoma
Rarely Metastasizing
Kaposi's sarcoma
Retiform hemangioendothelioma
Papillary intravascular angioendothelioma (malignant endovascular papillary angioendothelioma, Dabska tumor)
Composite hemangioendothelioma
MALIGNANT VASCULAR TUMORS
Epithelioid hemangioendothelioma
Angiosarcoma
Variants:
Idiopathic (head and neck)
Associated with chronic lymphedema (Stewart-Treves)
Postirradiation
Epithelioid
TUMORS OF LYMPH VESSELS
Lymphangioma
Variants:
Lymphangioma circumscriptum
Cavernous lymphangioma/cystic hygroma
Benign lymphangioendothelioma (acquired progressive lymphangioma)
Lymphangiomatosis
Lymphangiomyoma
Atypical vascular proliferation after radiotherapy
TUMORS OF PERIVASCULAR CELLS
Glomus tumor
Glomangiomatosis
Variant: Infiltrating glomus tumor
Glomangiosarcoma
Myopericytoma

RICH, rapidly involuting congenital hemangioma; NICH, noninvoluting congential hemangioma.

Reactive Angioendotheliomatosis

Reactive angioendotheliomatosis is an uncommon condition that almost exclusively affects the skin and presents in patients of either gender with a wide anatomic distribution and predilection for the limbs. Clinical presentation varies from erythematous or brown macules to papules and/or plaques that can be associated with purpura. A livedo-like pattern is sometimes present. In many cases, an association with systemic disease has been documented including cryoglobulinemia (6); paraproteinemia; renal disease; amyloidosis (7); antiphospholipid syndrome (8); rheumatoid arthritis (9); cirrhosis (9); polymyalgia rheumatica (9); sarcoidosis (10); myelodysplastic syndrome (11); and systemic infections, especially bacterial endocarditis (12). Localized forms of the disease are less frequent and include a variant associated with peripheral vascular atherosclerotic disease described as *diffuse dermal angiomatosis* (13–15). The latter presentation has also been described in association with iatrogenic arteriovenous fistulas (16).

Histopathology: Lesions are predominantly dermal and composed of closely packed, variably dilated vascular spaces (mainly capillaries) (Fig. 33-3) lined by bland but plump endothelial cells surrounded by pericytes. A minority of cases display endothelial cells with focal epithelioid change (9). Small lumina might be apparent, but some are obliterated by endothelial cells or fibrin thrombi. Often, the capillaries appear to proliferate in the lumina of dilated preexisting blood

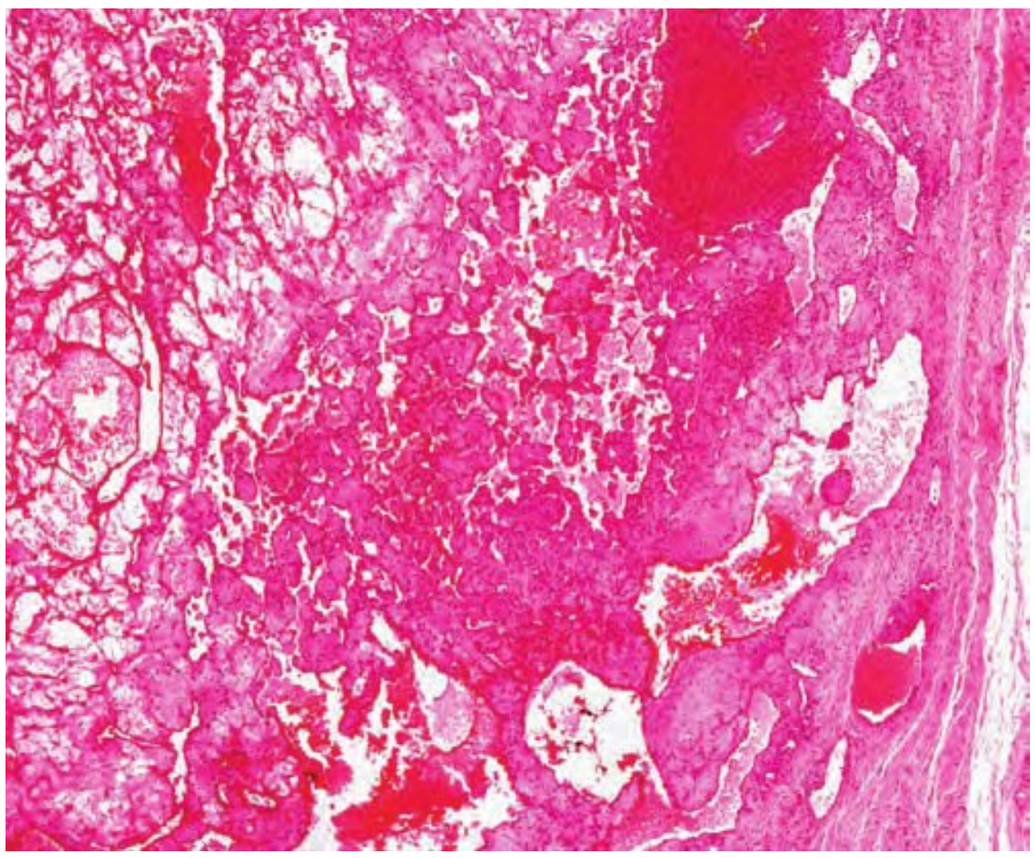


FIGURE 33-1. Primary intravascular papillary endothelial hyperplasia. Part of a markedly dilated vascular channel with prominent papillary structures intermixed with red blood cells and fibrin.

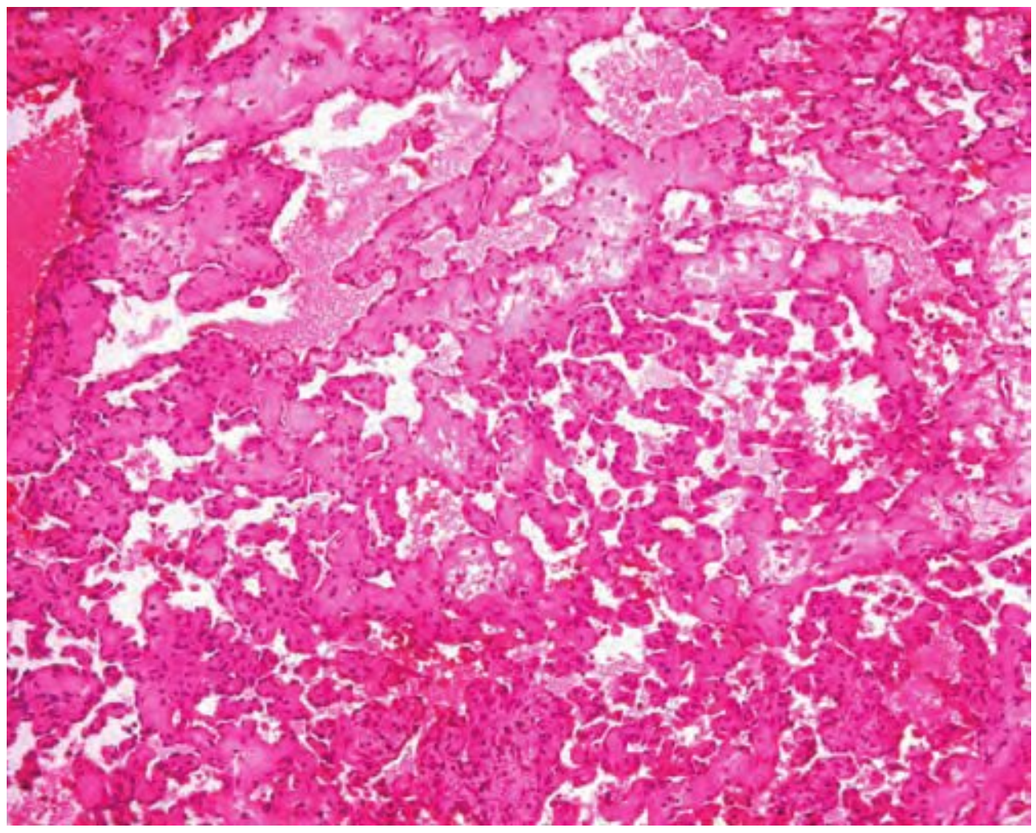


FIGURE 33-2. Intravascular papillary endothelial hyperplasia. Typical hyaline papillary projections lined by endothelial cells focally mimicking a dissection of collagen pattern.

vessels. Hyaline refractile eosinophilic thrombi representing immunoglobulins are present in cases associated with cryoglobulinemia (6) (Fig. 33-4). In diffuse dermal angiomatosis, the proliferating endothelial cells are not present within vascular channels but can be found between dermal collagen fibers. Rare cases of patients presenting with a clinical and histologic picture similar to that of reactive angioendotheliomatosis but showing intravascular cells with a histiocytic immunophenotype have been described. It is not clear whether this represents the early stages of reactive angioendotheliomatosis or a distinctive entity (17).

Histogenesis. Reactive angioendotheliomatosis, in contrast to malignant angioendotheliomatosis, displays universal reactivity for endothelial markers and negativity for leukocyte common antigen, proving that the proliferating cells are endothelial cells (12). It has been proposed that the endothelial cell proliferation is induced by a circulating angiogenic factor or, alternatively, especially in cases associated with cryoglobulinemia or atherosclerotic vascular disease, by occlusion of vascular spaces (6). In many instances, the vascular proliferation is triggered by luminal occlusion, and it is likely that thrombosis plays an important role in the pathogenesis (18).

Differential Diagnosis. The histologic distinction from tufted angioma may be difficult, but the clinical presentation of both

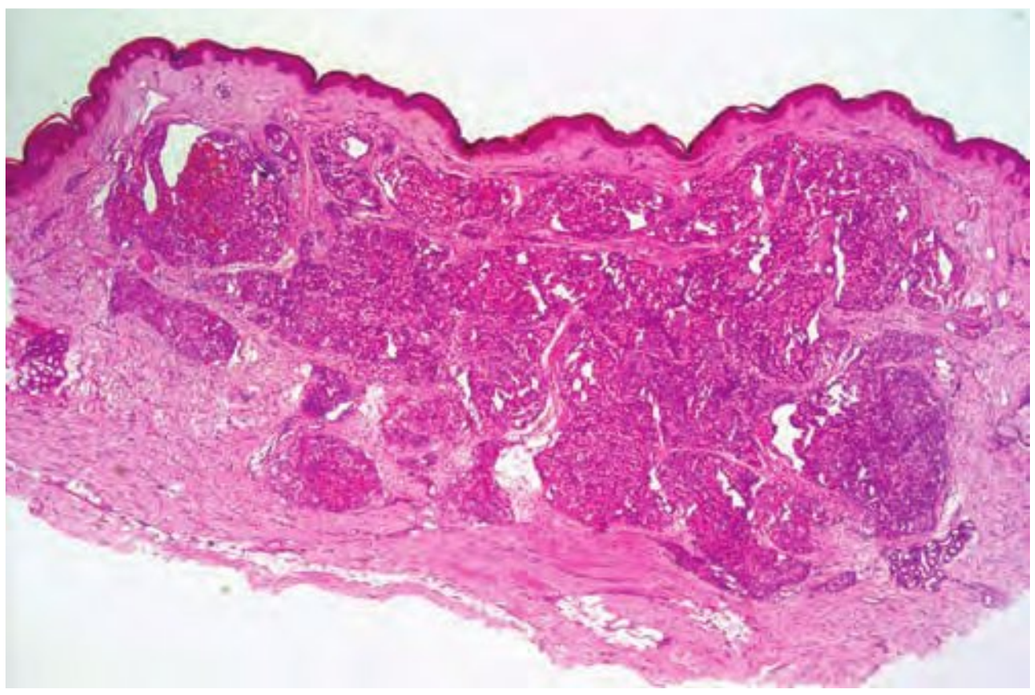


FIGURE 33-3. Reactive angioendotheliomatosis. Numerous closely packed capillaries within preexisting dilated blood vessels are seen throughout the dermis.

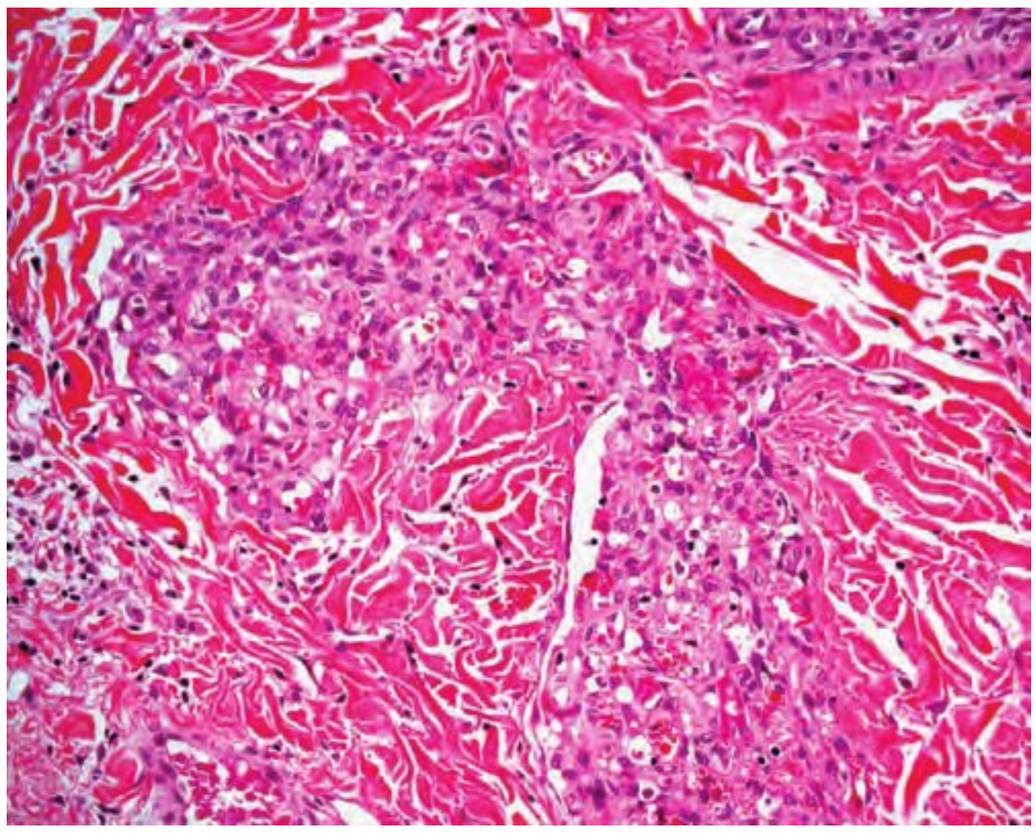


FIGURE 33-4. Reactive angioendotheliomatosis. Plump endothelial cells and intraluminal eosinophilic globules in a case associated with cryoglobulinemia.

entities is different, and tufted angioma shows clusters of capillaries in a typical cannonball distribution throughout the dermis with crescent-like dilated spaces that probably are lymphatic in nature in the periphery of many of the vascular tufts.

Glomeruloid Hemangioma

Glomeruloid hemangioma is a highly distinctive, rare, reactive vascular proliferation that presents in patients with POEMS syndrome (*P*olyneuropathy, *O*rganomegaly, *E*ndocrinopathy, *M*-protein, and *S*kin changes), usually but not always in association with multicentric Castleman's disease (18–20). The skin changes in POEMS syndrome include hypertrichosis, hyperpigmentation, hyperhidrosis, sclerodermoid features, and multiple small vascular papules on the trunk and limbs. Single or multiple lesions with similar morphology have been described in patients with no evidence of POEMS syndrome (21,22).

Histopathology. Most vascular lesions in POEMS syndrome show the features of cherry angiomas, and only a small number of lesions have the appearance of a glomeruloid hemangioma. Other lesions may display histologic features that do not fit exactly into a definitive diagnostic category. In glomeruloid hemangioma, there are numerous ectatic vascular spaces throughout the dermis that contain in their lumina clusters of small, congested capillaries surrounded by pericytes bearing a striking resemblance to renal glomeruli (Figs. 33-5 and 33-6). Although the endothelial cells are flat, a few scattered cells appear vacuolated and can show periodic acid-Schiff (PAS)-positive hyaline globules that correspond to deposition of immunoglobulins. Staining for human herpesvirus 8 (HHV-8) is negative.

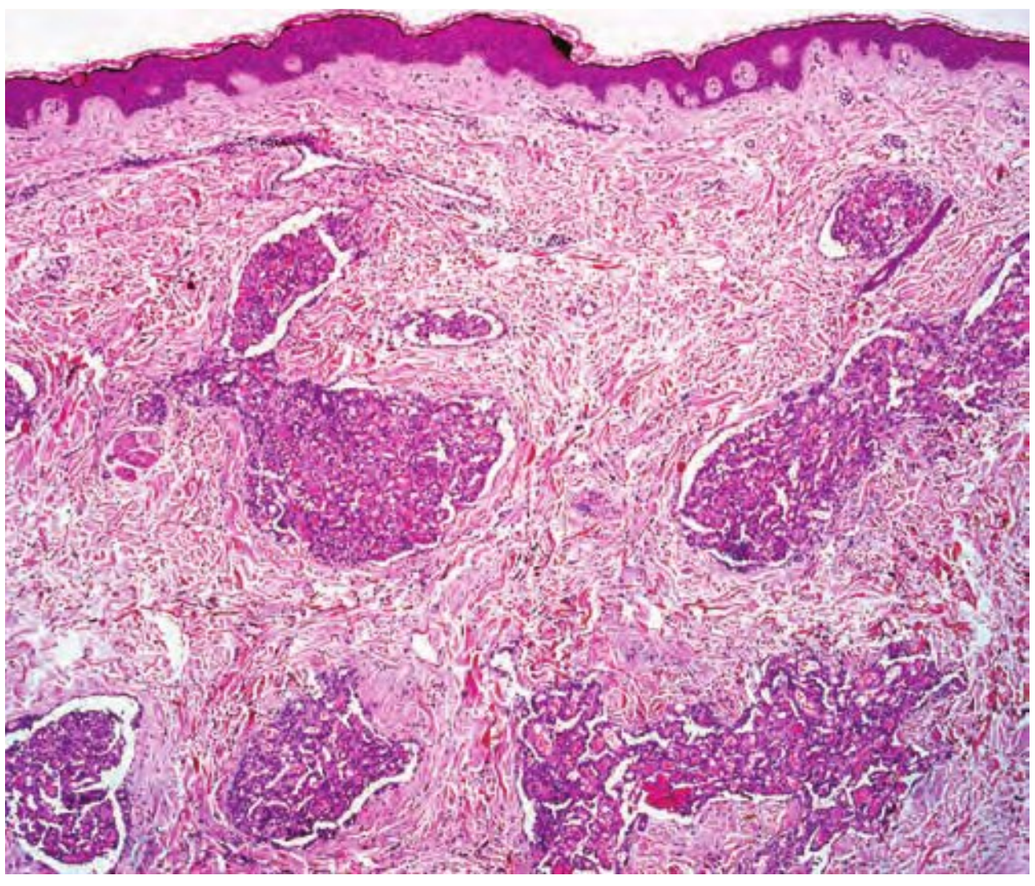


FIGURE 33-5. Glomeruloid hemangioma. Widely dilated preexisting vascular channels filled with smaller blood vessels. Note the low-power resemblance to reactive angioendotheliomatosis.

Histogenesis. Glomeruloid hemangioma probably represents a variant of reactive angioendotheliomatosis. The cause of the vascular proliferation in POEMS syndrome has not been established, but it may be induced by an angiogenic factor, possibly the abnormal immunoglobulin in the vascular spaces.

VASCULAR ECTASIAS

Nevus Flammeus

The term *nevus flammeus* is often used to refer to two different lesions: the *salmon patch* and the *port-wine stain*. Although both lesions are congenital, the former tends to involute in the first years of life and usually has no association with other types of anomalies, while the latter tends to be persistent and is often related to other malformations. The salmon patch is present in up to 50% of newborns of either gender as an ill-defined, red to pale pink macule mainly in the nape of the neck, the glabella, or the eyelids (23,24). The port-wine stain occurs in about 0.3% of newborns as a macular, usually unilateral, red-pink lesion with a predilection for the face (24). Later in life, the lesion becomes darker and raised.

Sturge-Weber syndrome (encephalotrigeminal angiomatosis) is characterized by the presence of a facial port-wine stain, often in the distribution of the trigeminal nerve associated with an ipsilateral leptomeningeal venous malformation, atrophy and calcification of the underlying cerebral cortex, epilepsy, mental retardation, ocular vascular malformations, glaucoma, and contralateral hemiparesis.

In *Klippel-Trenaunay syndrome* (osteohypertrophic nevus flammeus), hypertrophy of the soft tissues and bones of one or several extremities affected with a nevus flammeus are observed. Associated with this are varicosities or arteriovenous fistulas or both and, less commonly, spindle cell hemangioendotheliomas. Cases presenting with arteriovenous fistulas are

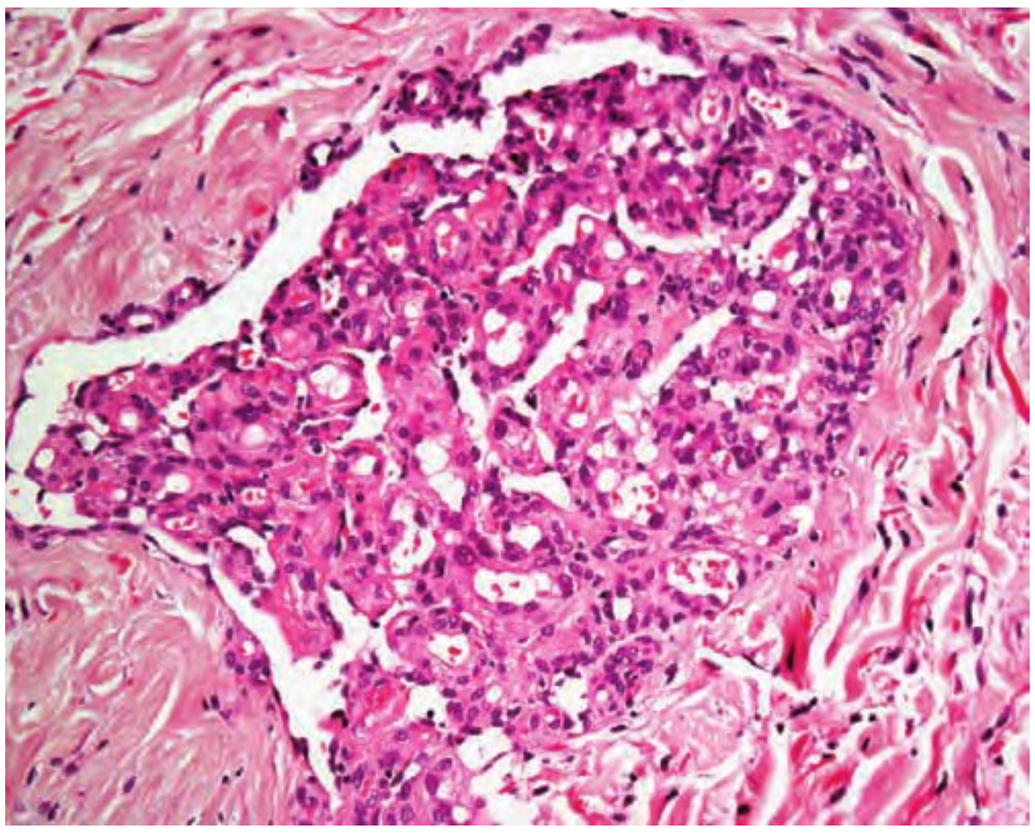


FIGURE 33-6. Glomeruloid hemangioma. Striking resemblance to a renal glomerulus.

sometimes known as Parkes-Weber syndrome. Complications of note are cutaneous ulcers and high-output cardiac failure.

Histopathology. In the *salmon patch*, dilated capillaries are seen in the papillary dermis. In the *port-wine stain*, no telangiectases are apparent histologically until the patient has reached about 10 years of age (25). The capillary ectasias thereafter gradually increase with age. Ultimately, when the lesion is raised or nodular, dilation appears not only the superficial capillaries but also in some of the blood vessels in the deeper layers of the dermis and in the subcutaneous layer. Many ectatic vessels are filled with red blood cells. Lesions with a deep component can be associated with a cavernous hemangioma or an arteriovenous malformation (25).

Histogenesis. Because no histologic abnormalities are present early in life with a port-wine stain, it appears likely that this malformation is the result of a congenital weakness of the capillary walls (25). Thus, the port-wine stain represents a progressive telangiectasia. Antibodies directed against components of the blood vessel wall, collagenous basement membrane protein (type IV collagen), fibronectin, and factor VIII–related antigen have an equivalent distribution and intensity in normal skin and nevus flammeus. Although this does not rule out a structural abnormality of these components, it has been suggested that the alteration may be related to the supporting dermal elements rather than to an intrinsic abnormality in the vessel wall (26). An abnormality in neuromodulation has been proposed as an alternate theory (27).

Angiokeratoma

Four types of angiokeratoma have been described that represent true ectasias of blood vessels of the superficial dermis (28):

1. *Angiokeratoma corporis diffusum.* Patients present with numerous clusters of tiny, red papules in a symmetrical distribution usually in the "bathing-trunk" area. Although often considered synonymous with Fabry's disease, which is an X-linked genetic disorder associated with deficiency of the lysosomal enzyme A-galactosidase, identical clinical appearances have been described in patients with other enzymatic deficiencies, including B-galactosidase, neuraminidase, L-fucosidase, and B-mannosidase (29–31). In exceptional cases, presentation is not associated with detectable biochemical abnormalities, and these cases may be familial (32,33).
2. *Angiokeratoma of Mibelli.* Several dark red papules with a slightly verrucous surface are seen on the dorsa of the fingers and toes. Usually, the lesions appear during childhood or adolescence and measure 3 to 5 mm in diameter (34).
3. *Angiokeratoma of Fordyce.* Multiple vascular papules of 2 to 4 mm in diameter are seen on the scrotum (35). Similar lesions have been described on the vulva (36). They arise in middle or later life. Early lesions are red, soft, and compressible; later, they become blue, keratotic, and noncompressible.

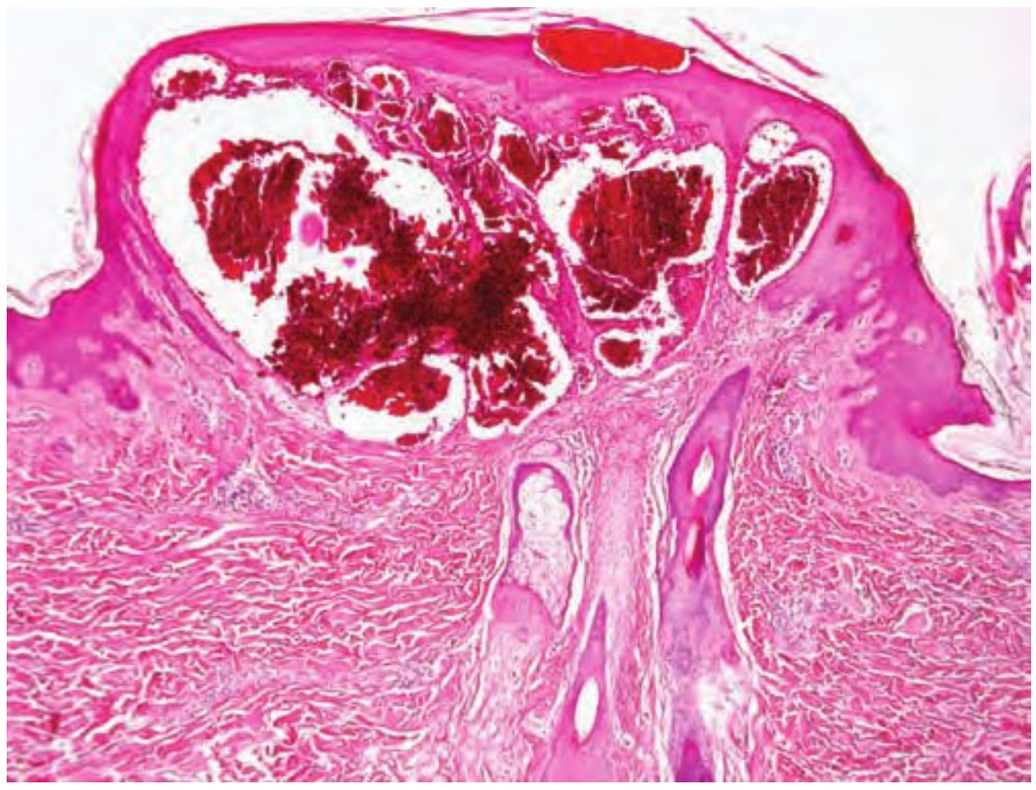


FIGURE 33-7. Angiokeratoma. Note ectatic blood vessels in the papillary dermis with overlying epidermal hyperplasia.

4. *Solitary or multiple angiokeratomas.* Usually one and occasionally several papular lesions arise in young adults, most commonly on the lower extremities. They may be congenital, and when located in a restricted area of the lower limbs, the term *angiokeratoma circumscriptum* is used (37). The lesions range from 2 to 10 mm in diameter. Early lesions appear bright red and soft, but they later become blue to black, firm, and hyperkeratotic (28). Thrombosed lesions are not uncommonly misdiagnosed clinically as malignant melanomas.

Histopathology. The histologic findings are essentially the same in all four above-mentioned types of angiokeratoma and consist of numerous, dilated, thin-walled, congested capillaries mainly in the papillary dermis underlying an epidermis that shows variable degrees of acanthosis with elongation of the rete ridges and hyperkeratosis (28) (Fig. 33-7). In cutaneous lesions of Fabry's disease, cytoplasmic vacuoles representing lipids can sometimes be detected in endothelial cells, fibroblasts, and pericytes.

Generalized Essential Telangiectasia

Widespread linear telangiectases, mainly on the extremities, may gradually develop in adults, predominantly in women (38,39).

Histopathology. Dilated, often congested, vessels are seen in the papillary dermis. The walls of the vessels are composed only of endothelium. The absence of alkaline phosphatase activity suggests that it is the venous portion of the capillary loop that participates in the disease process (38,39).

Cutaneous Collagenous Vasculopathy

This condition is very rare and presents in adults as asymptomatic, progressive, generalized telangiectasia with no involvement of the oral cavity or nails (40).

Histopathology. Superficial, small dermal vessels appear dilated, and their walls are thickened by amorphous hyaline material. This material is positive for PAS and also for colloidal iron. It represents collagen, as demonstrated by electron microscopy; by immunohistochemistry, it is positive for collagen type IV, laminin, and fibronectin. Ultrastructure examination demonstrates that the vessels involved are postcapillary venules.

Unilateral Nevoid Telangiectasia

Although unilateral nevoid telangiectasia may be congenital, in most instances, its onset is related to high estrogen levels associated with pregnancy, puberty, and chronic hepatic disease associated with alcoholism (41). The telangiectases, which are largely punctate and stellate rather than linear, follow a dermatomal distribution, particularly those associated with the trigeminal nerve and cranial nerves III and IV. Rare cases are associated with gastric involvement (42).

Histopathology. Numerous dilated vessels are seen in the upper and middle dermis and, to a lesser extent, in the deeper part of the dermis.

Histogenesis. It has been proposed that the changes seen in this condition are induced by an increase in estrogen receptors in a dermatomal distribution (43).

Angioma Serpiginosum

Angioma serpiginosum is a rare acquired vascular lesion that usually presents in the first two decades of life with a predilection for females. Anatomic distribution is wide, but lesions often present on the lower extremities. The disorder is asymptomatic, and slow progression occurs over the years. Focal spontaneous regression rarely occurs. Most cases are sporadic, but inherited cases have been reported (44). A typical lesion is characterized by deeply red nonpalpable puncta that are grouped closely together in a macular or netlike pattern. Irregular extension at the periphery of the macules may cause them to have serpiginous borders. The deeply red puncta represent dilated capillaries.

Histopathology. Dilated, thin-walled capillaries are seen in some of the dermal papillae and the superficial reticular dermis. Epidermal changes and extravasation of red blood cells does not occur.

Histogenesis. On electron microscopic examination, it is apparent that the thickening of the capillary walls is caused by a heavy precipitate of basement membrane–like material mixed with thin collagen fibers and an increased number of concentrically arranged pericytes (45). In addition, some of the dilated capillaries show slitlike protrusions of their lumina and endothelial lining into the surrounding thickened vessel walls. These findings indicate that angioma serpiginosum is not just a simple telangiectasia but represents a vascular malformation (45).

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Hereditary hemorrhagic telangiectasia, or Osler-Weber-Rendu disease, is inherited as an autosomal dominant trait. Although epistaxis may already begin in childhood, the characteristic telangiectases on the mucous membranes do not begin to appear until adolescence, and the cutaneous lesions often appear much later in life, particularly involving the upper part of the body. Typical lesions are small, bright red, nonpulsating papules.

Concomitant involvement of other organs including the gastrointestinal tract, liver, brain, lungs, spleen, kidneys, and adrenal glands is common. Associated vascular malformations are often a feature (46). Morbidity and mortality are mainly related to bleeding from internal organs.

Histopathology. Irregularly dilated capillaries and venules lined by flat endothelial cells are seen in the papillary and subpapillary dermis.

Histogenesis. On electron microscopy, the dilated vessels in the skin and oral mucosa are seen to be small postcapillary venules that normally do not possess pericytes. A defect in the perivascular supportive tissue has been found to be responsible for the breakdown of the junctions between endothelial cells and the resultant hemorrhage (47). The presence of a mild perivascular lymphocytic infiltrate has been regarded as important in inducing the pathologic changes (48).

Nevus Araneus (Spider Nevus)

Nevus araneus, or spider nevus, considered the most common form of telangiectasia, presents at any age, especially in children, with a predilection for the face and upper limbs (46). It is characterized by a central, slightly elevated, red punctum from which blood vessels radiate. Occasionally, pulsation can be observed. Although spider nevi often arise spontaneously, pregnancy, the use of oral contraceptives, and liver disease are factors predisposing to their appearance (46). Spontaneous regression is common as children grow older and after pregnancy.

Histopathology. In the center of the lesion is an ascending artery that branches and communicates with multiple dilated capillaries.

Venous Lake

Venous lake is a small, dark blue, slightly raised, soft lesion occurring on the exposed skin of elderly persons. It can usually be emptied of most of its blood by using sustained pressure. Usually, several lesions are present. The face, ears, and lips are the most common sites.

Histopathology. Venous lake represents a telangiectasia. In the upper dermis, close to the epidermis, the lesions show either one greatly dilated space or several interconnected dilated spaces filled with erythrocytes and lined by a single layer of

flattened endothelial cells and a thin wall of fibrous tissue (49). In some instances, in place of fibrous tissue, there is a thin irregular noncontinuous smooth muscle layer (50).

BENIGN TUMORS

Congenital Hemangiomas

The term *congenital hemangioma* was first proposed in 1996 to describe a group of hemangiomas that first appear *in utero* and are fully developed at birth (51). These lesions were probably classified in the past as infantile hemangiomas (52), vascular malformations, and even cavernous hemangiomas. These congenital hemangiomas have been divided into rapidly involuting congenital hemangiomas (RICH) and noninvoluting congenital hemangiomas (NICH). Although they seem to represent distinctive clinicopathologic entities, there is some degree of overlap not only between RICH and NICH but also between RICH and infantile hemangioma (53). This means that accurate diagnosis usually relies on close clinicopathologic correlation. It is still controversial whether these lesions are pathogenetically interconnected or whether they are linked (53).

Rapidly Involuting Congenital Hemangioma

RICH develops fully before birth and tends to regress during the first year of life. The tumor affects males and females equally and has a wide anatomical distribution with some predilection for the head and limbs (54,55).

Histopathology. Lesions are mainly subcutaneous and extend focally into the dermis. The architecture is lobular, and between tumor lobules, there are often bands of fibrosis (Figs. 33-8 and 33-9) with focal inflammation, dystrophic calcification, and hemosiderin deposition. Lobules are composed of variably congested capillaries, each of which is surrounded by a layer of pericytes. The overlying epidermis and adnexal structures usually appear atrophic. Larger vascular channels may be found in the fibrotic areas. Individual lobules may show variable fibrosis. Extramedullary hemopoiesis may be seen, and perineural extension is absent. GLUT-1 staining is usually negative in tumor lobules. However, in rare cases, focal positivity may be present.

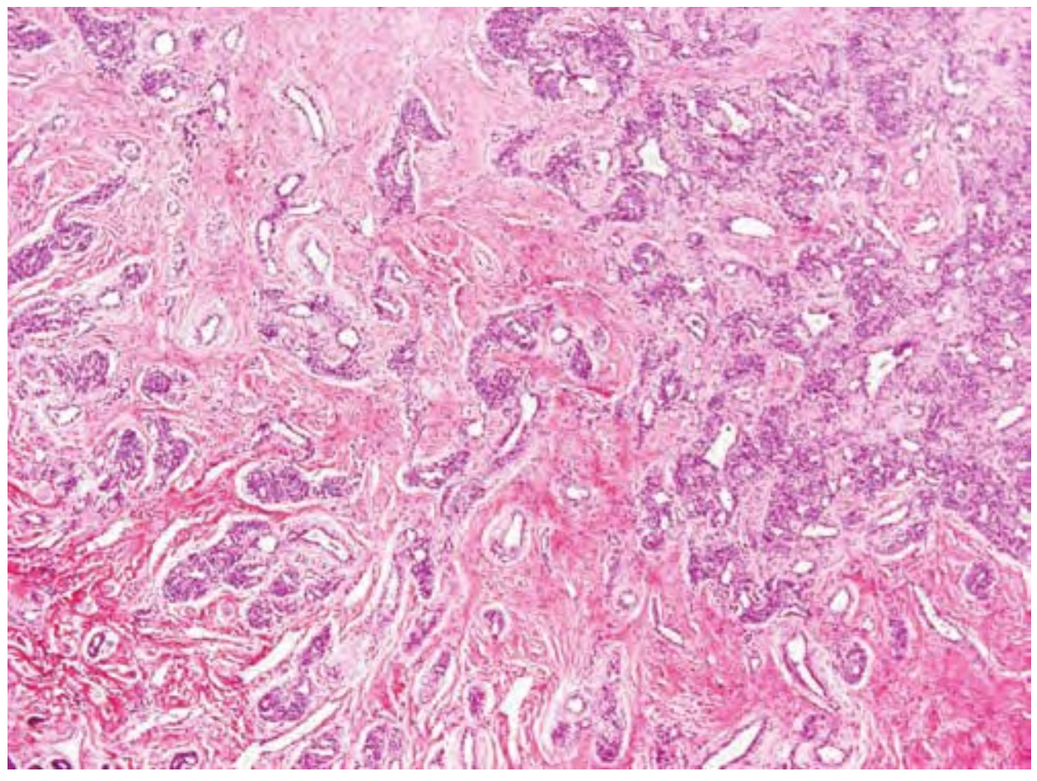


FIGURE 33-8. Rapidly involuting congenital hemangioma. Fibrous tissue is seen not only within individual tumor lobules but also between different tumor lobules. (Courtesy of H. Kozakevich, M.D., Boston, MA.)

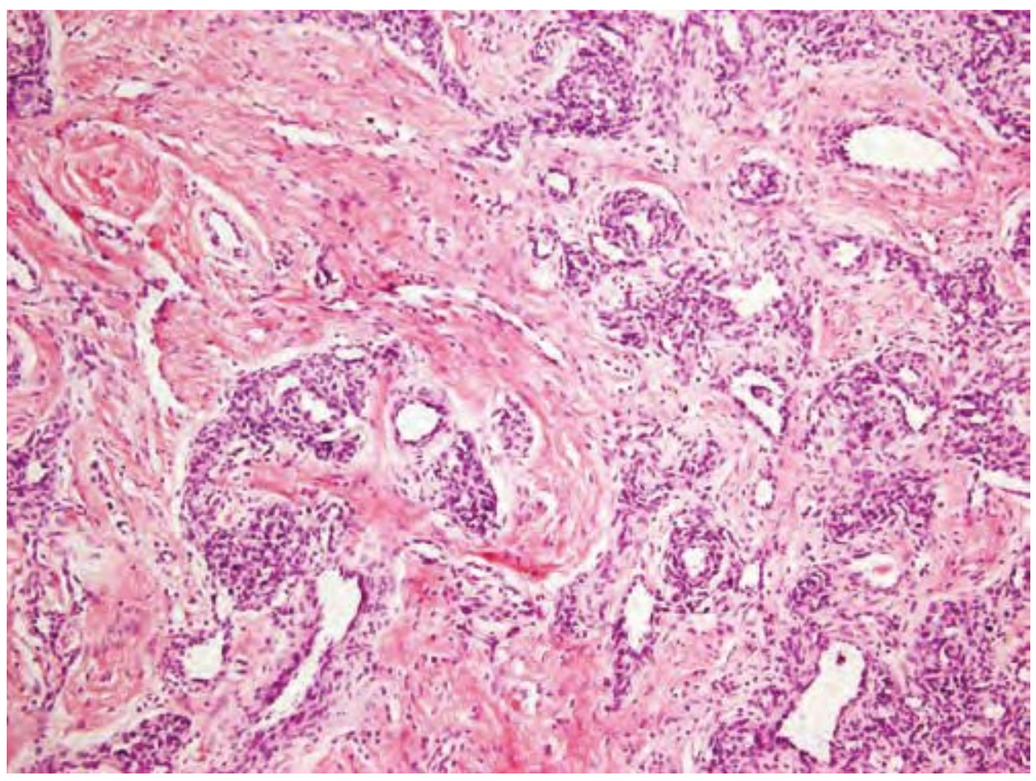


FIGURE 33-9. Rapidly involuting congenital hemangioma. Individual lobules are identical on high power to those seen in infantile hemangioma, but there is fibrosis with the lobules. (Courtesy of H. Kozakevich, M.D., Boston, MA.)

Differential Diagnosis. This is discussed below, under NICH.

Noninvoluting Congenital Hemangioma

NICH is fully developed at birth but shows no signs of regression, and it progresses over time (56). There is an equal sex incidence, and although anatomical distribution is wide, there is predilection for the head and limbs.

Histopathology. Vascular lobules tend to be large and are often composed of capillaries and larger, sometimes thicker blood vessels (Fig. 33-10). Draining larger blood vessels are present in tumor lobules. Surrounding the latter, there are areas of fibrosis containing large blood vessels with features of veins and arteries. Arteriovenous fistulas are also identified, and this closely mimics arteriovenous malformations. Histologic distinction can be very difficult, and close clinicopathologic correlation is often necessary. As opposed to vascular malformations, NICH does not tend to recur. GLUT-1 staining is usually negative.

Differential Diagnosis. The main differential diagnosis of RICH and NICH is infantile hemangioma. The latter typically develops shortly after birth, grows rapidly during the first year of life, and tends to involute over a period of several years. The lobules of RICH and infantile hemangioma are often identical, and it has been proposed that distinction between

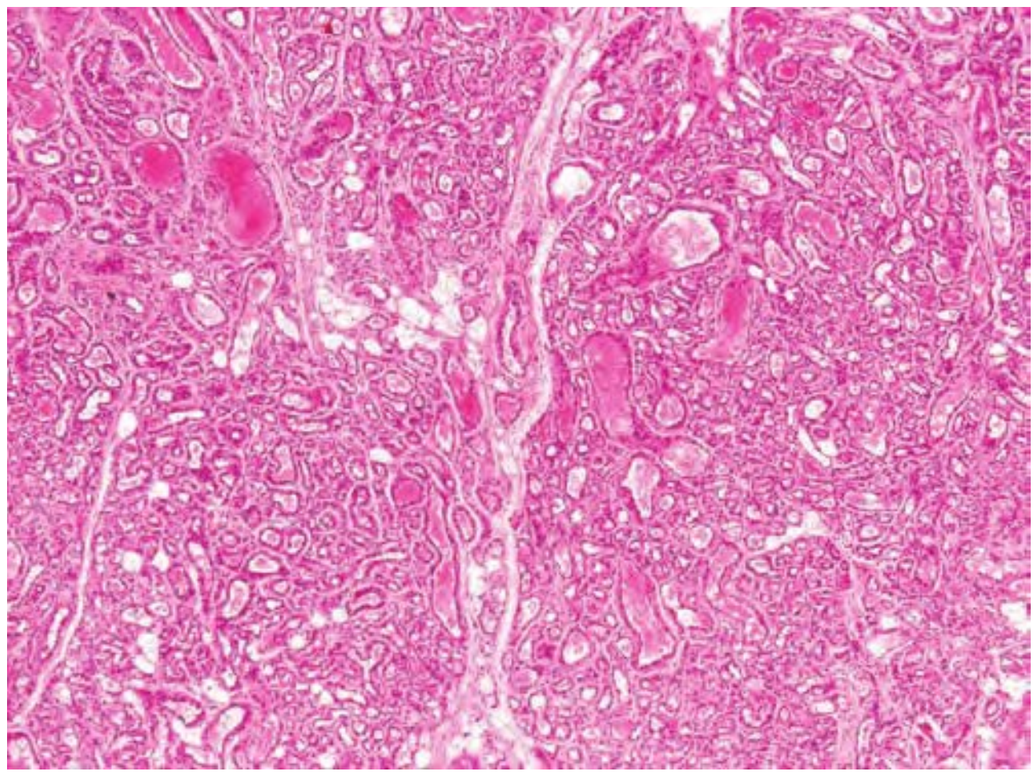


FIGURE 33-10. Noninvoluting congenital hemangioma. Tumor lobules vary more in size and contain a number of larger vascular channels.

both is mainly based in the presence of bands of fibrosis around tumor lobules, presence of atrophy of adnexal structures and epidermis, and lack of GLUT-1 positivity in the former. In practice, however, and especially in small biopsies, distinction may be very difficult and clinicopathologic correlation is paramount. Staining for GLUT-1, the human erythrocyte glucose transporter, is particularly helpful, as infantile hemangioma tends to be diffusely positive for this marker (57) while RICH is usually negative, and if positive, the pattern tends to be focal. Distinction between infantile hemangioma and NICH is easier, as the latter tends to display more variability in the size of vascular channels, GLUT-1 staining is usually negative, and arteriovenous fistulas are identified. The main problem with NICH, RICH, and infantile hemangioma is that there is some degree of overlap between the three entities, as demonstrated by the fact that infantile hemangioma may coexist with either RICH or NICH. The problem is further compounded by the fact that some cases of RICH fail to involute completely and behave more like NICH. In such cases, the histologic appearances overlap with those of RICH and NICH. At present, the pathogenetic relation between these groups of lesions remains obscure.

Capillary Hemangioma Variants

Infantile Hemangioma (Strawberry Nevus, Juvenile Hemangioendothelioma, Juvenile Hemangioma)

Capillary hemangioma, mostly represented by strawberry nevus, constitutes the most common vascular tumor of infancy, affecting as many as 1 in every 100 live births. Overall, it comprises between 32% and 42% of all vascular tumors (58,59). Lesions usually first appear between the third and fifth week of life, increase in size for several months to 1 year, and then start to regress. A typical lesion consists of one or several bright red, soft, lobulated tumors that vary greatly in size and have a wide anatomic distribution with a predilection for the head and neck area. Females are slightly more affected than males. On occasion, lesions can involve deeper soft tissues or even internal organs and can be associated with high morbidity, especially if located near vital structures. Complete spontaneous resolution is common, occurring in about 70% of capillary hemangiomas by the time the patient has reached the age of 7 years.

Contrary to what was believed in the past, capillary hemangiomas are not associated with Kasabach-Merritt syndrome. This syndrome, consisting of thrombocytopenia, microangiopathic hemolytic anemia, and acute or chronic consumption coagulopathy, is mainly seen with kaposiform hemangioendothelioma (see page 1038) and less commonly with cavernous hemangiomas (see page 1019) and tufted angioma (see page 1015).

Histopathology. All tumors have a lobular architecture (Fig. 33-11), but microscopic features change as the lesion evolves. During their period of growth in early infancy, capillary hemangiomas show considerable proliferation of their endothelial cells. The endothelial cells are large, mitotically active, and aggregated predominantly in solid strands and masses in which there are only a few small capillary lumina. Not uncommonly, crystalline intracytoplasmic inclusions can be seen in the endothelial cells. The lumina can be highlighted with the use of a reticulin stain. In maturing lesions, the capillary lumina are wider, and the lining endothelial cells then appear flatter (Fig. 33-12). In mature lesions, some of the lumina may be greatly dilated, focally resembling a cavernous hemangioma. In the involuting phase, there is progressive fibrosis with disappearance of the blood vessels. The vascular nature of the tumor may then be difficult to establish. However, the lobular pattern is often preserved. A worrying but entirely benign feature seen in a number of capillary hemangiomas is the presence of perineural invasion (60).

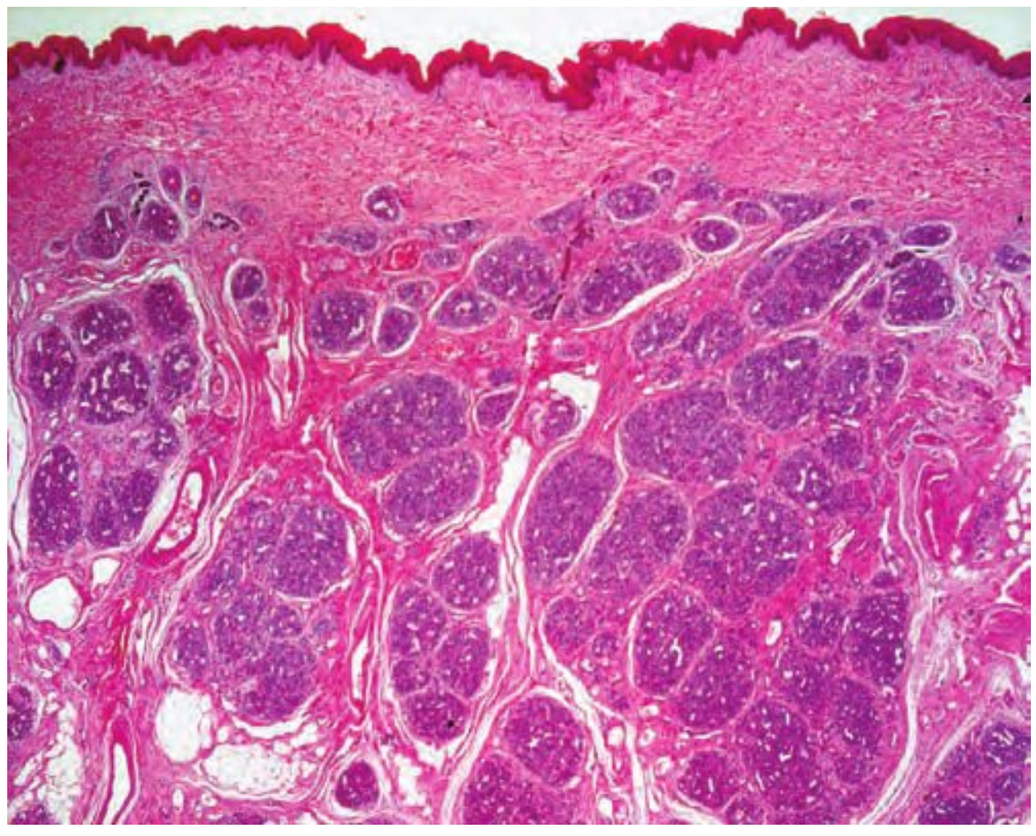


FIGURE 33-11. Infantile hemangioma. Involvement of the dermis and subcutis by multiple lobules composed of capillaries.

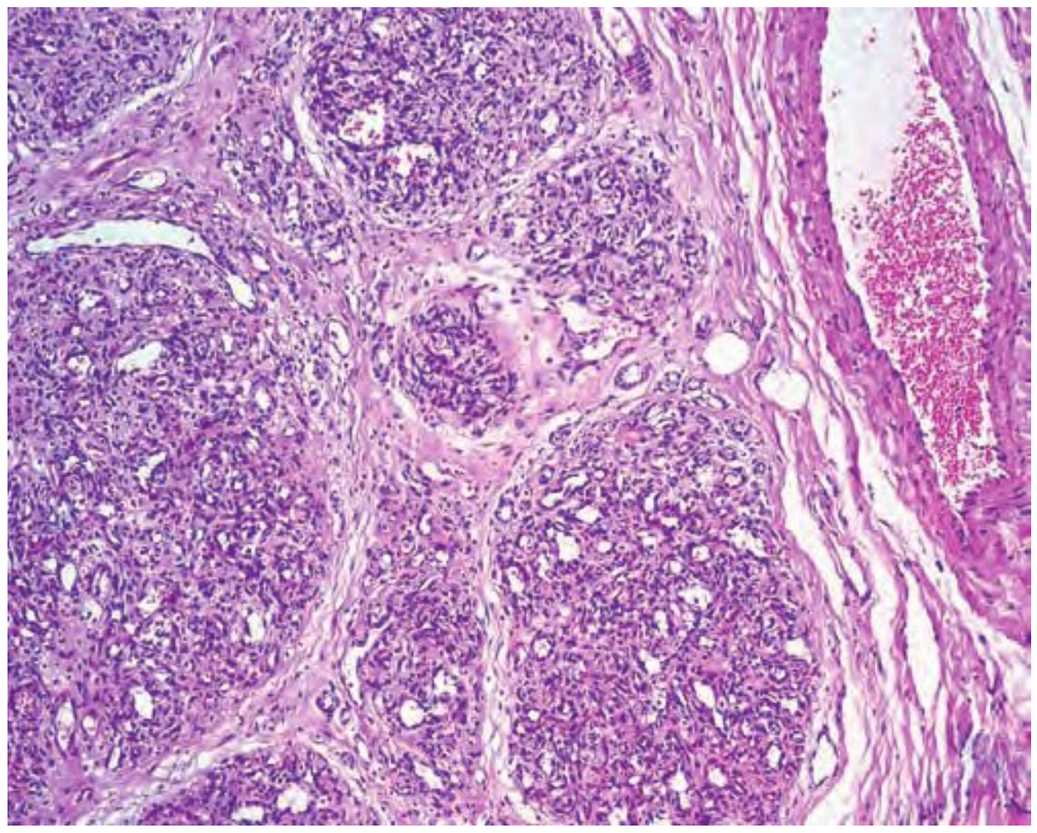


FIGURE 33-12. Infantile hemangioma. Mature lesion with well-formed canalized capillaries and a neighboring feeding vessel.

Pathogenesis. Ultrastructural and immunohistochemical studies of capillary hemangiomas have demonstrated that tumors show remarkable cellular heterogeneity. A large proportion of the cells in a given tumor are endothelial cells and pericytes, but fibroblasts, mast cells, and a population of as yet unidentified factor XIIIa–positive cells have been described (61–63). A complex interaction among these cell populations may modulate the progression and latter evolution of capillary hemangiomas (64). It has recently been described that juvenile hemangiomas share the same unique phenotype with human placenta (64). Immunohistochemical staining for GLUT-1 uniformly stains endothelial cells in infantile hemangioma (57).

Differential Diagnosis. Distinction between infantile hemangioma and RICH and NICH is discussed on pages 1013–1014.

Cherry Hemangioma (Senile Angioma, Campbell de Morgan Spot)

Cherry hemangiomas are bright red lesions varying in size from a hardly visible punctum to a soft, raised, dome-shaped lesion measuring several millimeters in diameter. This very common lesion, often present in large numbers, may start appearing in early adulthood, and the number of lesions increases with age. Cherry hemangiomas may occur anywhere on the skin, but the trunk and the upper limbs are the most common sites.

Histopathology. In the early stage of development, cherry hemangiomas have the appearance of true capillary hemangiomas, being composed of numerous newly formed capillaries with narrow lumina and prominent endothelial cells arranged in a lobular fashion in the subpapillary region. As the lesion ages, the capillaries become dilated. In a fully mature cherry hemangioma, numerous moderately dilated capillaries lined by flattened endothelial cells are observed. The intercapillary stroma shows edema and homogenization of the collagen. The epidermis is thinned and often surrounds most of the angioma as a collarette.

Differential Diagnosis. In its early stage, cherry hemangioma, like granuloma pyogenicum, shows capillary proliferation; however, endothelial proliferation is much less pronounced than in granuloma pyogenicum; thus, solid aggregates of endothelial cells are not seen.

Tufted Angioma (Angioblastoma)

Tufted angioma is a benign angiomatous condition that can be regarded as identical to the angioblastoma reported by Japanese authors (65,66). The angiomas affect the genders equally, usually arising between the ages of 1 and 5 years (67–69); occasionally, the lesions are present at birth (70,71), but they may develop in adults or even in old age (72). There are exceptional instances of angiomas arising in pregnancy, with regression after pregnancy (73), the occurrence in several members of a family (74), and the development of lesions after liver transplantation (75). The most common sites for the angiomatous papules and plaques are the upper trunk, neck, and proximal part of the limbs. Exceptionally, presentation may be in the oral cavity (76). The lesions usually slowly progress for several years and can eventually cover wide segments of the body; some are tender on palpation, and rare lesions regress (77). In rare cases, hypertrichosis may be seen in the skin overlying the lesion (69). Kasabach-Merritt syndrome is a rare association (78,79).

Histopathology. Circumscribed foci of closely set capillaries are found scatttered through the dermis and occasionally reach the subcutis. At lower magnification, these discrete, ovoid angiomatous lobules or tufts have been alluded to as giving rise to a "cannonball" appearance (Fig. 33-13). The vascular nature of the tufts may not be immediately apparent, as vascular lumina are compressed by enlarged endothelial cells and contain few red blood cells. Some of the vascular tufts appear to indent lymphatic-like channels (Figs. 33-14 and 33-15). Mitotic activity and cell atypia are insignificant.

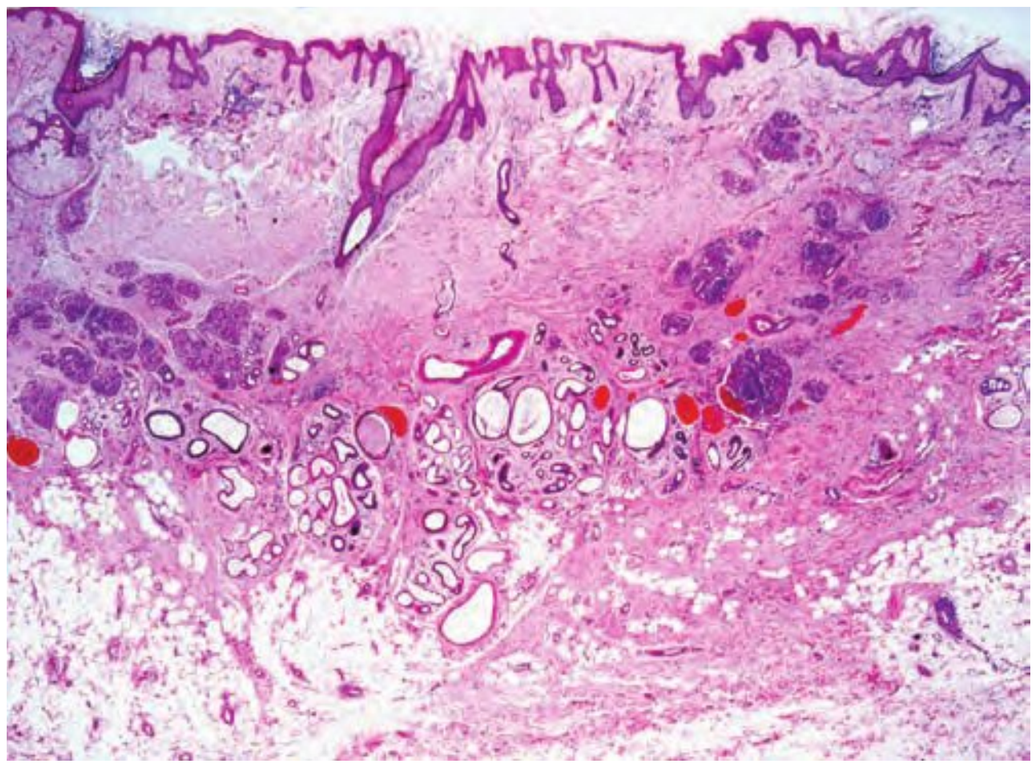


FIGURE 33-13. Tufted angioma. Scattered round or ovoid dermal lobules in a typical "cannonball" distribution.

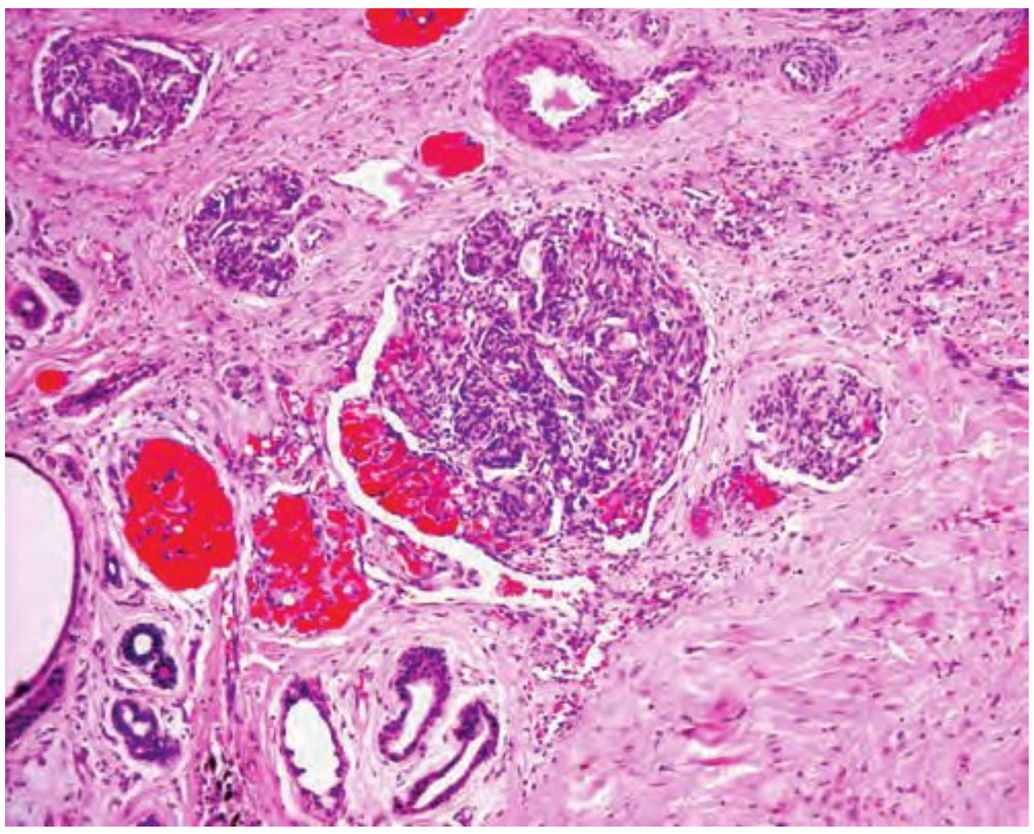


FIGURE 33-14. Tufted angioma. Lobule composed of bloodless capillaries surrounded by dilated crescent-shaped vascular channels.

The presence of strong labeling for actin indicates a prominent pericytic component among the tumor capillaries.

Differential Diagnosis. The main importance of this uncommon angioma, especially if it develops in adults, is the differential diagnosis from *Kaposi's sarcoma* or possibly a low-grade *angiosarcoma*. Endothelial cells in tufted angioma may show slight spindling but not the elongated spindle cells of Kaposi's sarcoma. The discrete focal arrangement of vascular tufts having few red blood cells also differs greatly from the mature lesions of Kaposi's sarcoma. The absence of cell atypia is the main distinguishing feature from angiosarcoma.

The hypertrophic cellular appearance of the tufts is similar to the angiomatous tissue in strawberry nevi, but the angiomatous aggregates are far more massive in the latter, where they tend to replace wide segments of the dermis and fat. It seems likely that tufted angioma is a variant of capillary hemangioma; this is supported by the finding of characteristic cytoplasmic crystalline lamellae in both disorders (80).

Distinction from kaposiform hemangioendothelioma is sometimes difficult, particularly in small biopsies, and it has been suggested that both tumors overlap (81). In difficult cases, immuonhistochemistry for D2-40 may be useful: As in kaposiform hemangioendothelioma, there is positivity for this marker within the tumor lobules, while in tufted angioma, the tufts of capillaries are negative for D2-40, which only stains the endothelium in the channels in the vicinity of the tufts (82).

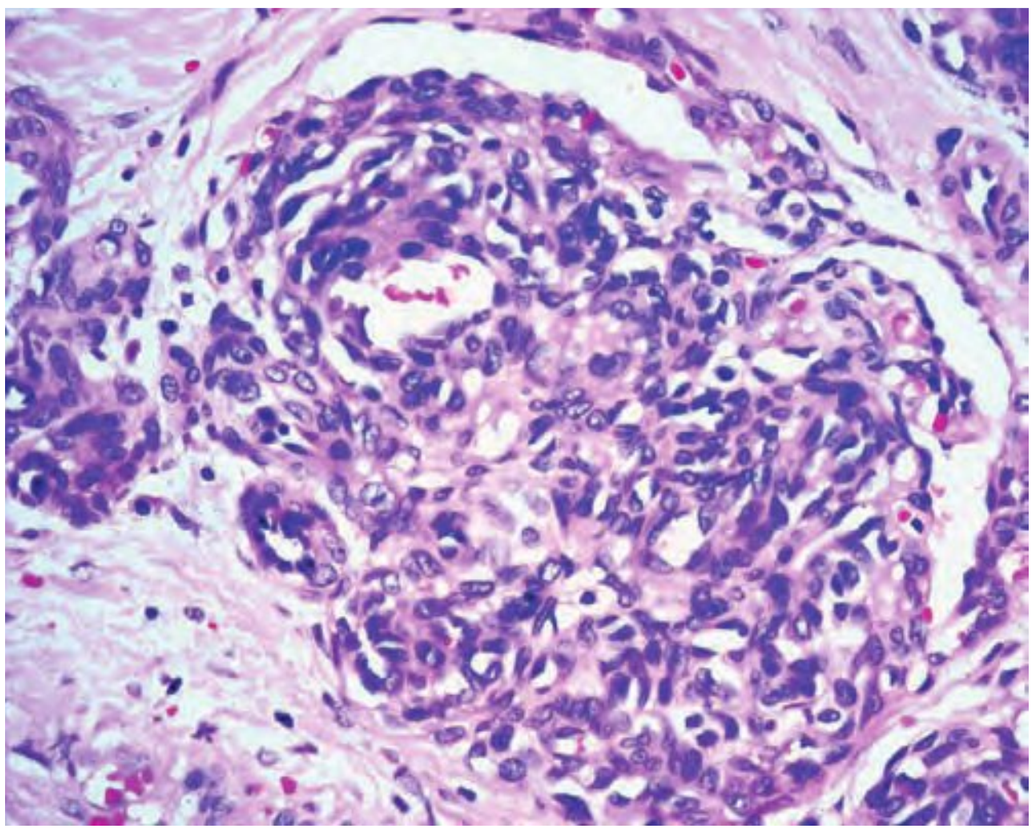


FIGURE 33-15. Tufted angioma. Often, the capillaries appear poorly canalized and pericytes are prominent.

Pyogenic Granuloma (Lobular Capillary Hemangioma)

Pyogenic granuloma, or lobular capillary hemangioma, is a common proliferative lesion that is often related to trauma. Typically, the lesion grows rapidly for a few weeks before stabilizing as an elevated, bright red papule, usually not more than 1 to 2 cm in size (Fig. 33-16); it may then persist indefinitely unless destroyed. Recurrence after surgery or cautery is not rare. Pyogenic granuloma most often affects children or young adults of either gender, but the age range is wide; the hands, fingers, and face, especially the lips and gums, are the most common sites (83,84). Pyogenic granuloma of the gingiva in pregnancy (epulis of pregnancy) is a special subgroup. Lesions may rarely develop within a port-wine stain (85,86).



FIGURE 33-16. Lobular capillary hemangioma (pyogenic granuloma). Ulcerated, polypoid papular lesion.

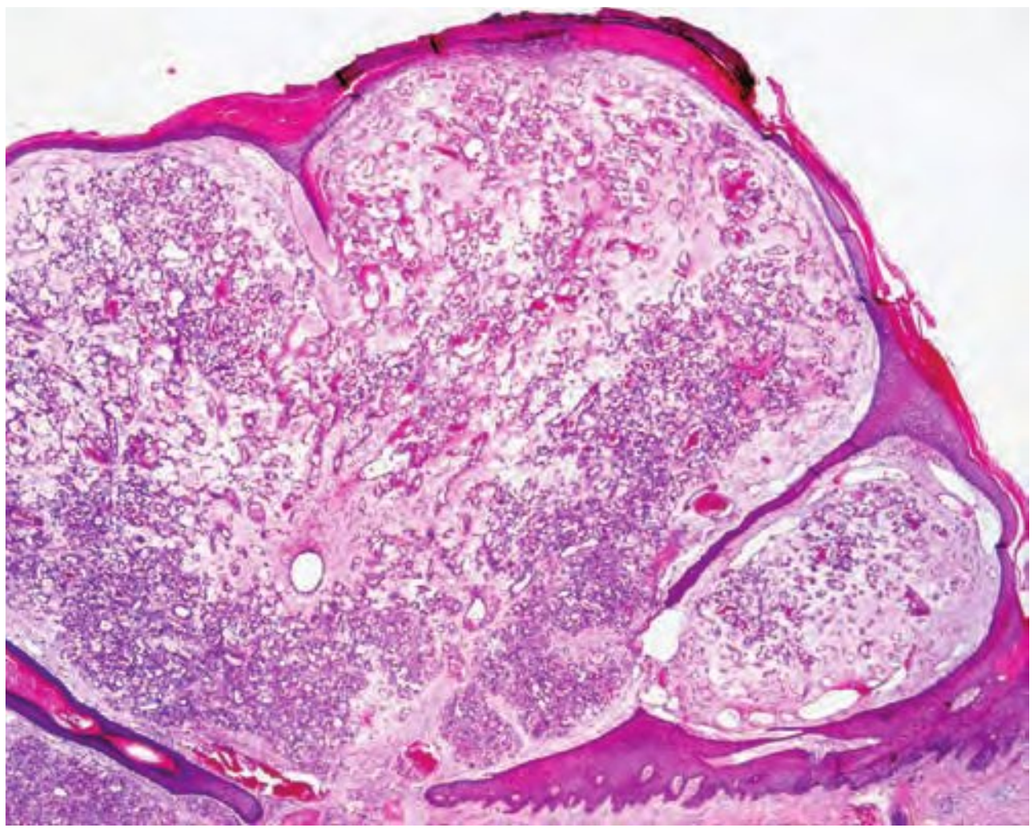


FIGURE 33-17. Lobular capillary hemangioma (pyogenic granuloma). Early, nonulcerated lesion with the typical epithelial collarette.

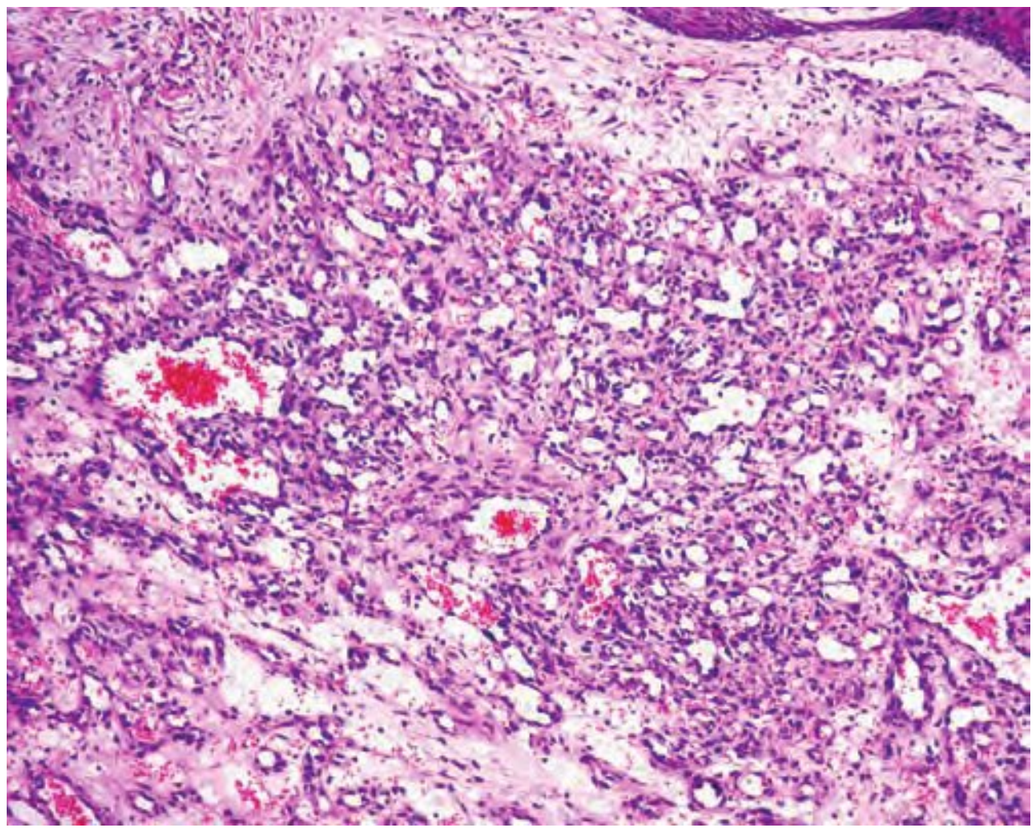


FIGURE 33-18. Lobular capillary hemangioma (pyogenic granuloma). Distinctive lobules of dilated and congested capillaries in an edematous stroma.

A rare and alarming event is the development of multiple satellite angiomatous lesions at and around the site of a previously destroyed pyogenic granuloma (87,88). This usually occurs following lesions on the shoulder or upper trunk in children. Histologically, lesions that are similar to pyogenic granuloma can occur in the deep dermis, the subcutaneous tissue (89), and even within dilated venous channels (90,91). Widely scattered angiomatous lesions resembling pyogenic granulomas have also been described (92–94), sometimes in association with visceral disease.

Histopathology. The typical lesion presents as a polypoid mass of angiomatous tissue protruding above the surrounding skin. It is often constricted at its base by a collarette of acanthotic epidermis (Fig. 33-17). An intact, flattened epidermis may cover the entire lesion, but surface erosions are common. In ulcerated lesions, a superficial inflammatory cell reaction can give rise to an appearance suggestive of granulation tissue, but inflammation does not appear to be an intrinsic feature. Inflammation is usually slight in the deeper part of the lesion and may be absent when the epidermis is intact. The angiomatous tissue tends to occur in discrete masses or lobules, resembling a capillary hemangioma—hence, the preference by Mills and associates (83) for the term *lobular capillary hemangioma* to describe this condition (Fig. 33-18). The angiomatous tissue is surrounded by myxoid stroma containing scattered spindle- and stellate-shaped connective tissue cells and occasional mast cells. The angiomatous tissue is composed of a variably dilated network of blood-filled capillary vessels and groups of poorly canalized vascular tufts. Mitotic activity varies and can be prominent. Feeding vessels often extend into the adjacent dermis, and rare lesions show a deep component in the reticular dermis. Occasionally, foci of intravascular papillary endothelial hyperplasia occur within the larger deep vessels. Focal epithelioid endothelial cells can sometimes be seen. Focal cytologic atypia may be present, particularly in lesions arising in mucosal surfaces such as the mouth (95). The histology of recurrent or satellite lesions is similar, but the angiomatous proliferation can extend more deeply into the dermis. Pyogenic granulomas of the subcutaneous tissue or in veins show similar histologic features but lack an inflammatory component. Intravascular lesions can so distend the veins that the surrounding muscle coat can be thinned and difficult to detect (Fig. 33-19).

Pathogenesis. It was once assumed that granuloma pyogenicum was caused by pyogenic infection. However, the histologic picture of early lesions suggests a capillary hemangioma, and even in eroded lesions that show inflammation,

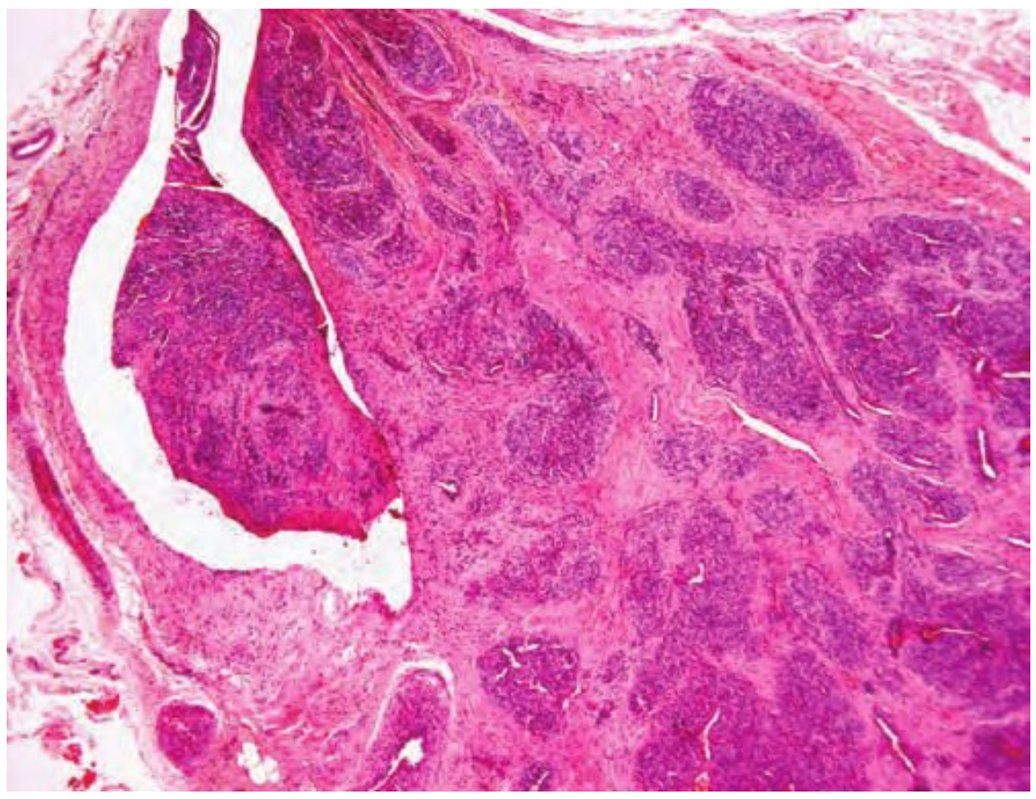


FIGURE 33-19. Intravascular lobular capillary hemangioma (pyogenic granuloma). Some cases occur entirely in an intravenous location.

the appearance mimics that of a capillary hemangioma in its deeper portions. Therefore, the term *lobular capillary hemangioma* has been suggested (83).

Immunohistochemical studies demonstrate positive labeling of endothelial cells for vascular markers, including CD31, and also of pericytes for smooth muscle actin.

Differential Diagnosis. Both Kaposi's sarcoma and angiosarcoma should be considered as part of the differential diagnosis, especially when multiple lesions are present. Elevated polypoid lesions are rare in Kaposi's sarcoma; most show obvious spindle cells woven between delicate vascular spaces, unlike in pyogenic granuloma. A much greater degree of cell atypia with intraluminal spreading of malignant cells characterizes well-differentiated angiosarcomas. Focal areas of intravascular papillary endothelial hyperplasia within a pyogenic granuloma occasionally can simulate angiosarcoma, but, even so, nuclear atypia is slight.

In recent years, a further differential diagnosis of pyogenic granuloma is with bacillary angiomatosis, an infectious, vascular proliferation seen in HIV-infected patients and caused by *Bartonella henselae* or less commonly by *Bartonella quintana*, which are small, gram-negative rods belonging to the family Bartonellaceae (96–98) (see Chapter 21). Bacillary angiomatosis is now rarely seen in the Western world, as HIV-positive patients are treated with HAART and with prophylactic antibiotics. Clinically, and especially histologically, lesions of bacillary angiomatosis can look remarkably similar to a pyogenic granuloma. The low-power architecture in superficial lesions may be almost identical to that seen in pyogenic granuloma (Fig. 33-20). In bacillary angiomatosis, however, the endothelial cells often have

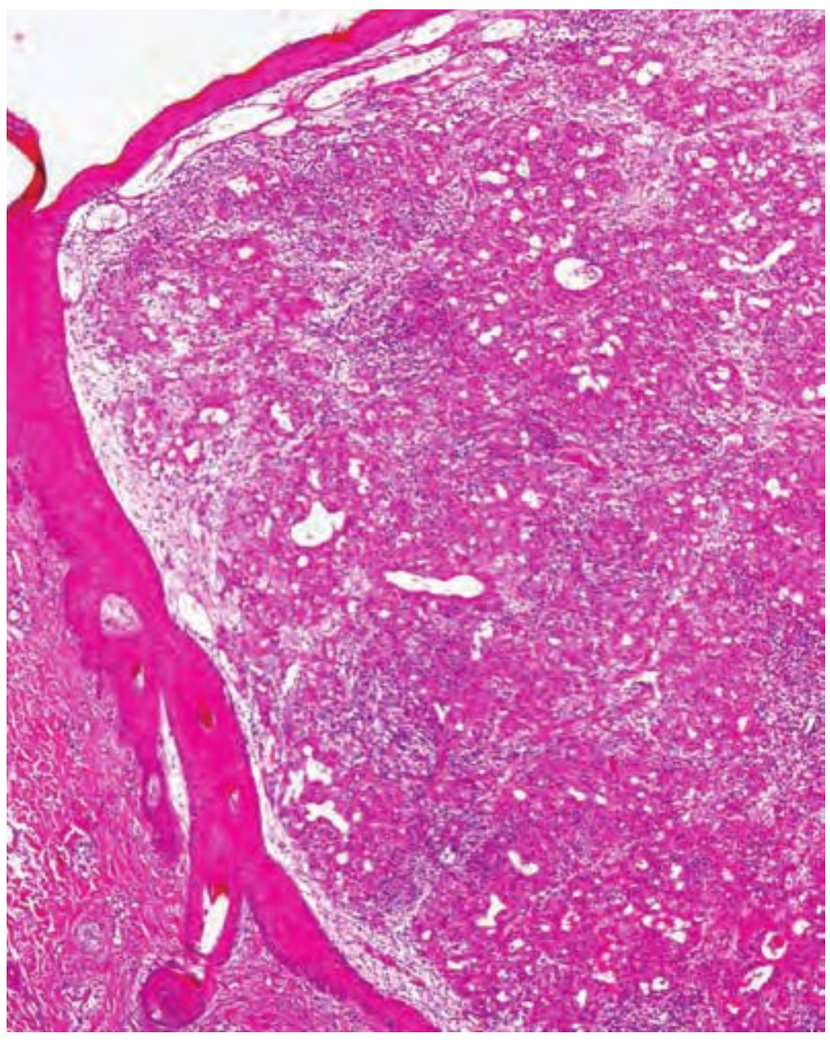


FIGURE 33-20. Bacillary angiomatosis. Similar low-power architecture to lobular capillary hemangioma, but there is more prominent inflammation in the background.

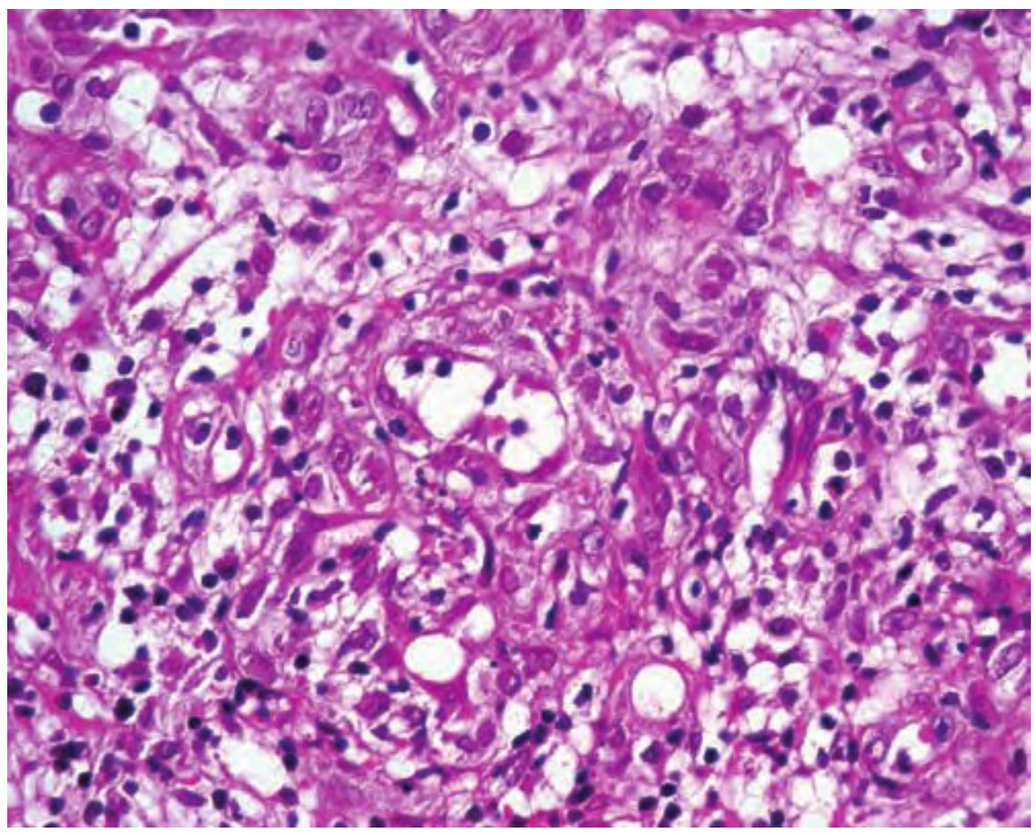


FIGURE 33-21. Bacillary angiomatosis. The vascular channels are lined by pale epithelioid endothelial cells. Often, neutrophils with nuclear dust are seen in the surrounding stroma.

abundant pale cytoplasm (Fig. 33-21), and aggregates of neutrophils are present throughout the lesion, often in relation to clumps of granular basophilic material. This basophilic material shows bacilli when stained with Warthin-Starry (Fig. 33-22) or Giemsa stains. The presence of the organism may also be detected by PCR.

Vascular granulomatous lesions mimicking pyogenic granulomas occasionally arise as a complication of systemic or topical retinoid therapy, but the histology is that of nonspecific vascular granulation tissue lacking a lobular architecture (99–101). Pyogenic granuloma–like lesions have also been described during capecitabine therapy (102).

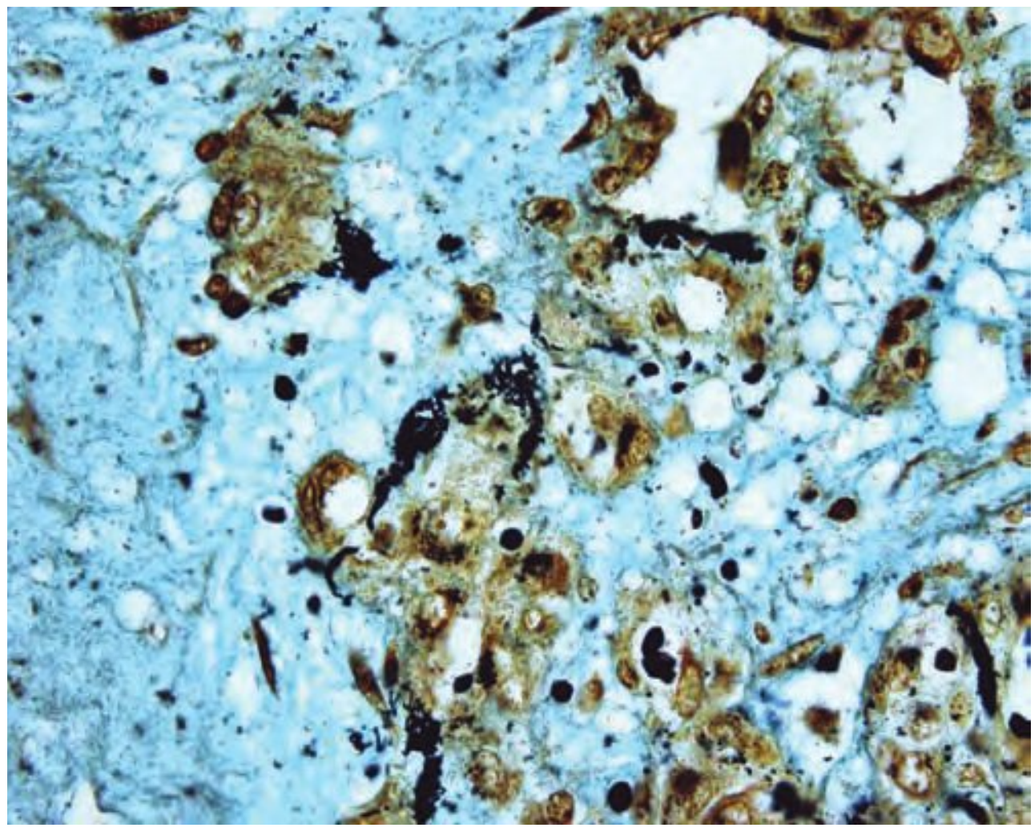


FIGURE 33-22. Bacillary angiomatosis. Warthin-Starry stain showing numerous clumps of bacilli.

Distinction from a nodular lesion of orf or milker's nodule may be difficult, as the low-power architecture may resemble a lobular capillary hemangioma. However, in the former, there is often prominent hyperplasia of the epidermis and the infundibular portion of the hair follicles. The prominent vascular component represents granulation tissue with only a focal lobular architecture, and the keratinocytes often show typical viral inclusions.

Cavernous Hemangioma

Sharing with strawberry nevus the same age, gender, and anatomic distribution, cavernous hemangioma is still less common and tends to be larger, deeper and less well-defined than the former and shows no tendency for spontaneous regression (58,59). Rare cavernous hemangiomas may be associated with an overlying capillary hemangioma. There are two rare conditions in which numerous cavernous hemangiomas occur: Maffucci's syndrome and the blue rubber bleb nevus.

Maffucci's Syndrome

The outstanding features of Maffucci's syndrome are dyschondroplasia resulting in defects in ossification; fragility of the bones, causing severe deformities; and osteochondromas, which may develop into chondrosarcomas (24). In addition, large, compressible subcutaneous cavernous hemangiomas may be present at birth or appear in childhood or early adulthood.

Blue Rubber Bleb Nevus

In the blue rubber bleb nevus, cavernous hemangiomas are present at birth but may subsequently increase in size and number. The hemangiomas have a distinct appearance, and most of them are protuberant, dark blue, soft, and compressible; some are pedunculated. They vary from a few millimeters to 3 cm in diameter. In addition, subcutaneous hemangiomas are felt on palpation. There are also hemangiomas in the oral mucosa, the gastrointestinal tract, and less commonly in other organs (24). Some blue rubber bleb nevi are probably telangiectatic glomangiomas in which the glomus cells are sparse.

Histopathology. Cavernous hemangiomas appear in the lower dermis and the subcutaneous tissue with large, irregular spaces containing red blood cells and fibrinous material (Fig. 33-23). The spaces are lined by a single layer of thin endothelial cells. Not uncommonly, a capillary component is present, especially in the superficial portion of a tumor. Dystrophic calcification is often present.

Variant of Cavernous Hemangioma: Sinusoidal Hemangioma

Sinusoidal hemangioma is a relatively rare variant of cavernous hemangioma (60,103). The lesion presents as a bluish subcutaneous mass, especially in middle-aged adults, and has a predilection for females. Although the anatomic distribution is wide, tumors often present in the breast, and in this setting, angiosarcoma is considered in the differential diagnosis.

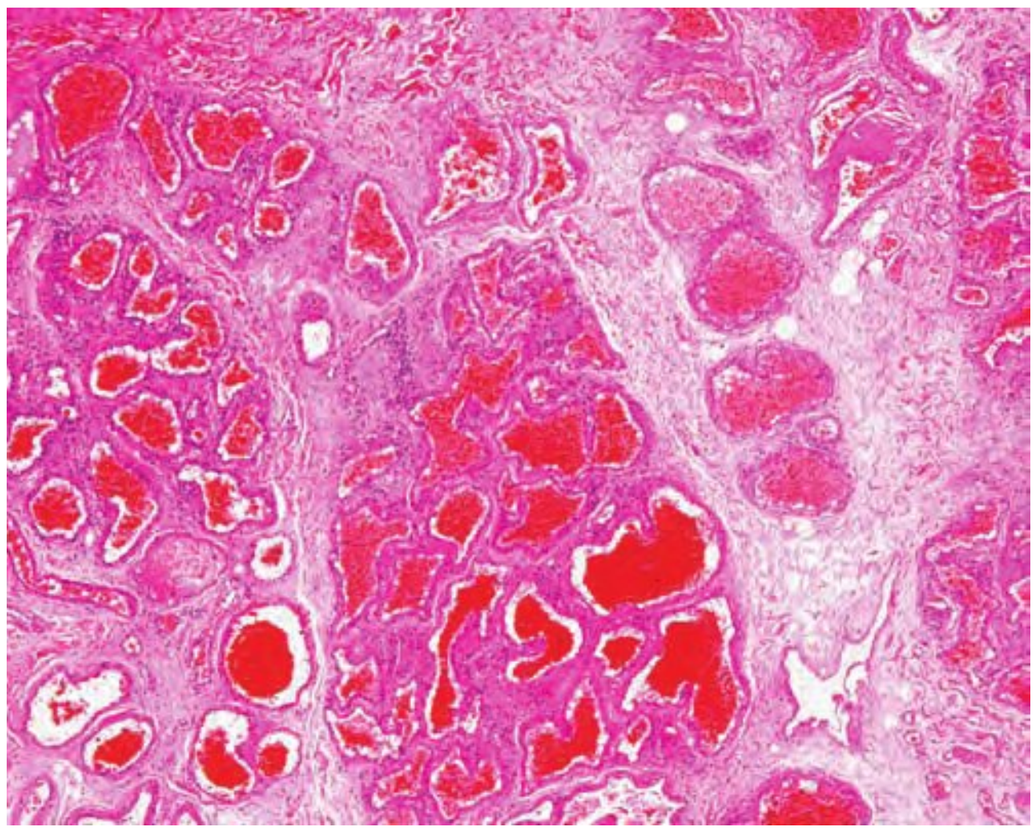


FIGURE 33-23. Cavernous hemangioma. Markedly dilated and congested vascular spaces.

Histopathology. Sinusoidal hemangioma is lobular and focally ill-defined with partial or total replacement of subcutaneous fat lobules. The typical feature is the presence of gaping, markedly dilated and congested, thin walled, back-to-back vascular spaces in a sievelike or sinusoidal arrangement (Fig. 33-24). Pseudopapillary structures due to cross-sectioning of these spaces focally resemble intravascular papillary endothelial hyperplasia (Fig. 33-25). The blood vessels are lined by bland, flat endothelial cells, which can be focally prominent and mildly pleomorphic. Thrombosis, hyalinization, dystrophic calcification, and even areas of infarction can be seen in older lesions. Distinction from a well-differentiated angiosarcoma is based on the presence in the latter of an infiltrative growth pattern, cytologic atypia, and multilayering. In breast lesions, it is

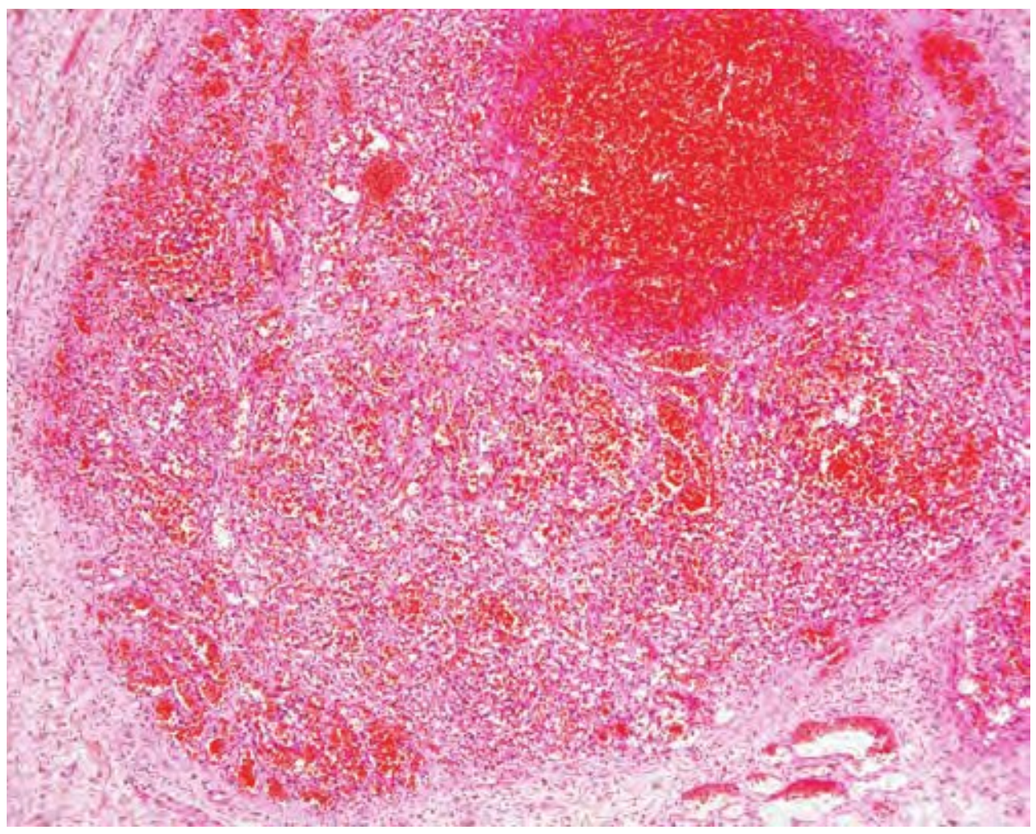


FIGURE 33-24. Sinusoidal hemangioma. Congested anastomosing vascular channels with a sievelike appearance.

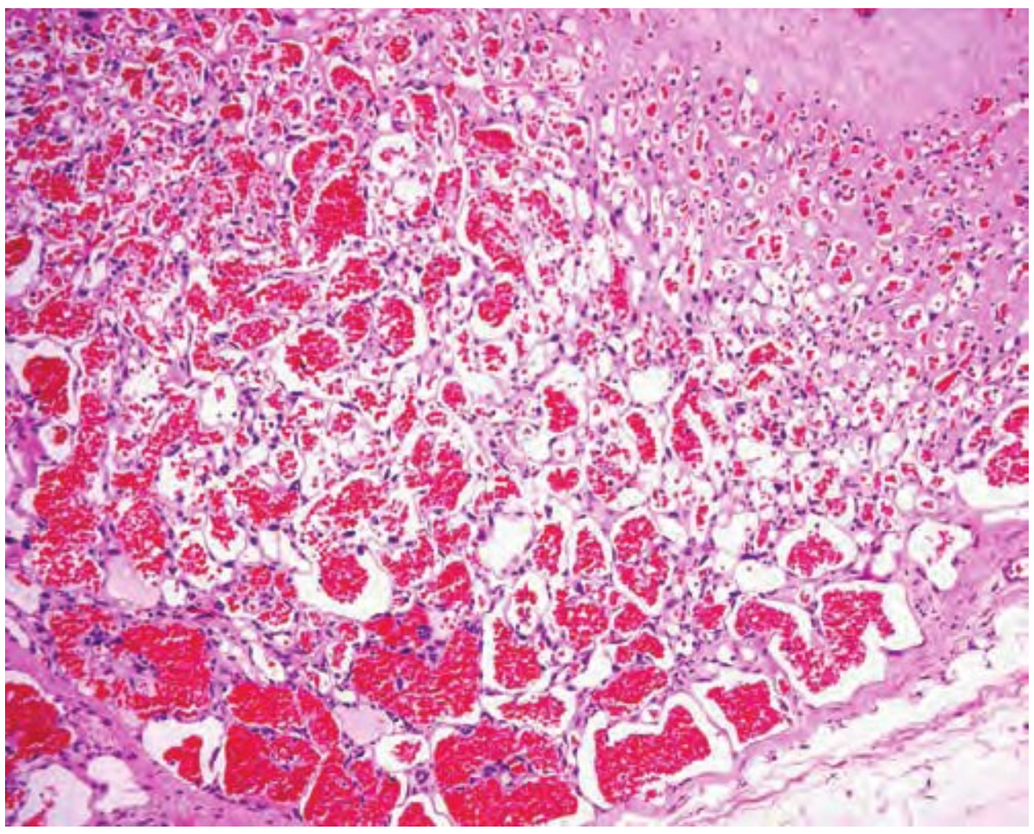


FIGURE 33-25. Sinusoidal hemangioma. Higher magnification reveals a typical sinusoidal appearance.

worth remembering that mammary angiosarcomas are always intraparenchymal.

Verrucous Hemangioma

Verrucous hemangioma is a rare form of vascular malformation that is usually congenital and only rarely presents later in life. Most cases present as wartlike, dark blue papules or nodules with special predilection for the distal lower limbs (Fig. 33-26). Although the majority of cases are solitary, an exceptional case with multiple lesions on different parts of the body has been reported (104). Often, cases are confused clinically and histologically with angiokeratomas, but verrucous hemangiomas always have a deep component, and recurrence after incomplete excision occurs in up to one third of cases (105).

In *Cobb syndrome*, a lesion identical to a verrucous hemangioma presents on the trunk with a dermatomal distribution and in association with an underlying meningospinal hemangioma (106).

Histopathology. The superficial portion of a verrucous hemangioma is indistinguishable from an angiokeratoma. However, a combination of congested capillaries and cavernous-like vascular spaces is seen extending into the deep dermis and subcutaneous tissue (Fig. 33-27). These vascular spaces are lined by flattened endothelial cells and are usually surrounded by a layer of pericytes. A lobular growth pattern is often apparent in the deep component.



FIGURE 33-26. Verrucous hemangioma. Verrucous vascular plaques are typically seen.

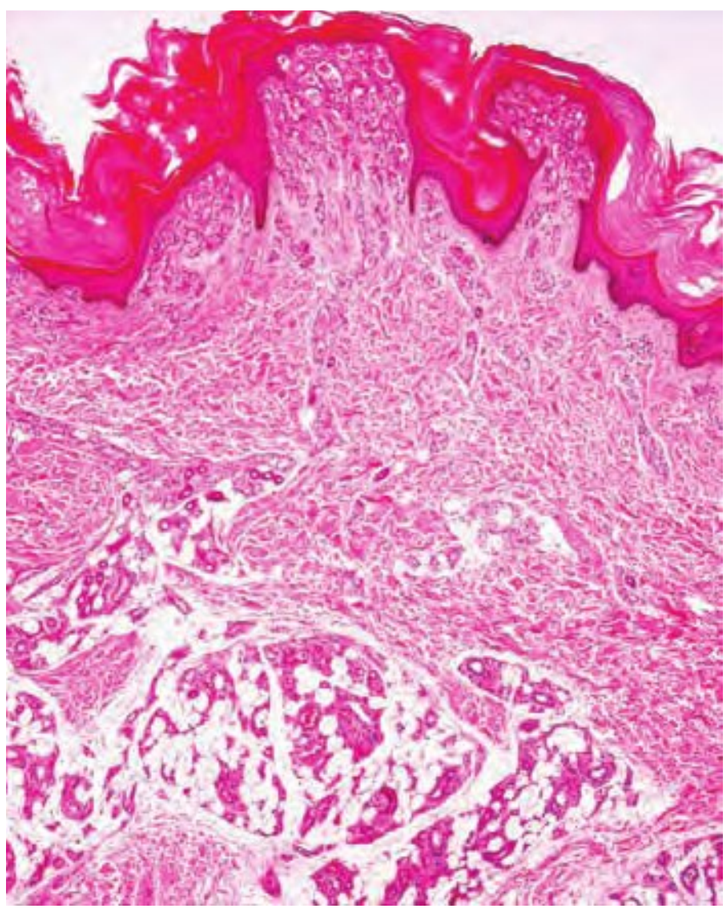


FIGURE 33-27. Verrucous hemangioma. Note the superficial component similar to angiokeratoma but with a deep component extending to the subcutaneous tissue.

Microvenular Hemangioma

This is a relatively rare, acquired vascular lesion that usually arises as a small, reddish lesion in young to middle-aged individuals of either gender (107,108). The arms, trunk, and legs are favored sites. The development of lesions in relationship to pregnancy or a change in the use of oral contraception may suggest a hormonal influence on the disease in women (109).

Histopathology. Histologically, thin, branching capillaries and small venules with narrow or slightly dilated lumina are found widely throughout the dermis (Fig. 33-28). There is no obvious endothelial cell atypia or accompanying inflammation, but slight dermal sclerosis is often present (Fig. 33-29). The collagen bundles around the vascular channels appear somewhat

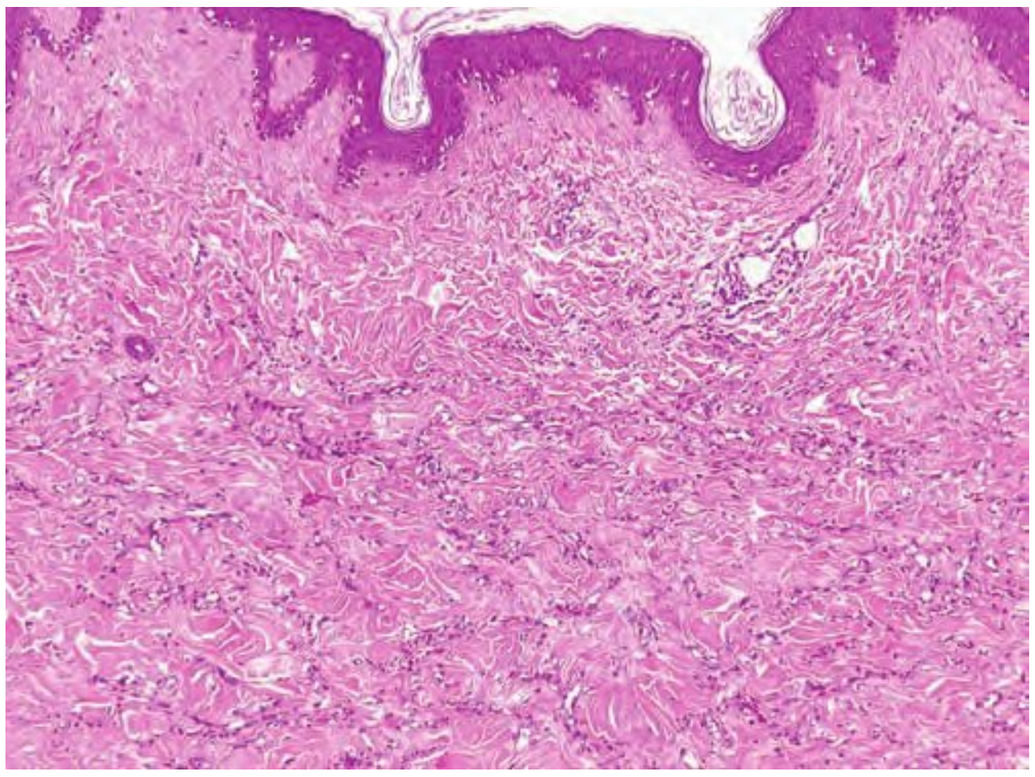


FIGURE 33-28. Microvenular hemangioma. Irregular, branching, thin-walled venules within the dermis.

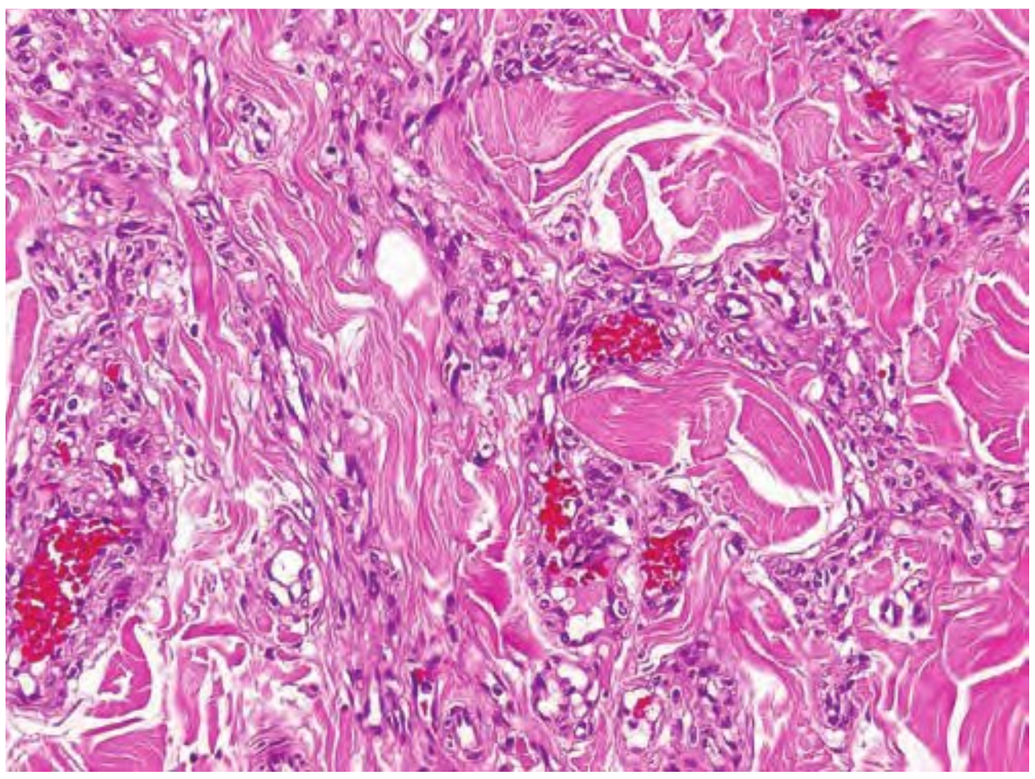


FIGURE 33-29. Microvenular hemangioma. Note small venules surrounded by somewhat hyalinized collagen bundles.

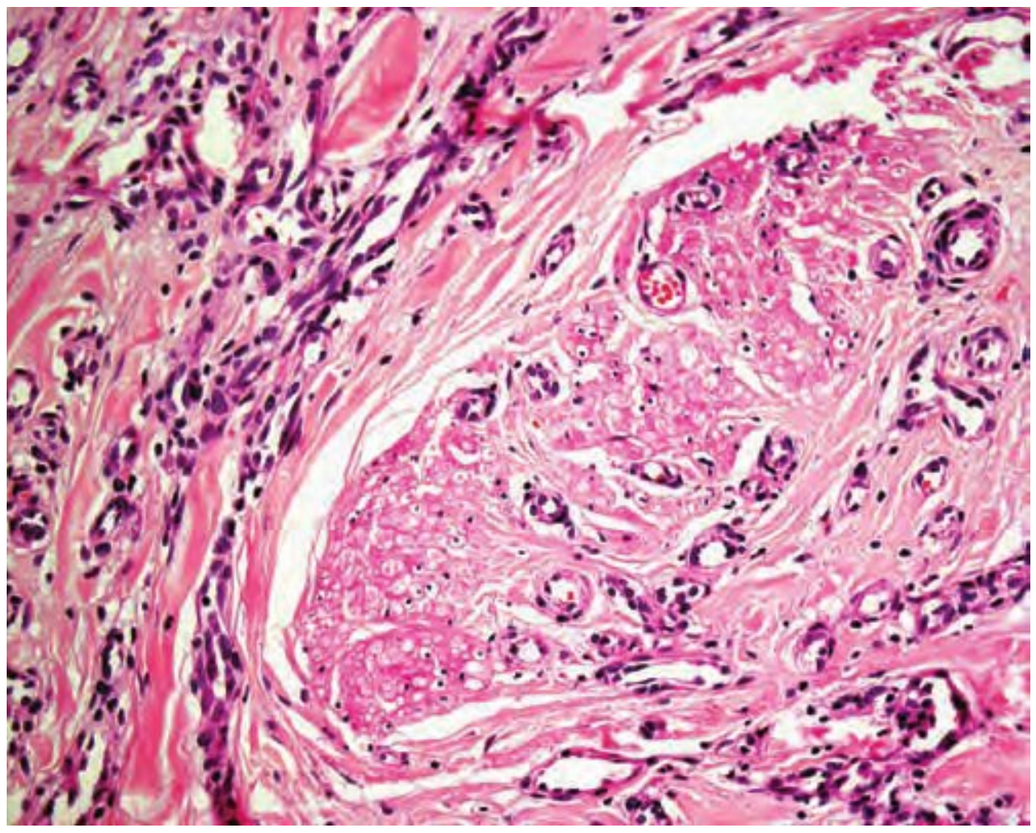


FIGURE 33-30. Microvenular hemangioma. Prominent infiltration of the arrector pili muscle.

sclerotic. A fairly constant feature in many cases is the prominent infiltration of arrector pili muscles by the proliferating vascular channels (Fig. 33-30). The cells lining the vessels are strongly positive for von Willebrand factor and CD34. In two cases, angiomatous tufts in the deeper part of the lesion have suggested a possible relationship with tufted angioma (108).

Differential Diagnosis. The importance of microvenular hemangioma as an acquired vascular anomaly in young persons lies in the differential diagnosis from an early or macular lesion of Kaposi's sarcoma. The lymphangioma-like channels of Kaposi's sarcoma are more delicate, do not contain erythrocytes, show angulated outlines, and tend to wrap around collagen bundles. Furthermore, plasma cells and other inflammatory cells are common in Kaposi's sarcoma but not in microvenular hemangioma. HHV-8 is consistently positive in Kaposi's sarcoma and negative in microvenular hemangioma. Only a single case of HHV-8–positive microvenular hemangioma in a patient with POEMS syndrome has been reported (110).

Hobnail Hemangioma (Targetoid Hemosiderotic Hemangioma)

Hobnail hemangioma, or targetoid hemosiderotic hemangioma, is a relatively uncommon vascular tumor that usually presents in the trunk or extremities of young or middle-aged adults with a male predominance (111–113). Rare cases occur in the oral mucosa. The descriptive name initially given to this tumor reflects a typical clinical appearance characterized by a small solitary lesion consisting of a brown to violaceous papule, 2 to 3 mm in diameter, surrounded by a thin, pale area and a peripheral ecchymotic ring. However, these features are only present in a small percentage of cases, and most often, the clinical appearance is that of a red-blue or brown papule. The alternative name of *hobnail hemangioma*, which emphasizes a more constant special histologic feature, has therefore been proposed (see text following). Interestingly, some lesions in females change during the menstrual cycle, suggesting that there is a direct hormonal influence (114).

Histopathology. In the superficial reticular dermis, there are a number of thin-walled, dilated, and irregular vascular spaces (Fig. 33-31) often lined by bland endothelial cells with scanty cytoplasm and rounded nuclei that protrude into the lumina and closely resemble hobnails (Figs. 33-32 and 33-33). Focally, epithelioid cells are rarely present. Intraluminal papillary projections and fibrin thrombi can be seen in the superficial blood vessels (Fig. 33-33). The vascular channels in the deeper dermis become much less conspicuous and eventually disappear completely. These deeper channels are irregular and angulated, lined by flattened endothelial cells, and dissect between collagen bundles.

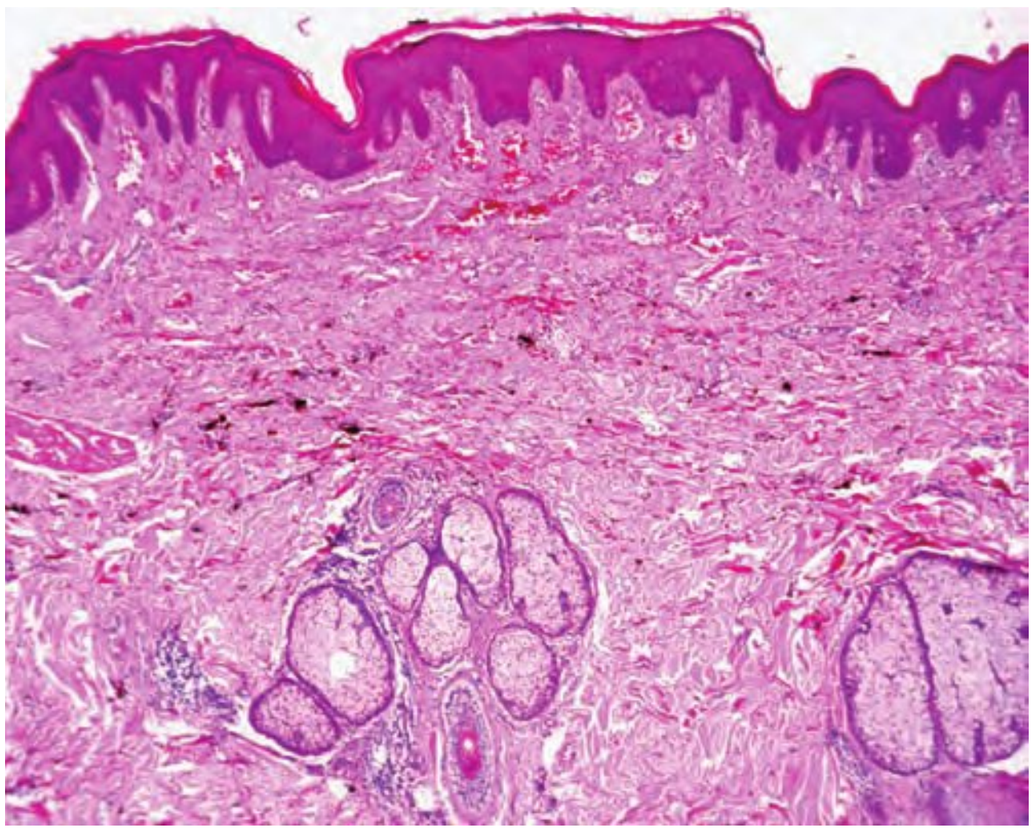


FIGURE 33-31. Hobnail hemangioma. Typical wedge-shaped architecture with a prominent superficial component. Note prominent hemosiderin deposition.

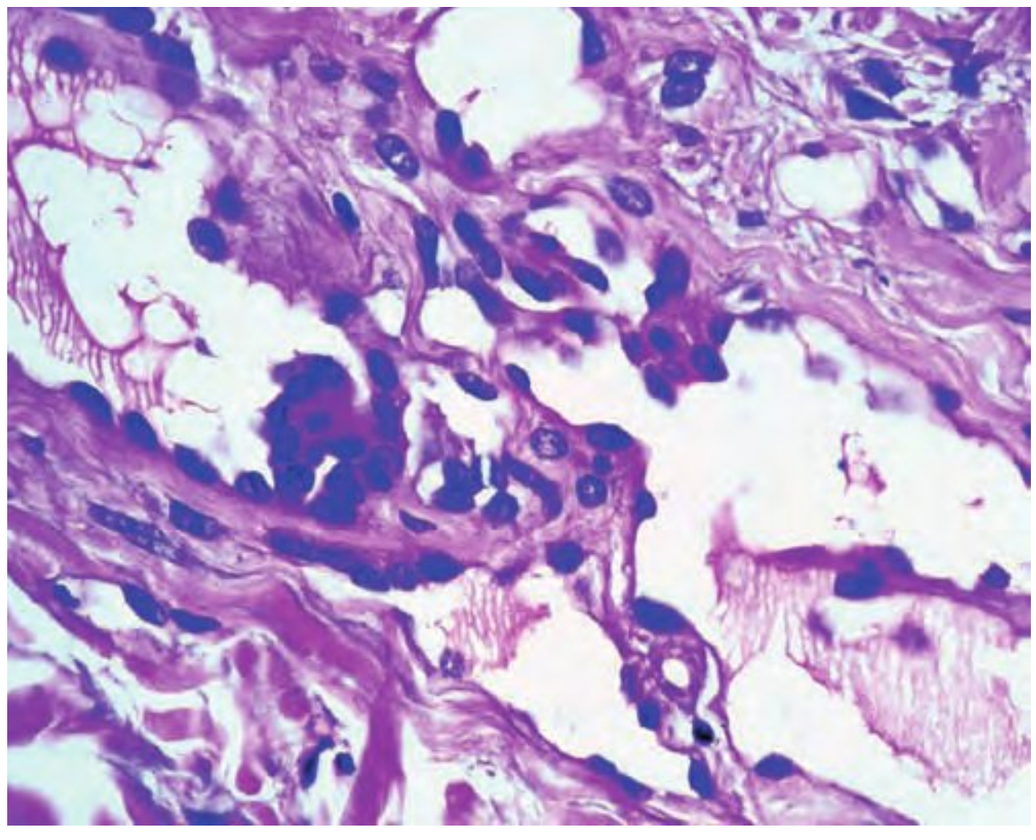


FIGURE 33-33. Hobnail hemangioma. Hobnail endothelial cells and small papillary projections.

Extensive red blood cell extravasation, inflammatory aggregates predominantly of lymphocytes, and, in a later stage, extensive stromal hemosiderin deposition are commonly seen.

Pathogenesis. Because there is a family of vascular tumors characterized by epithelioid endothelial cells, it has been proposed that this tumor represents the benign end of the spectrum of a group of vascular tumors characterized by hobnail endothelial cells that includes *Dabska's tumor* and *retiform hemangioendothelioma* (115). Based on the positivity of the endothelial cells for vascular endothelial growth factor receptor 3 (VEGFR-3), it has been proposed that these tumors display lymphatic differentiation (113). However, it has become apparent that VEGFR-3 is not a specific marker of lymphatic differentiation (116).

Differential Diagnosis. This includes patch-stage Kaposi's sarcoma, retiform hemangioendothelioma, and benign lymphangioendothelioma (see page 1045).

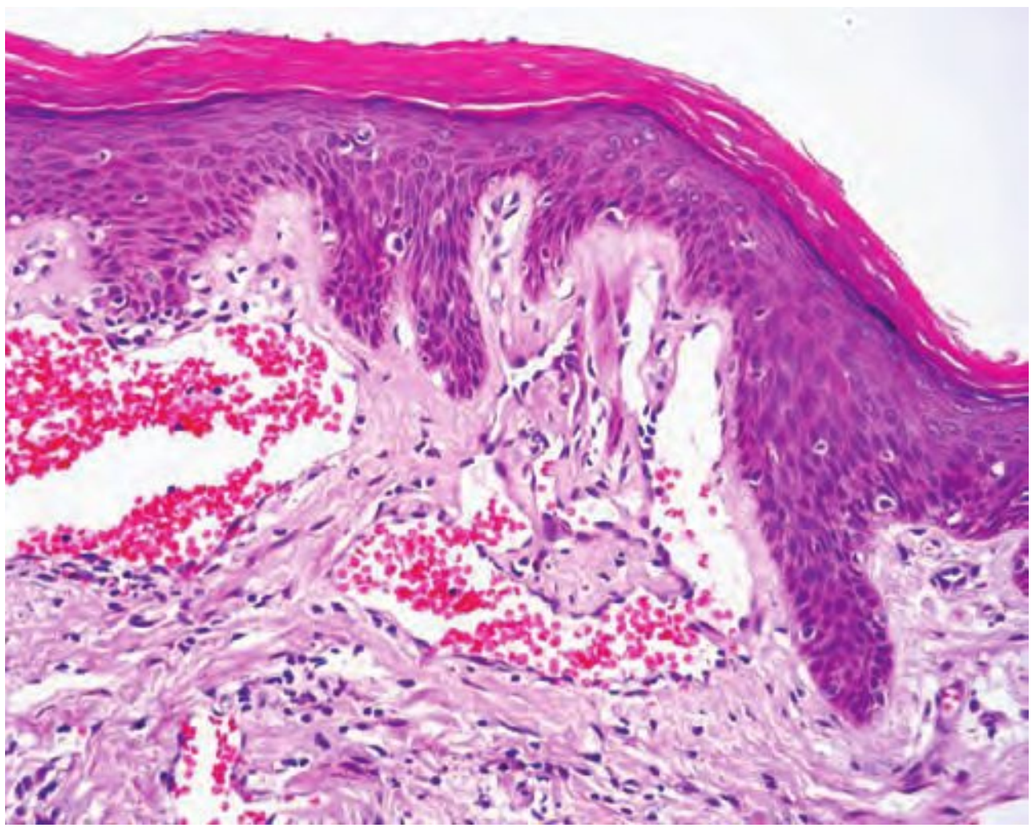


FIGURE 33-32. Hobnail hemangioma. Irregular congested vascular channels, some of which are lined by hobnail endothelial cells.

Epithelioid Hemangioma (Angiolymphoid Hyperplasia With Eosinophilia)

The terms *epithelioid hemangioma* and *angiolymphoid hyperplasia with eosinophilia* highlight the controversy about whether this entity represents a vascular neoplasm or a reactive process consequent to trauma or some other stimulus. Previously, lesions included within this group were referred to as *histiocytoid hemangiomas*, but this name has been abandoned because as originally proposed it included other entities that do not qualify as epithelioid hemangioma (117,118). It is not clear whether this entity represents a reactive proliferation secondary to diverse stimuli including trauma (119) or a neoplastic process, but the latter is favored. Therefore, the term *epithelioid hemangioma* is generally preferred to encompass vascular lesions at the benign end of the spectrum of conditions characterized by endothelial cells that have an epithelioid morphology (117,118).

Clinical Features. Most lesions arise either superficially in the dermis or in the subcutaneous tissue or deeper tissues, although occasionally both superficial and deep tissues are affected together (120). Blood eosinophilia has been reported in up to 15% of patients (118,120). Local recurrence may be seen in up to 30% of cases.

Superficial lesions. Young to middle-aged women are mainly affected with the development of pruritic papules



FIGURE 33-34. Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia). Single or multiple vascular papules often present in the ear.

(Fig. 33-34) and plaques at or around the external ear. The lesions can be numerous but are limited to one side. Typically, the clinical course is chronic over several years despite excision and other treatment modalities. Such superficial lesions were originally referred to as *pseudopyogenic granuloma*. Occlusion of the external auditory canal can bring patients to the attention of ear, nose, and throat specialists. Sometimes, other areas in the head and neck region, especially the occipital region and the vicinity of the temporal artery, are affected.

Lesions of subcutaneous and deeper tissues. Adults are mainly affected, and there is no gender predilection. The typical lesion is a solitary, slowly growing, firm, subcutaneous swelling 2 to 10 cm in size in the head and neck region, with some predilection for the pre- or postauricular sites. Sometimes, more than one lesion arises. Most lesions are asymptomatic except for occasional pruritus. Lymphadenopathy is usually not seen. Occasionally, other body sites are affected, such as the arm, hands, axillae, or inguinal region (120–122). Rare cases have been documented in association with a traumatically induced arteriovenous fistula involving the popliteal artery (123). Origin from the radial artery has also been documented (124). The condition can persist for years, but serious complications do not occur.

Epithelioid hemangioma may also rarely occur in the oral cavity (125), tongue (126), lymph node (127), bone (128), and testis (129). A case has also been reported in an ovarian teratoma (130). Epithelioid hemangiomas occurring at sites different from the skin often lack the inflammatory component.

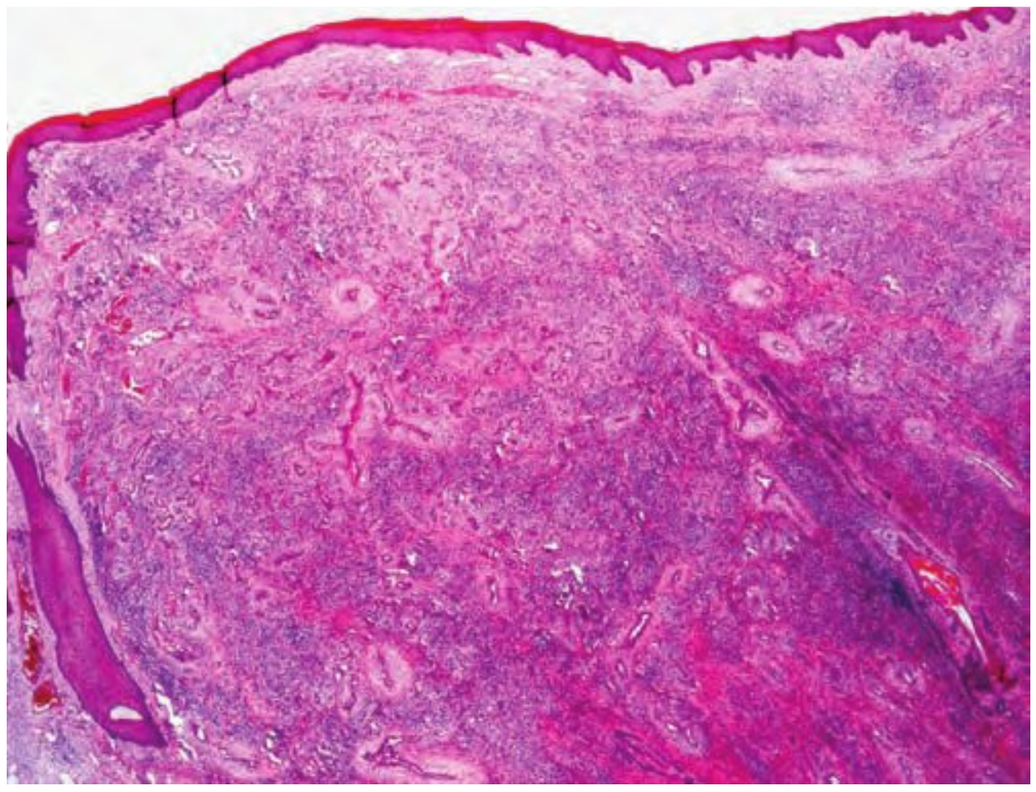


FIGURE 33-35. Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia). Superficial lesion from the ear showing typical lobular architecture and a prominent inflammatory cell infiltrate.

Histopathology. The main components of the pathology include the following:

1. Proliferation of small- to medium-sized blood vessels often showing a lobular architecture (Fig. 33-35). Many of these vascular channels are lined by greatly enlarged (epithelioid) endothelial cells (Figs. 33-36 and 33-37).
2. A perivascular inflammatory cell infiltrate composed mainly of lymphocytes and eosinophils.
3. Nodular areas of a lymphocytic infiltrate with rare follicle formation.
4. Frequent origin from a small artery or a vein. Rarely, the whole lesion is intravascular (Fig. 33-38). The condition

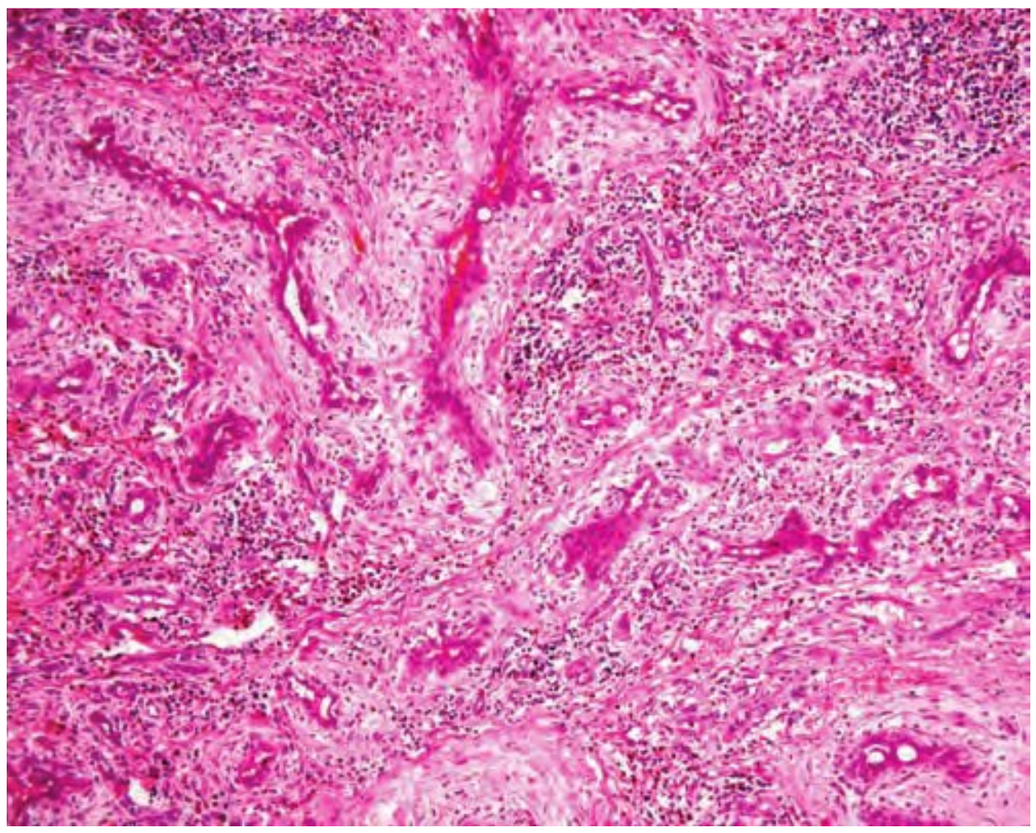


FIGURE 33-36. Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia). Numerous vascular channels lined by prominent large, pink epithelioid endothelial cells and surrounded by inflammation.

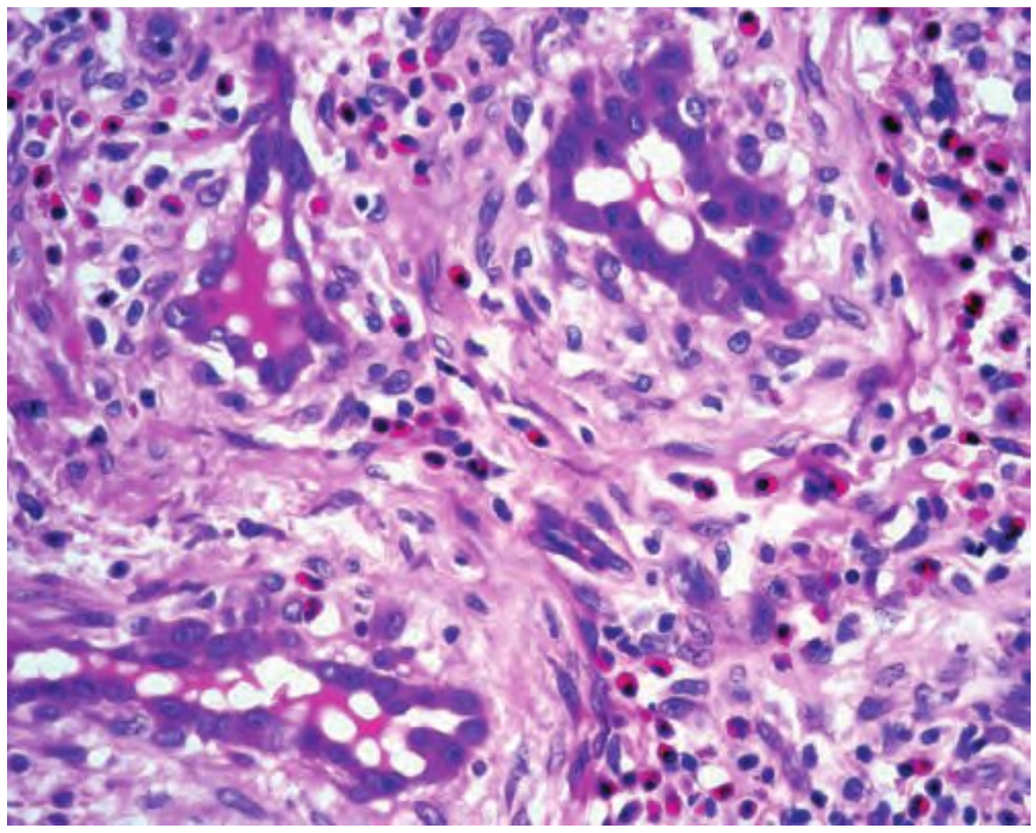


FIGURE 33-37. Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia). Prominent endothelial cells with abundant eosinophilic cytoplasm and numerous eosinophils in the surrounding stroma. Note perivascular fibrosis and numerous eosinophils.

originally described as intravenous atypical vascular proliferation likely represents a variant of intravascular epithelioid hemangioma (131).

In superficial lesions, there is variable degree of vascular hyperplasia that can include areas in which the proliferation is almost angiomatous. A distinctive feature is the "cobblestone" appearance of enlarged endothelial cells that project into the lumina of some vessels. The nucleus of these cells is ovoid and orthochromatic without atypia or evidence of mitotic activity. Affected vessels often show endothelial cells with intracytoplasmic vacuoles, which is a prominent feature of diagnostic value (Fig. 33-37). The most abnormal blood vessels are usually surrounded by stellate and spindle-shaped cells in a mucoid stroma. The associated perivascular inflammatory cell infiltrate is usually loosely scattered around the affected vessel, but it may be almost completely absent in some places. Generally, eosinophils make up 5% to 15% of the cells. Lesions with few inflammatory cells are rarely seen. Inflammatory cells also decrease markedly in late stages when a prominent fibrotic component is often present.

The epidermis above the lesions may show acanthosis or erosions due to superficial trauma. The skin appendages are usually unaffected except for the occasional finding of follicular mucinosis (132).

In subcutaneous lesions, the inflammatory cell infiltrate is usually more massive, with a central, poorly circumscribed nodule that replaces the fat. The nodule is composed of confluent sheets of small lymphocytes and eosinophils in which a network of poorly canalized thick-walled capillaries is embedded. Satellite smaller islands of lymphoid cells with lymphoid follicles usually surround the central nodule. Eosinophils can form up to 50% of the cell population.

In about 50% of cases, evidence of involvement of medium- to large-sized arteries can be found. A variable degree of blood vessel damage occurs, with infiltration of the vessel wall by inflammatory cells and occlusion of the lumen. Partial loss of the internal elastic lamina is often seen.

Histogenesis. The etiology and pathogenesis of angiolymphoid hyperplasia is at present uncertain. Occasionally, trauma (119) or external otitis can precede the onset of the disease. Ultrastructural studies have not confirmed that the enlarged endothelial cells are developing histiocytic properties, as has been suggested. There is no relation to HHV-8, but transient angiolymphoid hyperplasia with eosinophilia and Kaposi's sarcoma have been described after primary infection with HHV-8 in an HIV-positive patient (133,134).

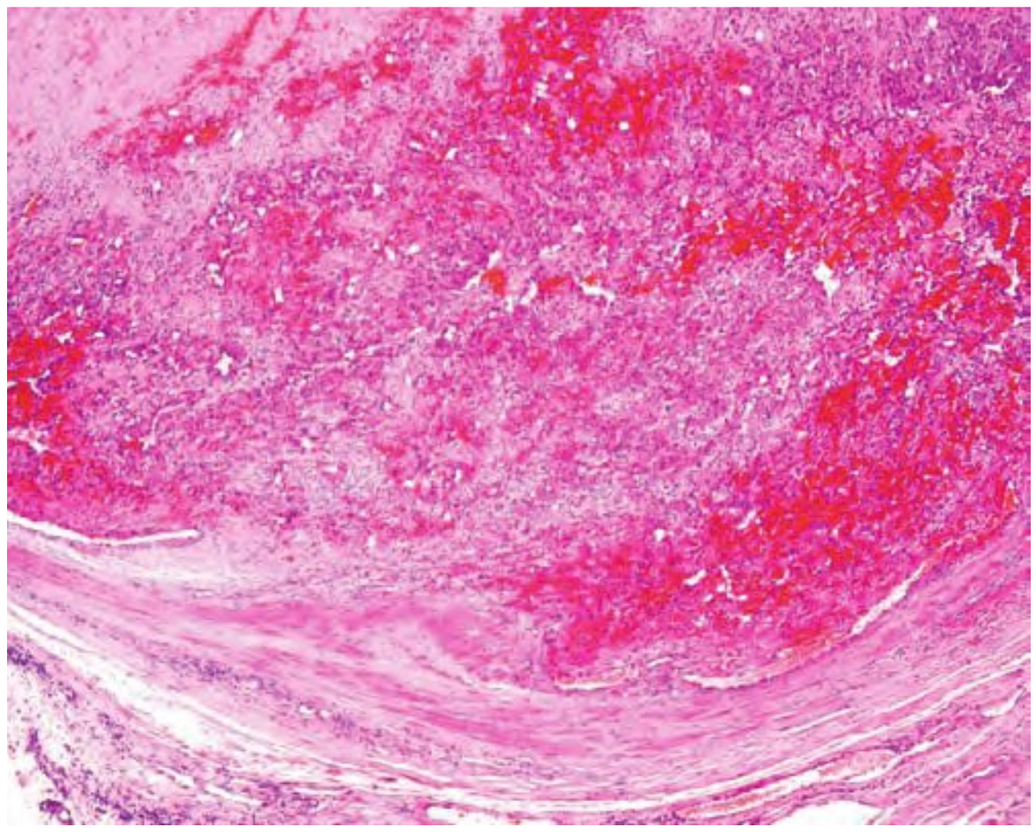


FIGURE. 33-38. Intravascular epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia). Some cases of epithelioid hemangioma are entirely intravascular.

Differential Diagnosis. The proliferation of endothelial-lined channels with large irregular cells can be misinterpreted as angiosarcoma. The latter can be accompanied by a lymphocytic infiltrate, but eosinophils are rarely present. The main distinguishing feature is the presence of nuclear atypia with hyperchromatism, mitotic activity, and dissection of collagen pattern in angiosarcoma but not in epithelioid hemangioma. Distinction from the recently described retiform hemangioendothelioma is easy: Angiolymphoid hyperplasia lacks a retiform growth pattern and does not show tall, narrow endothelial cells with a typical hobnail appearance, as is the case in retiform hemangioendothelioma.

Angiolymphoid hyperplasia can be distinguished from most benign angiomas or ectasias by the absence of an intrinsic inflammatory cell infiltrate in the latter. Greatly enlarged endothelial cells with an eosinophilic cytoplasm rarely feature in benign angiomas, although they can be seen focally in lobular capillary hemangioma (pyogenic granuloma).

Persistent insect-bite reactions can show overlapping histologic features with angiolymphoid hyperplasia, but the

vascular proliferation is rarely as exuberant. A somewhat similar pathology can also arise as a reaction to injected vaccines (135,136). The histology is characterized by a deep lymphoid infiltrate with lymphoid follicles, tissue eosinophilia, and fibrosis. Vascular hyperplasia is, however, less marked than in angiolymphoid hyperplasia, and epithelioid endothelial cells are not a feature. A diagnostic feature is the presence of aluminium-containing histiocytes as demonstrated by solochrome-azurine when aluminium-adsorbed vaccines have been used (135). The presence of aluminium may also be demonstrated by energy dispersive x-ray microanalysis.

When angiolymphoid hyperplasia with eosinophilia was first described in Western Europe, similarities to *Kimura's disease* as reported in the Far East were noted. Indeed, many authors thought that both conditions might be part of one disease spectrum (137). However, more recently, most authorities emphasize differences between the two entities (137–140). Subcutaneous angiolymphoid hyperplasia and Kimura's disease occur most commonly in the head and neck region in adults and both share the histologic features of extensive lymphoid proliferation, tissue eosinophilia, and evidence of vascular hyperplasia. Kimura's disease, however, demonstrates a wider age span, with a male predominance and a tendency for more extensive lesions to occur, often with involvement of salivary tissue and lymph nodes and at sites distant from the head and neck region. Authors from the Far East have stressed the histologic differences, the most important of which are the lesser degree of exuberant vascular hyperplasia, lacking prominent eosinophilic endothelial cells, and the absence of uncanalized blood vessels in Kimura's disease. Other points of difference are eosinophilic abscesses and marked fibrosis around the lesions in Kimura's disease and the absence of lesions centered around damaged arteries. There is an important association between Kimura's disease and renal disease, particularly nephrotic syndrome (141).

Cutaneous Epithelioid Angiomatous Nodule

Cutaneous epithelioid angiomatous nodule is a recently described lesion within the spectrum of vascular tumors with epithelioid endothelial cells (142–144). It is rare and presents in adults as a papule or nodule with predilection for the trunk followed by the limbs and face. Occasionally, multiple lesions may be seen, and there is no tendency for local recurrence.

Histopathology. Scanning maginification shows a superficial, well-circumscribed proliferation (Fig. 33-39) often surrounded by an epidermal collarete. It is composed of sheets of epithelioid endothelial cells with abundant pink cytoplasm, vesicular nuclei, and a single, small nucleolus (Fig. 33-40). Cytologic atypia is absent, and mitotic figures may be focally seen (Fig. 33-41). There is little tendency for formation of vascular channels, but individual endothelial cells often contain intracytoplasmic vacuoles. There is very little stroma between tumor cells, and in the background, scattered mononuclear inflammatory cells and eosinophils may be seen.

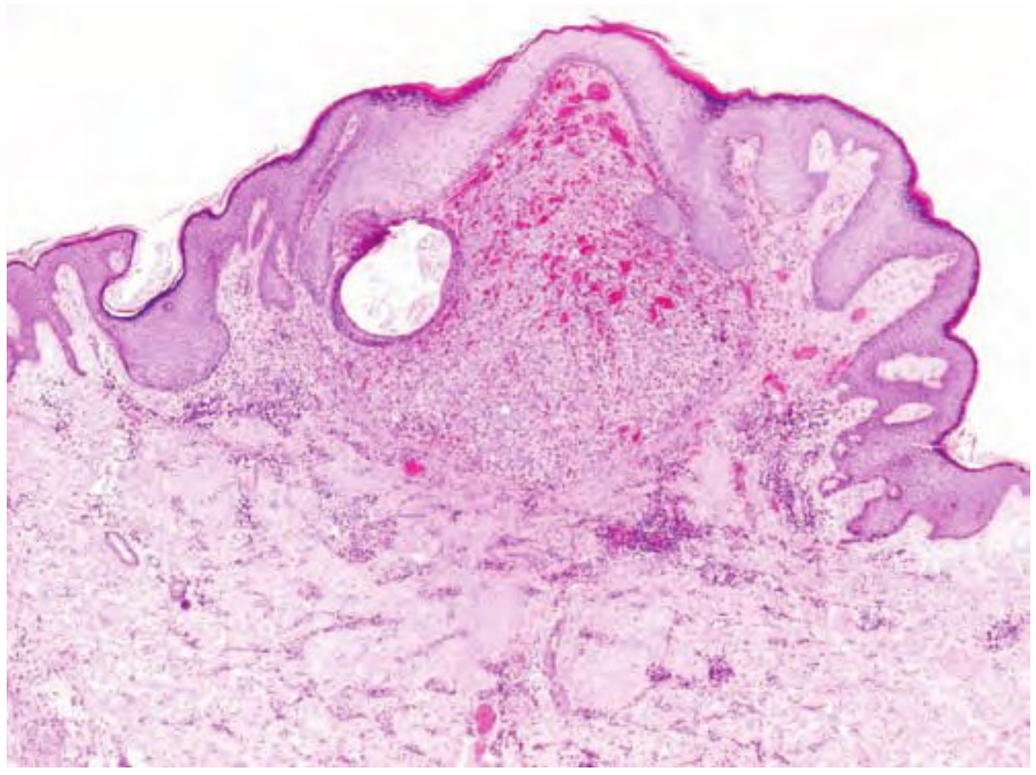


FIGURE 33-39. Cutaneous epithelioid angiomatous nodule. Superficial, well-defined polypoid lesion.

Differential Diagnosis. Distinction from epithelioid hemangioma is easy, as the clinical setting in the latter is different, and lesions are composed of vascular channels lined by epithelioid endothelial cells and not by solid sheets of epithelioid endothelial cells. Bacillary angiomatosis can be distinguished from epithelioid angiomatous nodule, as lesions in the former are usually multiple, and histologically there is formation of vascular channels lined by pale epithelioid endothelial cells and associated amorphous basophilic aggregates and neutrophils indicating the areas where the bacteria are located. Distinction from epithelioid angiosarcoma is based on the infiltrative growth pattern, pleomorphism, and mitotic activity in the latter.

Acquired Elastotic Hemangioma

Acquired elastotic hemangioma is a recently described and distinctive relatively rare vascular lesion that develops in

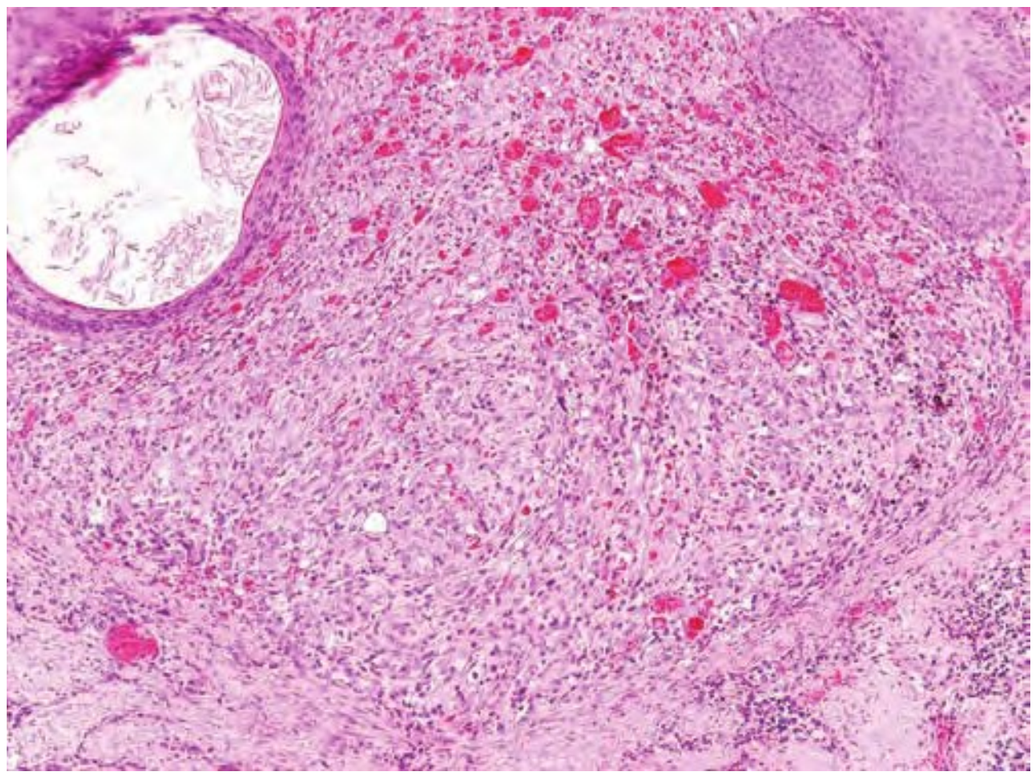


FIGURE 33-40. Cutaneous epithelioid angiomatous nodule. Sheets of epithelioid endothelial cells with focal intracytoplasmic lumina.

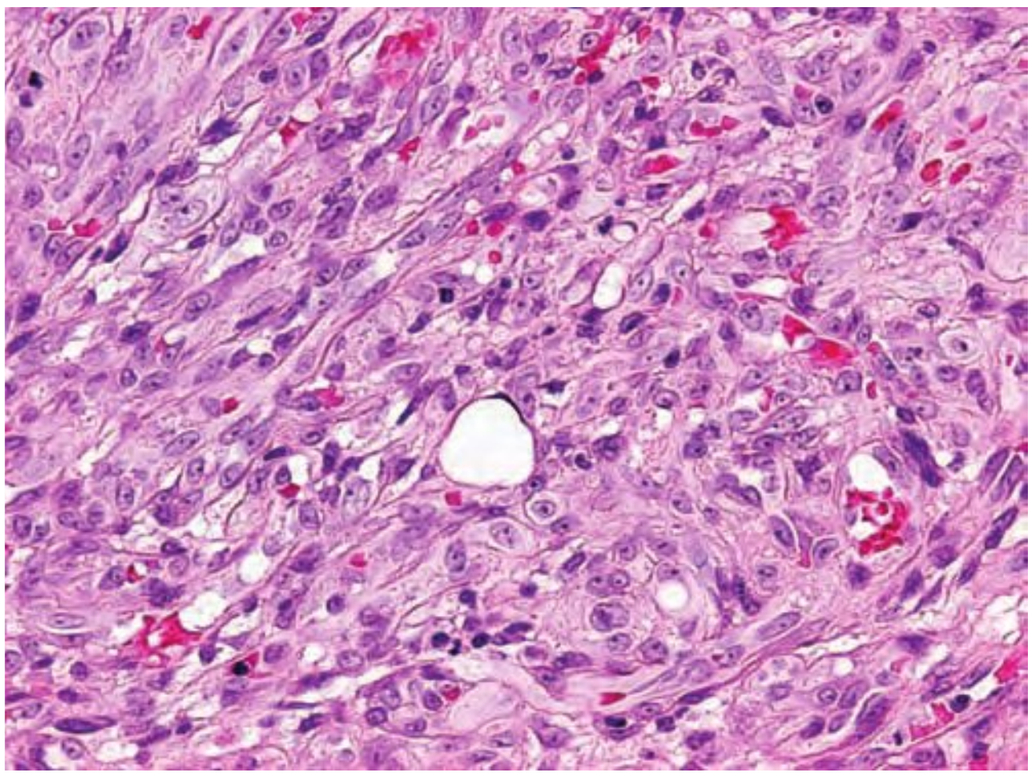


FIGURE 33-41. Cutaneous epithelioid angiomatous nodule. Cytologic atypia is mild or absent, and there are rare mitotic figures.

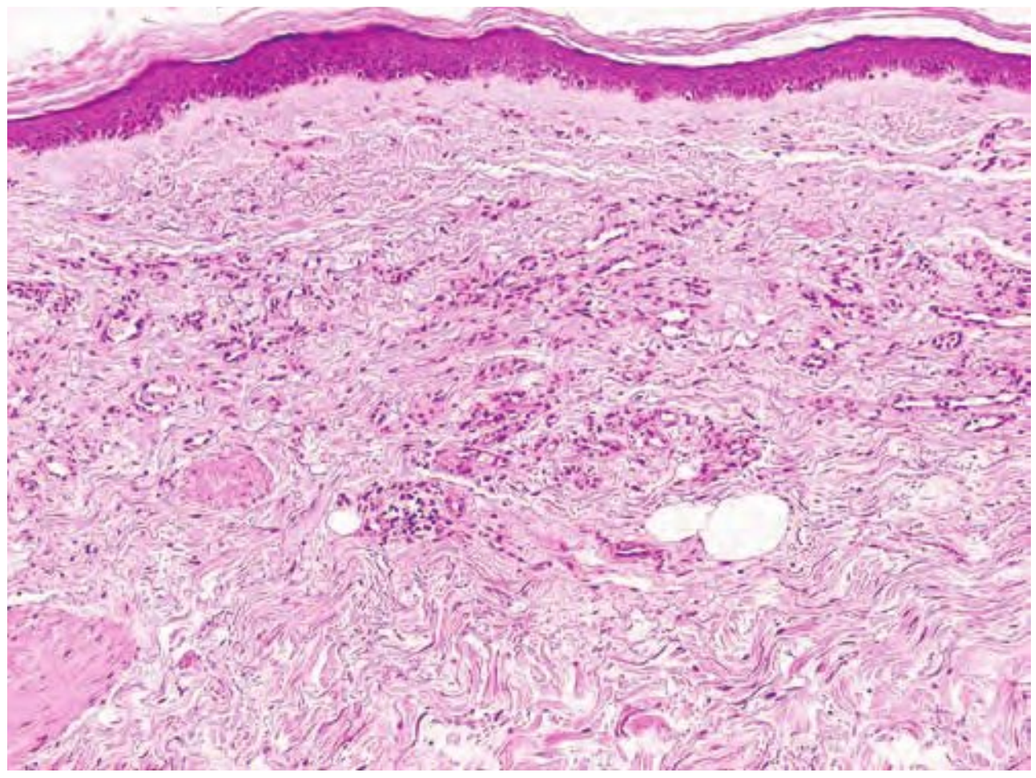


FIGURE 33-42. Acquired elastotic hemangioma. Superficial plaque-like proliferation of small, round vascular channels. (Courtesy of Dr. T. Mentzel, Friedrichshafen, Germany.)

sun-exposed skin, mainly of the forearms and neck of middle-aged to elderly patients, with predilection for females. The clinical presentation consists of a small, red or blue, circumscribed and asymptomatic plaque (145).

Histopathology. Lesions are well circumscribed and consist of a superficial, bandlike proliferation of capillaries in the background of solar elastosis (Figs. 33-42 and 33-43). Each capillary is surrounded by a layer of pericytes.

Arteriovenous (Venous) Hemangioma (Cirsoid Aneurysm)

Arteriovenous (venous) hemangioma, or cirsoid aneurysm, usually occurs as a solitary dark red papule or nodule on the face (especially the lip) or, less commonly, on the extremities of adults, with equal gender incidence (146,147). Rare cases present in the oral cavity (148). Most of the lesions measure <1 cm in diameter.

Histopathology. Within a circumscribed area, usually restricted to the dermis (Fig. 33-44), densely aggregated, thick-walled and thin-walled vessels lined by a single layer of endothelial cells are observed (Fig. 33-45). The walls of the thick-walled vessels consist mainly of fibrous tissue but in most instances also contain some smooth muscle. Internal elastic lamina is found in very few vessels, indicating that most of the blood vessels are veins. Many vessels contain red blood cells, and thrombi are occasionally seen (148). Lesions with similar histologic appearances can be seen in the deeper soft tissues of

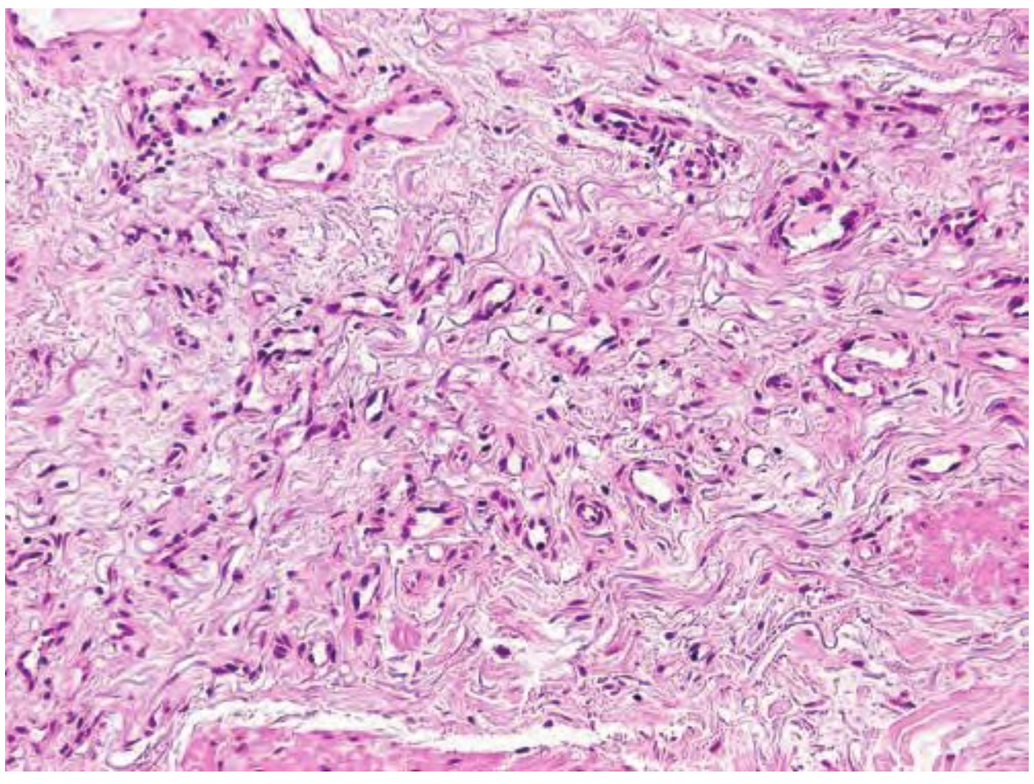


FIGURE 33-43. Acquired elastotic hemangioma. Note solar elastosis in the background. (Courtesy of Dr. T. Mentzel, Friedrichshafen, Germany.)

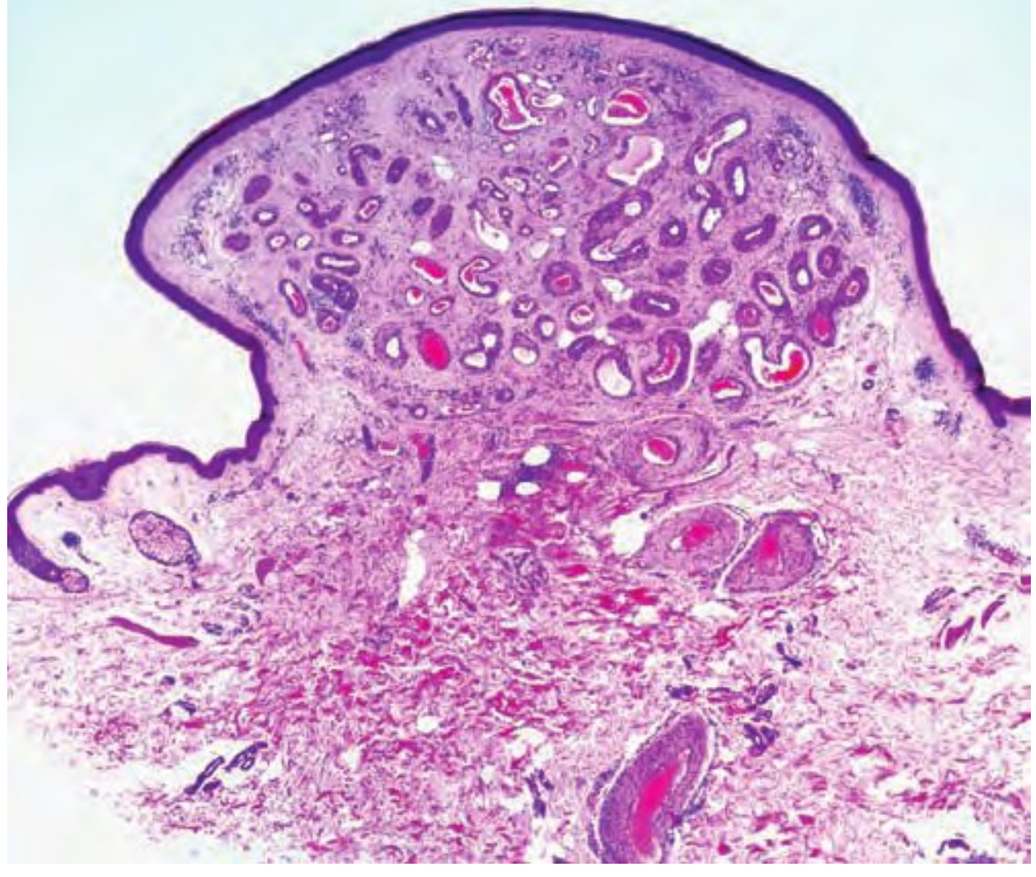


FIGURE 33-44. Cirsoid aneurysm. Polypoid superficial lesion composed of dilated, thick-walled vascular channels.

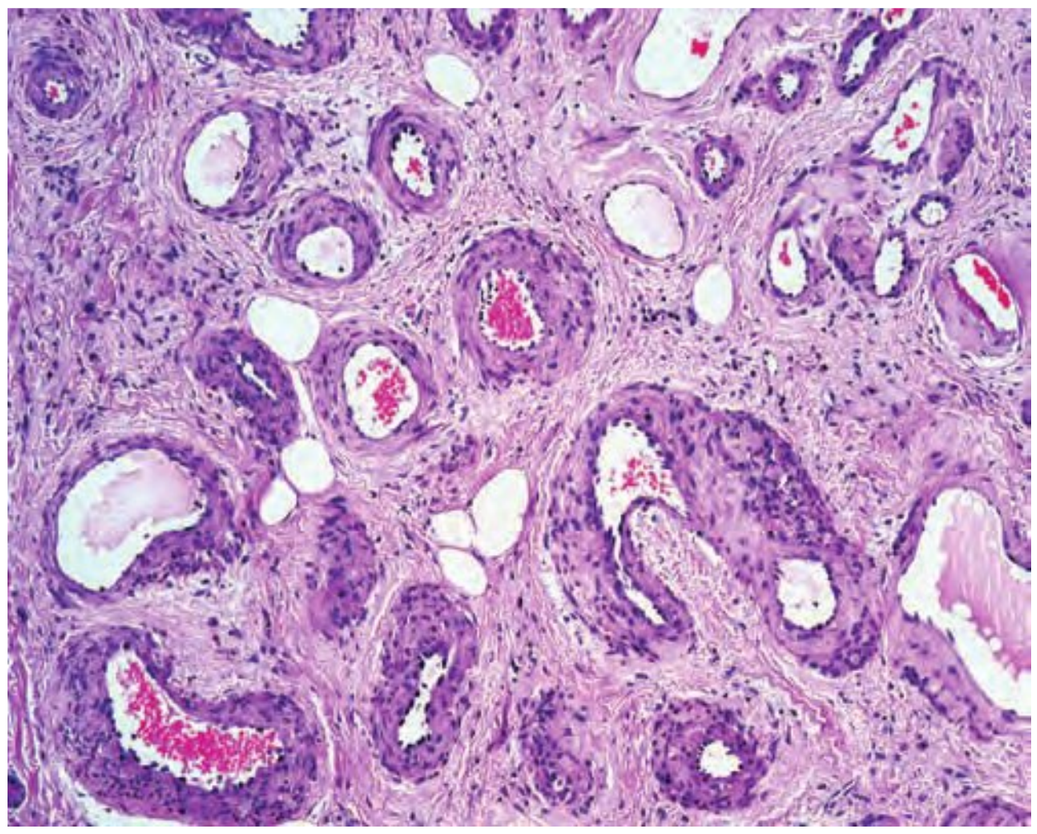


FIGURE 33-45. Cirsoid aneurysm. A combination of small veins and arteries.

younger patients and can be associated with hemodynamic complications due to shunting.

Histogenesis. It seems likely that many of these lesions represent pure venous hemangiomas, some of which have arterialized veins (148).

Angiomatosis

Angiomatosis is an uncommon condition that presents exclusively in children and adolescents and is defined as a diffuse proliferation of blood vessels affecting a large contiguous area of the body (149–151). Anatomic distribution is wide, but there is a preference for limb involvement. A typical case presents with involvement of the skin, underlying soft tissues, and even bones. Associated limb hypertrophy is common. Involvement of parenchymal organs and the central nervous system can be present. Due to extensive involvement, surgical treatment is difficult and recurrences are common.

Histopathology. Most tumors are composed of abundant mature fat intermixed with blood vessels in two histologic patterns (150). The most common pattern is a mixture of veins with irregular walls, cavernous vascular spaces, and capillaries. The veins often show an incomplete muscular layer, and smaller blood vessels can be seen in the walls of larger vessels. The second pattern is composed mainly of capillaries with a focal lobular architecture. Perineural invasion can be a feature in both patterns.

Spindle Cell Hemangioma

Spindle cell hemangioma is a tumor that was first described in 1986 (152) as a form of low-grade angiosarcoma, although mounting evidence in recent years widely favors a nonneoplastic process most likely related to a vascular malformation (see Pathogenesis). Gender incidence is equal, and most lesions arise in the second or third decade of life. It presents as multiple red-blue nodules in the dermis and subcutaneous tissue, most commonly involving the distal aspects of the extremities with a predilection for the hands. Visceral lesions do not occur, and involvement of deeper soft tissues is rare (153). The clinical course is indolent, with multiple new lesions appearing over the years. Spontaneous regression is exceptional. In approximately 10% of cases, associated anomalies include lymphedema, Maffucci's syndrome, Klippel-Trenaunay syndrome, and early-onset varicose veins (152–155).

Histopathology. Tumors tend to be poorly circumscribed and may present totally or partially in an intravascular location, especially involving medium-sized veins. A typical lesion is composed of two elements (Fig. 33-46): irregularly dilated, thin-walled congested cavernous spaces often with organizing thrombi and phleboliths intermixed with more solid areas composed of spindle-shaped cells (Fig. 33-47) generally bland in appearance, although rare cases may show focal degenerative cytologic atypia. Mitotic figures are rare. Commonly, in the solid areas, focal aggregates of epithelioid cells with eosinophilic cytoplasm and bundles of smooth muscle are seen. The epithelioid cells may show vacuolation or intracytoplasmic lumina (Fig. 33-48). Slitlike vascular spaces are common in the solid areas and are accompanied by scattered extravasated red blood cells and hemosiderin-laden macrophages. Focal areas with changes resembing Masson's tumor can be a feature. Irregular, thick-walled vascular spaces reminiscent of those seen in vascular malformations are often seen in the periphery of many lesions. Occasionally, cases show combined features of epithelioid and spindle cell hemangioendothelioma (156,157). However, these cases are likely to represent examples of composite hemangioendothelioma (see page 1037).

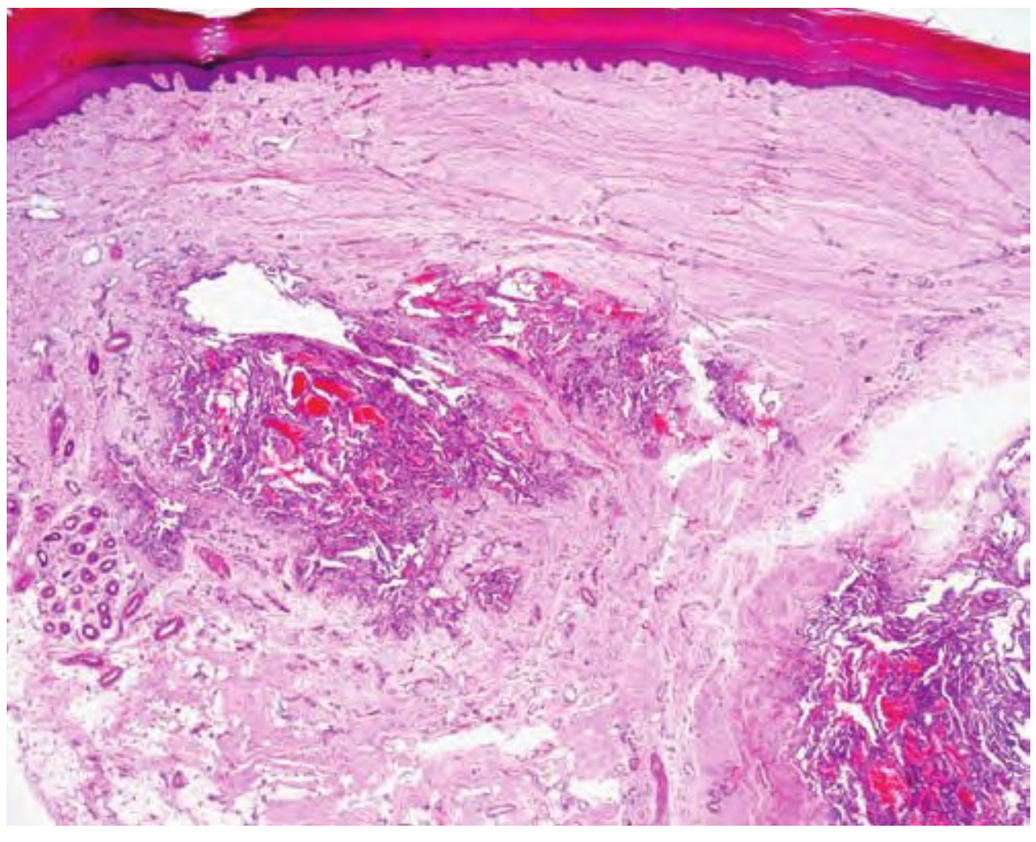


FIGURE 33-46. Spindle cell hemangioma. Multifocal lesions combining dilated and congested vascular spaces and more cellular areas.

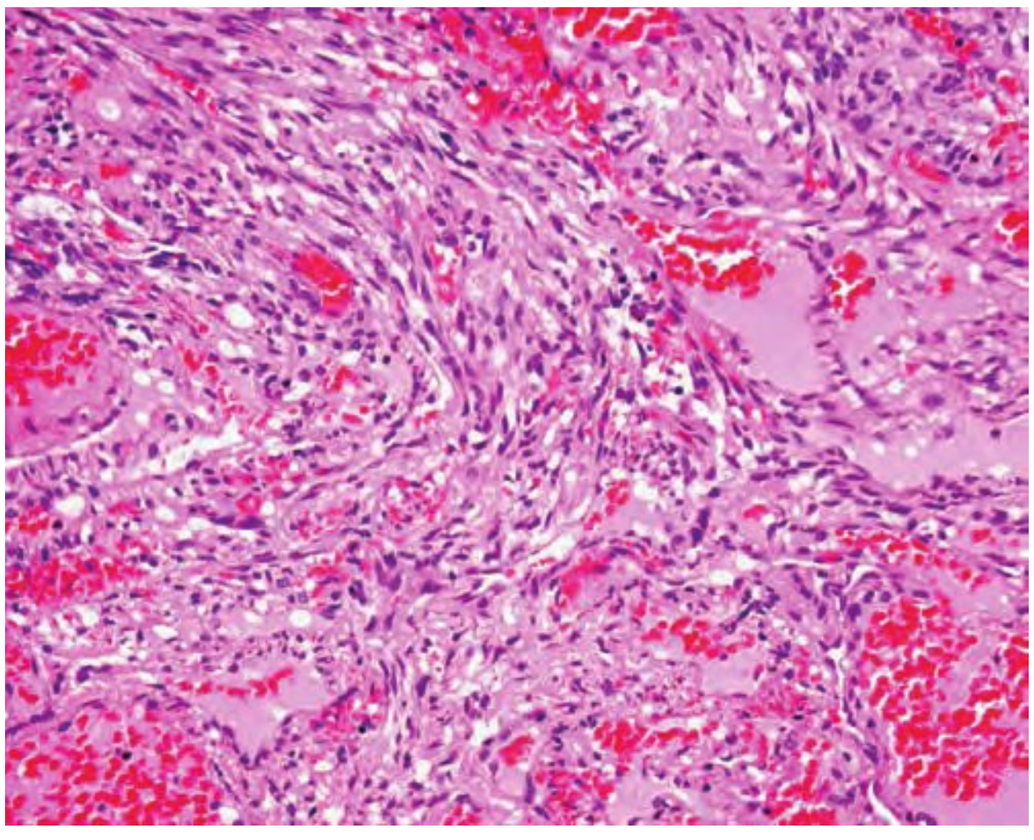


FIGURE 33-47. Spindle cell hemangioma. Thin-walled, dilated vascular spaces and bland spindle-shaped cells.

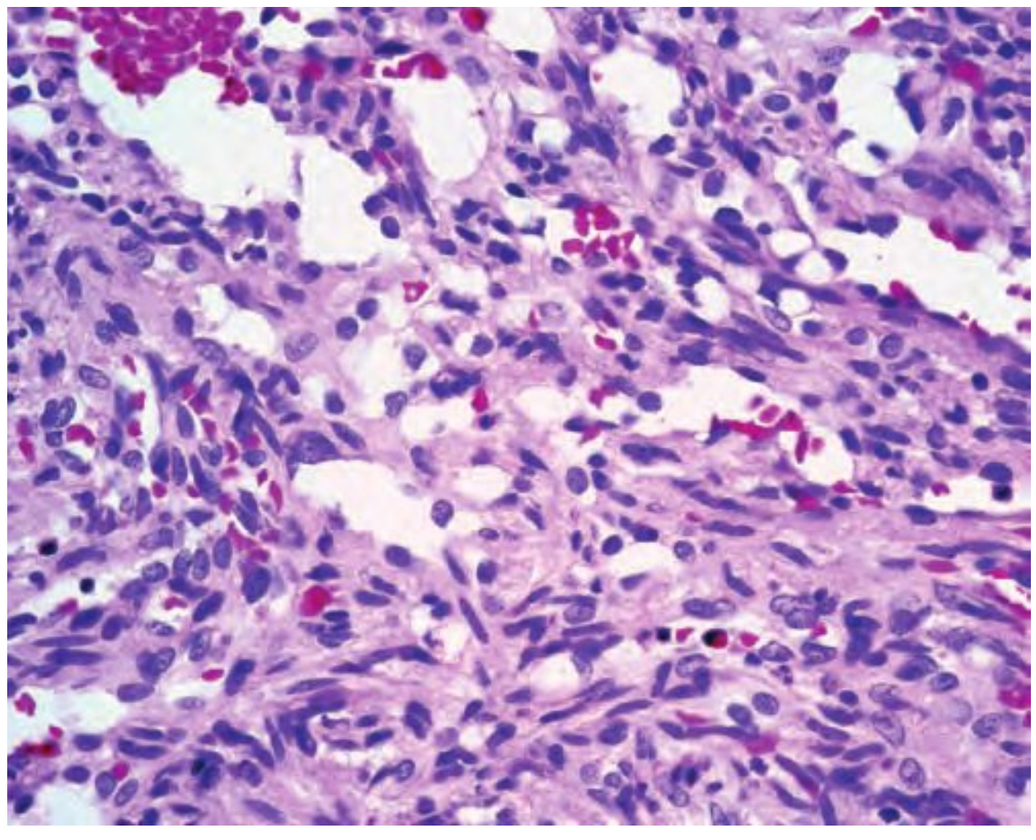


FIGURE 33-48. Spindle cell hemangioma. Spindle-shaped cells and focal epithelioid pale pink vacuolated cells.

Pathogenesis. Original classification of this tumor as a form of low-grade angiosarcoma was based on the development of lymph node metastasis in one of the patients reported (152). However, the patient had been treated with radiotherapy, and it is very likely that the metastasis was from a radiation-induced sarcoma. Further case series in recent years have provided evidence favoring the theory that spindle cell hemangioendothelioma represents a reactive condition or a form of vascular malformation (154,158–160).

By immunohistochemistry, the endothelial cells lining the vascular spaces and the epithelioid cells in the solid areas stain variably with endothelial markers. The spindle cells stain focally with actin and less commonly with desmin.

Differential Diagnosis. The main differential diagnosis is with nodular stage Kaposi's sarcoma, as discussed below (page 1035).

Symplastic Hemangioma

Symplastic hemangioma is not a distinctive variant of hemangioma but rather represents extensive degenerative changes in a preexisting hemangioma closely mimicking malignancy (161–163). Very few cases have been reported, but from personal experience with a limited number of cases, the preexisting hemangioma is often not identifiable or it represents a cirsoid aneurysm.

Histopathology. Lesions are often polypoid and well circumscribed and do not tend to be ulcerated (Fig. 33-49). Dilated and congested thin- to thick-walled vascular spaces are surrounded by a variable cellular stroma that is often myxoid and hemorrhagic. Stromal cells and smooth muscle cells within the vessel walls display variable cytologic atypia consisting of nuclear enlargement and hyperchromatism (Fig. 33-50). The endothelial cells lining the vascular spaces do not show cytologic atypia (Fig. 33-51). Other cells have a bizarre appearance, and multinucleation is not uncommon. Mitotic figures may be found but are not common. Very occasional atypical mitotic figures may also be seen.

Differential Diagnosis. The main differential diagnosis to consider is angiosarcoma. However, in symplastic angioma, the endothelial cells lining the vascular channels are bland, with no mitotic acitivity or multilayering. A further differential diagnosis is with pleomorphic hyalinizing angiectatic tumor of soft parts (164). The latter is an infiltrative tumor that mainly occurs in the subcutis or deeper soft tissues and is characterized by thin-walled dilated vascular spaces with prominent perivascular hyalinization and pleomorphic stromal cells with low mitotic activity and frequent intranuclear inclusions.

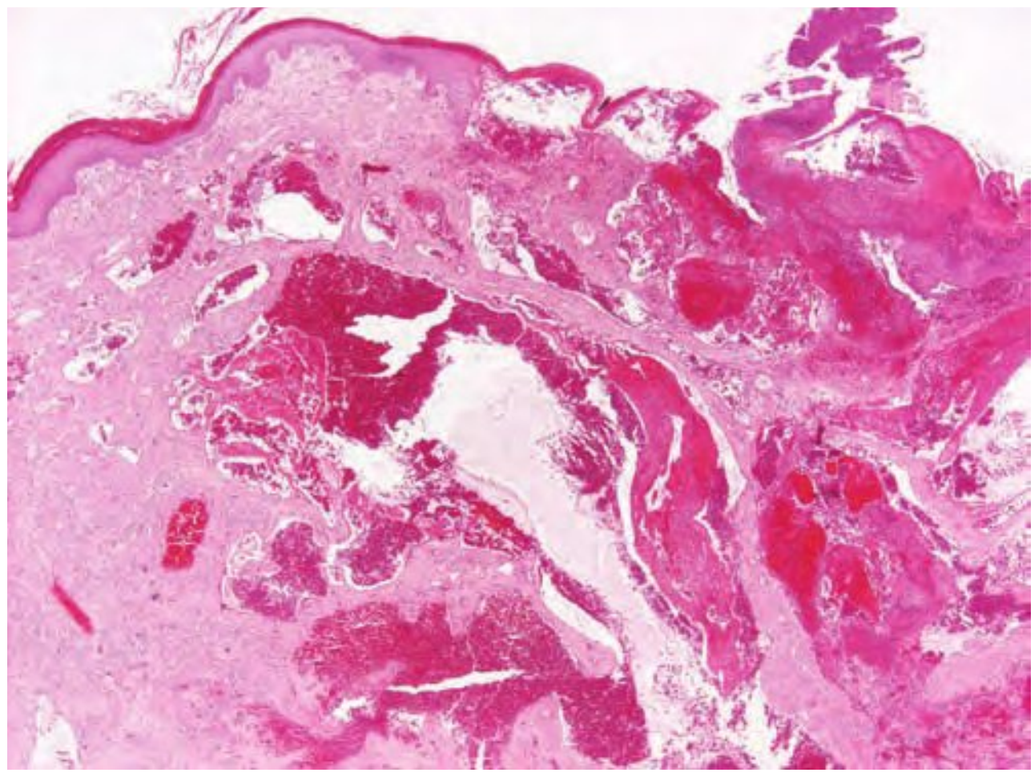


FIGURE 33-49. Symplastic hemangioma. Lesions are often polypoid, and their vascular nature is apparent at scanning magnification.

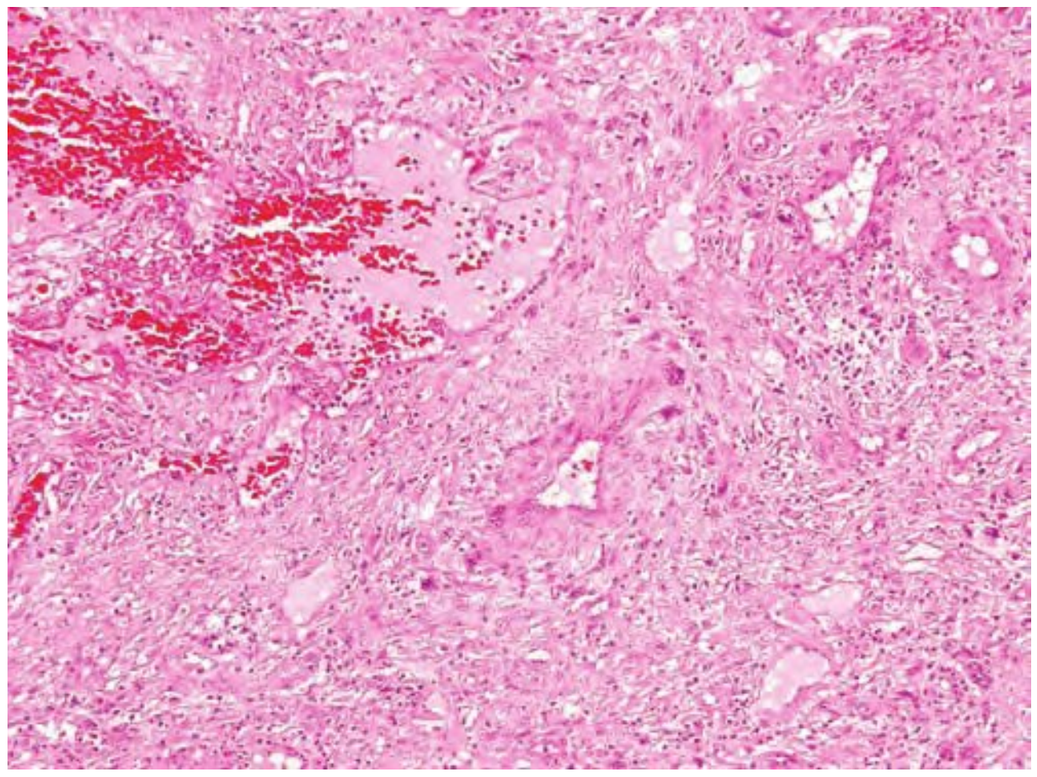


FIGURE 33-50. Symplastic hemangioma. Atypical cells both within the stroma and in the blood vessel walls.

VASCULAR TUMORS OF INTERMEDIATE MALIGNANCY

Malignant tumors of endothelial cell origin can be broadly divided into intermediate and high-grade malignancy. Strictly used, the term *intermediate malignancy* refers to a tumor that has potential for aggressive local behavior with a tendency for local recurrence and low or negligible potential for metastatic spread. There is a tendency to designate malignant vascular tumors with true potential for metastatic spread as angiosarcomas and low-grade tumors as hemangioendotheliomas. However, some authors use the terms interchangeably, and progress in understanding of some of these tumors has led to certain neoplasms being either upgraded as fully malignant (e.g., epithelioid hemangioendothelioma) or downgraded as benign (e.g., spindle cell hemangioma). It must also be remembered that the term *hemangioendothelioma* was used in the past to refer to some benign vascular tumors, especially strawberry nevus in children. The category of vascular tumors of intermediate malignancy also includes lesions like Kaposi's sarcoma, a generally indolent process in which a truly neoplastic origin has not clearly been demonstrated.

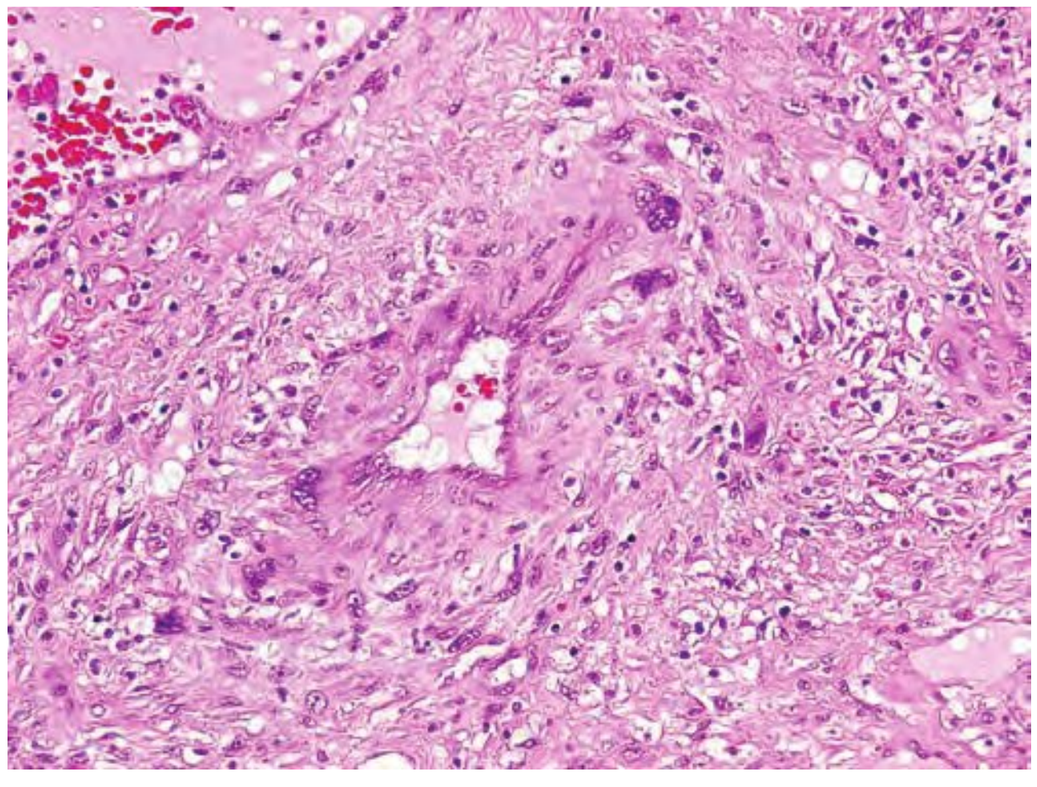


FIGURE 33-51. Symplastic hemangioma. Endothelial cells show no atypia or mitotic activity.

Kaposi's Sarcoma

Until the late 1960s, Kaposi's sarcoma was described as an uncommon, slowly progressive, multifocal tumor arising mostly in elderly male patients of eastern and southern European descent, a clinical pattern now referred to as the *classic* form of the disease. During the last two decades of the last century, intense interest developed as Kaposi's sarcoma became a prime marker of AIDS. Although with the advent of highly active antiretroviral therapy (HAART) the incidence of Kaposi's sarcoma in HIV/AIDS has decreased dramatically in the Western world, the same is not true in Third World countries, particularly in Africa, where access to HAART is still very limited. In addition, Kaposi's sarcoma can arise in association with other causes of immunodeficiency, especially when drug induced, particularly in the setting of organ transplantation and less commonly in different forms of inherited immune deficiency. Despite recent great advances in knowledge regarding the etiology and pathogenesis of Kaposi'sarcoma, there remain many unusual facets about the disease that as yet defy adequate scientific explanation. Although it has been demonstrated that all types of Kaposi's sarcoma are associated with a novel variant of herpesvirus, HHV-8, it is still controversial whether Kaposi's sarcoma is a multifocal reactive process or a neoplastic condition.

Clinical Features. Nearly all cases of Kaposi's sarcoma can be classified into four groups (165–171):

1. *Classic Kaposi's sarcoma.* This arises 10 to 15 times more commonly in men than women, affecting mainly patients of eastern European, Jewish, and Mediterranean origin (172). The disease mainly arises in patients over the age of 50 years with the slow development of angiomatous nodules and plaques on the lower extremities (Fig. 33-52). Chronic lymphedema is not an infrequent association. Affected patients may survive 10 to 20 years; even at late stages with widespread skin nodules, visceral disease is unusual, although asymptomatic involvement of lymph nodes, lungs, or gastrointestinal tract can often be found at necropsy. Occasionally, before the advent of AIDS, an aggressive type of Kaposi's sarcoma occurred in young adults or children with early lymph node involvement (168).
2. *Endemic African Kaposi's sarcoma.* In the 1960s, it was realized that Kaposi's sarcoma was quite common among native blacks in Central Africa, representing the most common tumor in pathology departments in Uganda and parts of what was known as Zaire (now the Democratic Republic



FIGURE 33-52. Clinical Kaposi's sarcoma. Typical endemic case with plaques and nodules on an acral location.

of Congo). In South Africa, it has been estimated that Kaposi's sarcoma is ten times more common in blacks than whites (Fig. 33-53). In Africans, the disease can run a similar indolent course as in classic Kaposi's sarcoma, but a higher proportion of young people are affected, with a more aggressive disease manifested by widespread tumors, deep infiltrative or elevated fungating lesions, and bone involvement. A distinctive childhood type of Kaposi's sarcoma occurs with massive lymph node involvement and early death. Mucocutaneous lesions are usually a late or minor clinical feature in this lymphadenopathic form (168). The male-to-female ratio in these children is approximately 3:1. Most cases of Kaposi's sarcoma that have occured in sub-Saharan Africa in the last 25 years are in patients with HIV/AIDS (169–171).

3. *AIDS-associated Kaposi's sarcoma.* In the early 1980s, reports of groups of young homosexual males in New York and California who were developing Kaposi's sarcoma was one of the keys in establishing the existence of AIDS. Originally, about 40% of patients with AIDS had concomitant Kaposi's sarcoma, but this high percentage has gradually and dramatically fallen in the United States (165,168) and Europe since the advent of HAART (173). Collected data from the Centers for Disease Control and Prevention in the United States has suggested that Kaposi's sarcoma was at least 201,000 times more common with AIDS than in the general population (165). The risk of Kaposi's sarcoma occurring with AIDS is much greater in active homosexuals than in heterosexual males or females, such as hemophiliacs who receive contaminated blood products or drug abusers who share needles.

   The clinical features of AIDS-related Kaposi's sarcoma differ from the classic disease in the rapid evolution of the lesions, their atypical distribution affecting the trunk, and the mucosal involvement (167) (Fig. 33-54). Visceral involvement is very common at autopsy (174,175), but such internal lesions are often unapparent clinically during life. Visceral involvement may be present without any skin lesions. In patients on HAART and according to the degree of restoration of the immune system, lesions may regress, and if they develop during treatment, they are usally limited in number and extent.
4. *Kaposi's sarcoma and iatrogenic immunosuppression.* Drug-induced immunosuppression to prevent rejection of transplanted organs greatly increases the risk of developing lymphomas and other tumors, including Kaposi's sarcoma (176,177). In a large retrospective study over 23 years, Kaposi's sarcoma developed in 3.9% of cases of kidney transplant patients (176). A peculiarity of this type of Kaposi's sarcoma is the frequent regression or apparent cure on discontinuation of immunosuppressive therapy. The male-dominant gender ratio is much smaller in this group.

   Kaposi's sarcoma can also occur in other causes of immunosuppression, including genetic diseases (178).

Histopathology. The histopathology of fully developed nodules of Kaposi's sarcoma in all types of the disease is distinctive



FIGURE 33-53. Clinical Kaposi's sarcoma. In endemic African cases, associated lymphedema is often seen.



FIGURE 33-54. Kaposi's sarcoma. Oral lesions are often seen in HIV/AIDS, particularly in patients not on HAART.

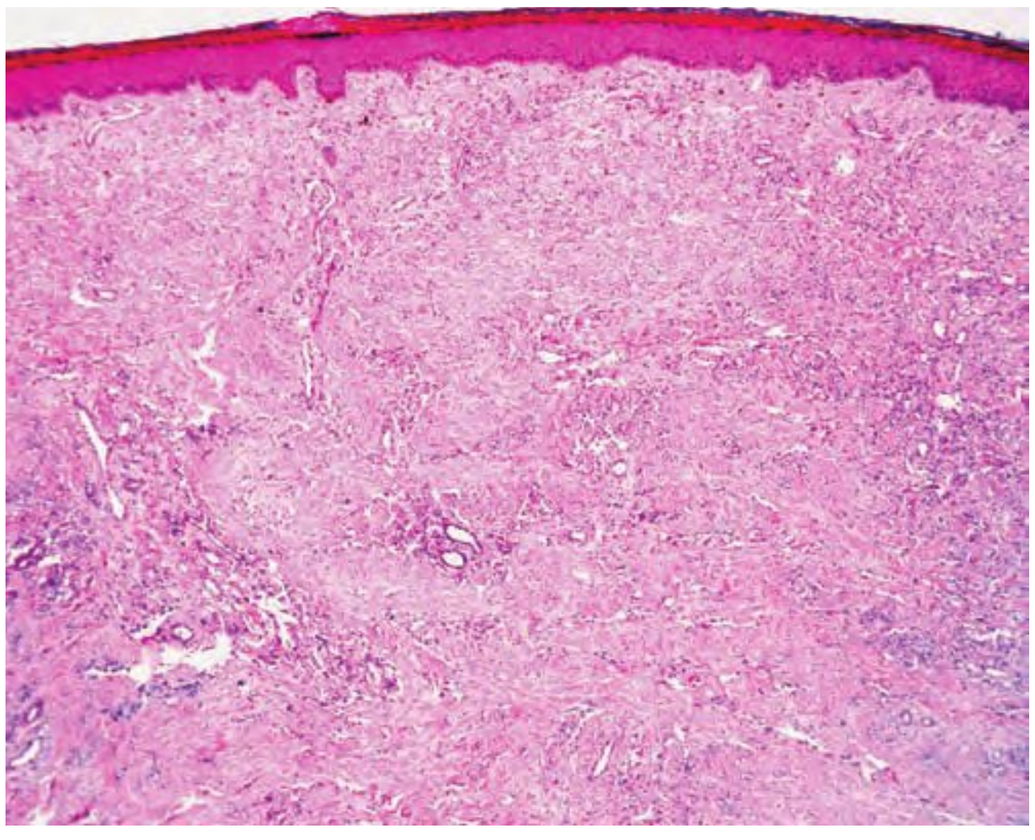


FIGURE 33-55. Patch-stage Kaposi's sarcoma. Numerous slitlike spaces throughout the dermis in the background of hemorrhage.

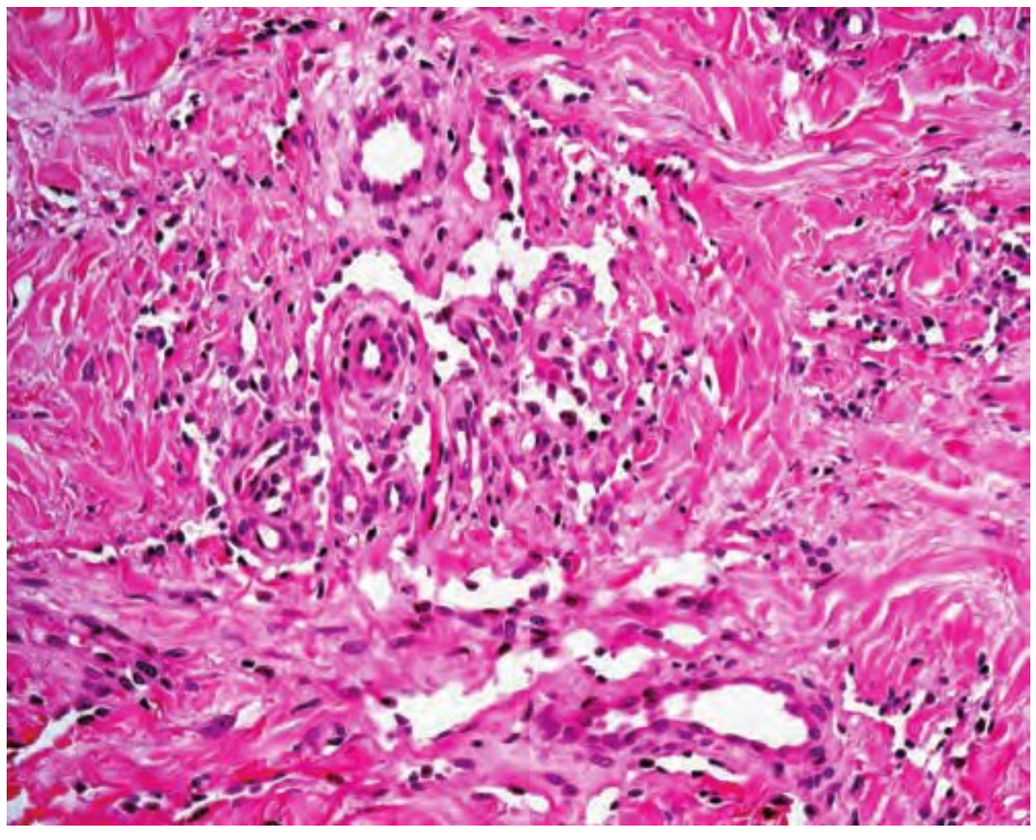


FIGURE 33-57. Patch-stage Kaposi's sarcoma. A normal blood vessel protruding into newly formed blood vessels ("promontory sign") lined by bland endothelial cells.

and should rarely cause problems for pathologists. The diagnostic pitfalls lie mainly in the early macular lesions, where misinterpretation as banal inflammation or some form of minor angiomatous or lymphatic anomaly is easy to make. Despite the name of sarcoma, cytologic atypia is minimal in tumor cells in all stages of evolution of Kaposi's sarcoma.

For descriptive convenience, the histologic spectrum can be divided into stages roughly corresponding to the clinical type of lesion: early and late macules, plaques, nodules, and aggressive late lesions. In reality, there is overlap between stages and multiple biopsies taken at the same time, or even a single biopsy may show features of different histologic stages. There are no differences in the pathology of the disease in the different risk groups.

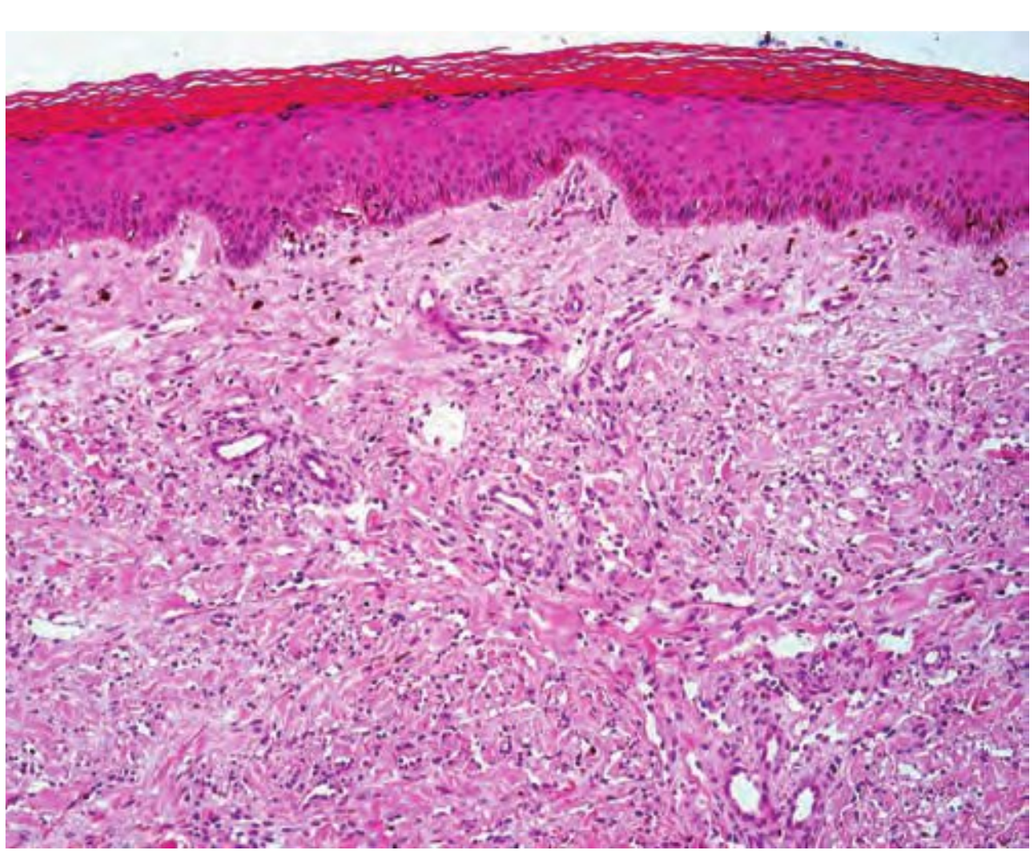


FIGURE 33-56. Patch-stage Kaposi's sarcoma. Irregular, jagged, thin-walled small vascular channels in association with hemosiderin deposition and focal inflammation.

1. *Macular (patch stage).* In early macules, there is usually a patchy, sparse, dermal perivascular infiltrate consisting of lymphocytes and plasma cells. Narrow cords of cells, insinuated between collagen bundles, may at first suggest histiocytes or connective tissue cells, but close inspection should reveal evidence of luminal differentiation or connection with discernable small vessels (Fig. 33-55). Usually, a few dilated irregular or angulated lymphatic-like spaces lined by delicate, bland endothelial cells are also present. Vessels with "jagged" outlines tending to separate collagen bundles are especially characteristic (Fig. 33-56). Normal adnexal structures and preexisting blood vessels often protrude into newly formed blood vessels (Fig. 33-57). This finding, known as the *promontory sign*, is commonly present but is not specific to Kaposi's sarcoma. In late macular lesions, there is a more extensive infiltrate of vessels in the dermis: "jagged" vessels and cords of thicker-walled vessels similar to those in granulation tissue. Some of these vessels may in part be reactive rather than an intrinsic part of the tumor. At this stage, red blood cell extravasation and the presence of siderophages may be encountered. In some lesions, ramifying variably dilated bloodless lymphatic-like spaces dissect out collagen to give an appearance that suggests a well-differentiated angiosarcoma or progressive lymphangioma. This exaggerated lymphangioma-like appearance has led some authors to designate this as a special variant of the disease (179) (Fig. 33-58). Occasional fascicles of spindle-shaped cells may occur independent of blood vessels. In some cases, dilated, congested, thin-walled vascular channels with a sievelike (Fig. 33-59) appearance mimicking a hemangioma are seen.

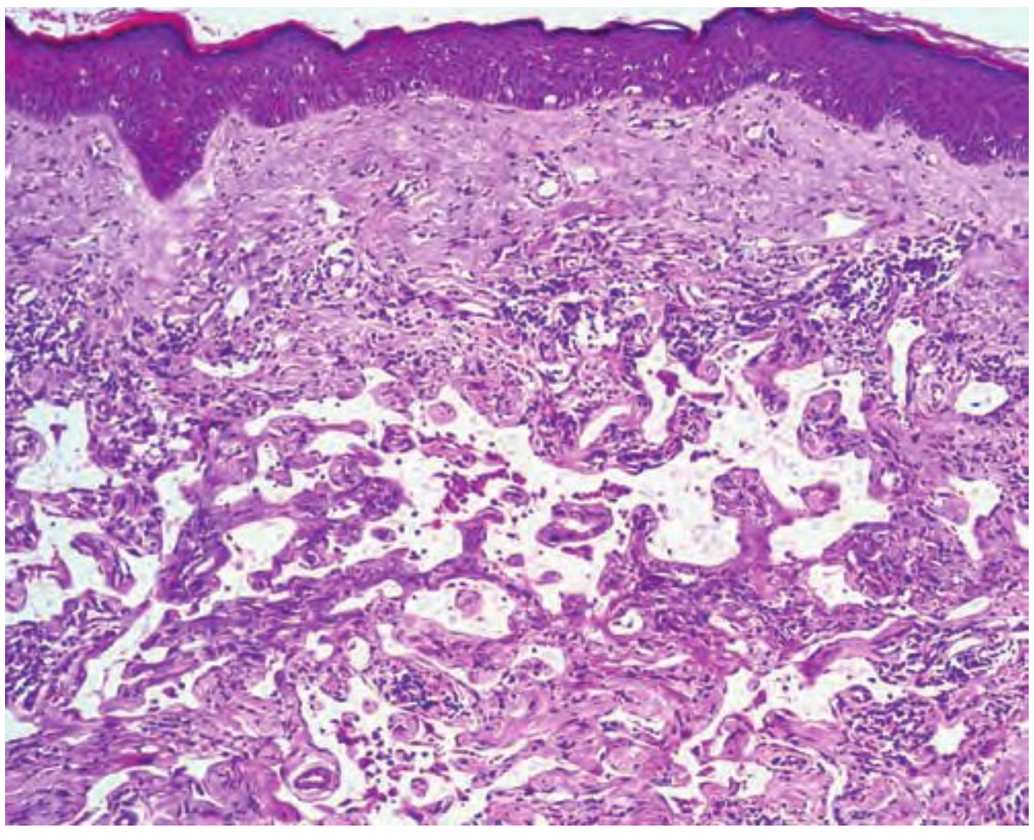


FIGURE 33-58. Lymphangiomatous Kaposi's sarcoma. Numerous, irregular, dilated, bloodless vascular channels with a striking lymphangioma-like appearance.

2. *Plaque stage.* In this stage, a diffuse infiltrate of small blood vessels extends through most parts of the dermis and tends to displace collagen (Fig. 33-60). The vessels show variable morphology, with some occurring as poorly canalized cords, some as blood-containing ovoid vessels, and some showing lymphatic-like features. Loosely distributed spindle cells, arranged in short fascicles, are also encountered (Fig. 33-61). Intracytoplasmic hyaline globules (180) may be found in areas with a denser infiltrate.

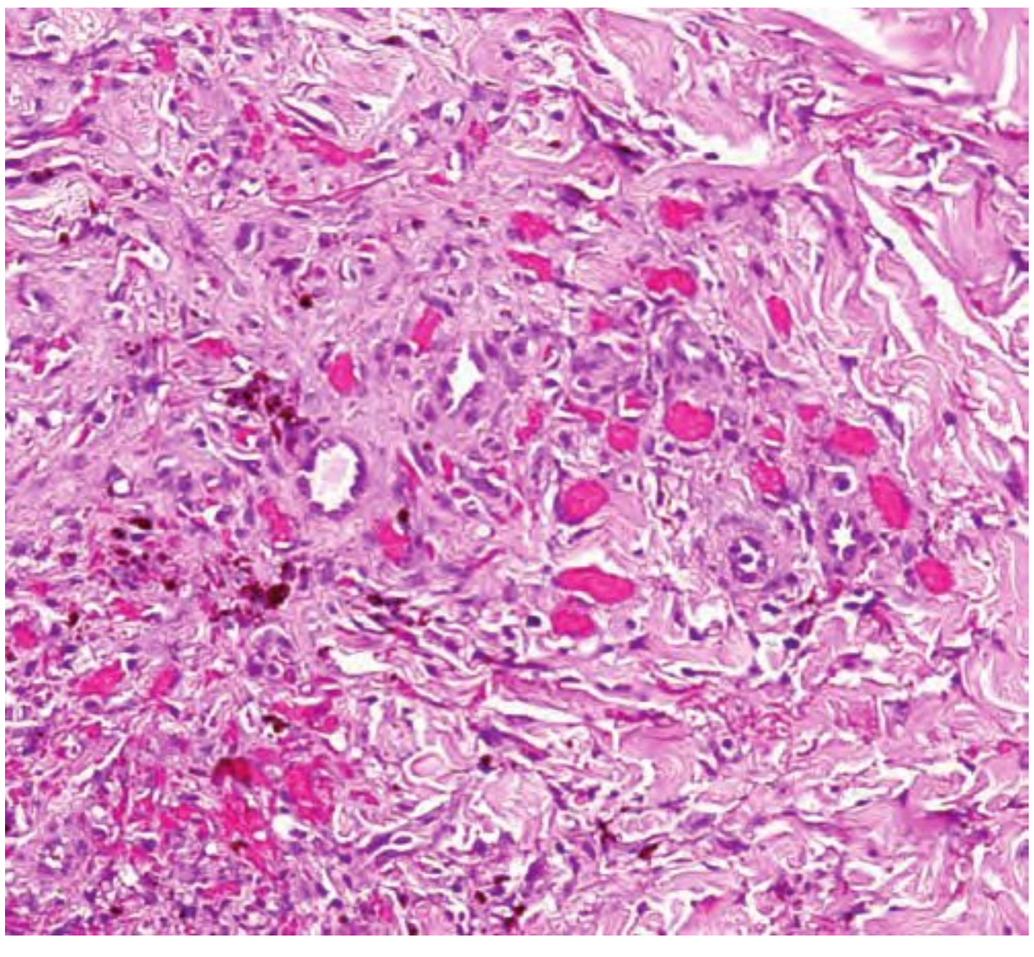


FIGURE 33-59. Angiomatous Kaposi's sarcoma. Congested small vascular channels in a focal sievelike pattern.

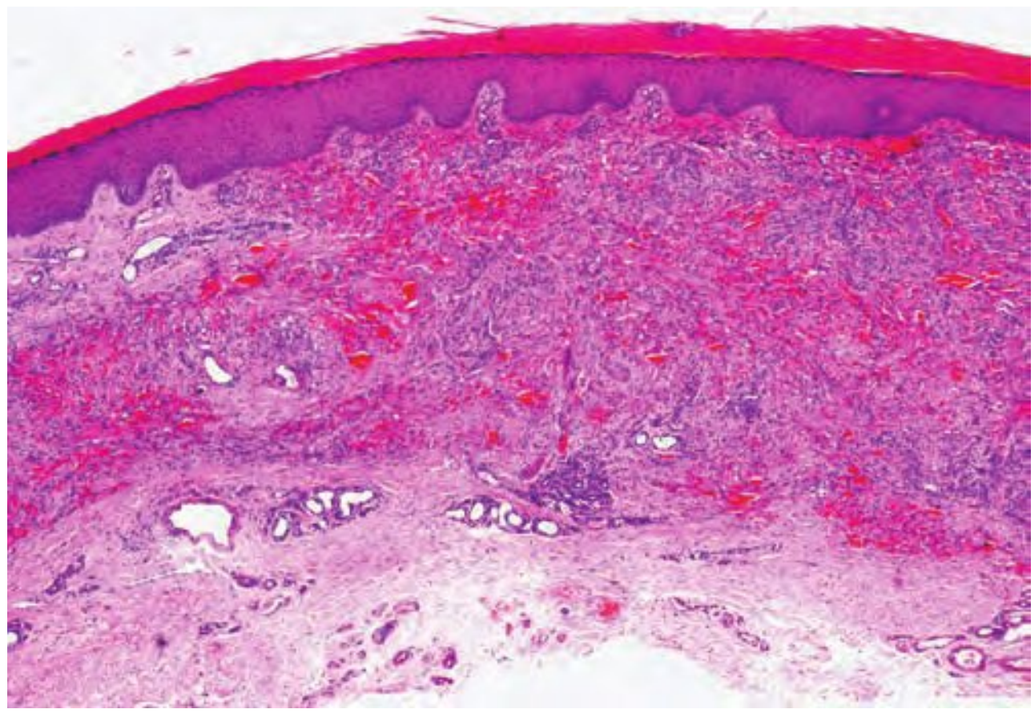


FIGURE 33-60. Plaque-stage Kaposi's sarcoma. A more cellular dermis with extensive hemorrhage.

These hyaline globules are seen more often in lesions from patients with AIDS.

3. *Nodular stage.* In the tumor stage, well-defined nodules composed of vascular spaces and spindle cells replace dermal collagen (Fig. 33-62). These tumor nodules tend to be compartmentalized by dense bands of fibrocollagenous tissue. Dilated lymphatic spaces can also be seen between tumor aggregates. The characteristic feature is a honeycomb-like network of blood-filled spaces or slits that are closely associated with interweaving spindle cells (Fig. 33-63). Although generally vascular spaces and fascicles of spindle cells are present, either element can focally predominate. The vascular lumina in the angiomatous tissue are so

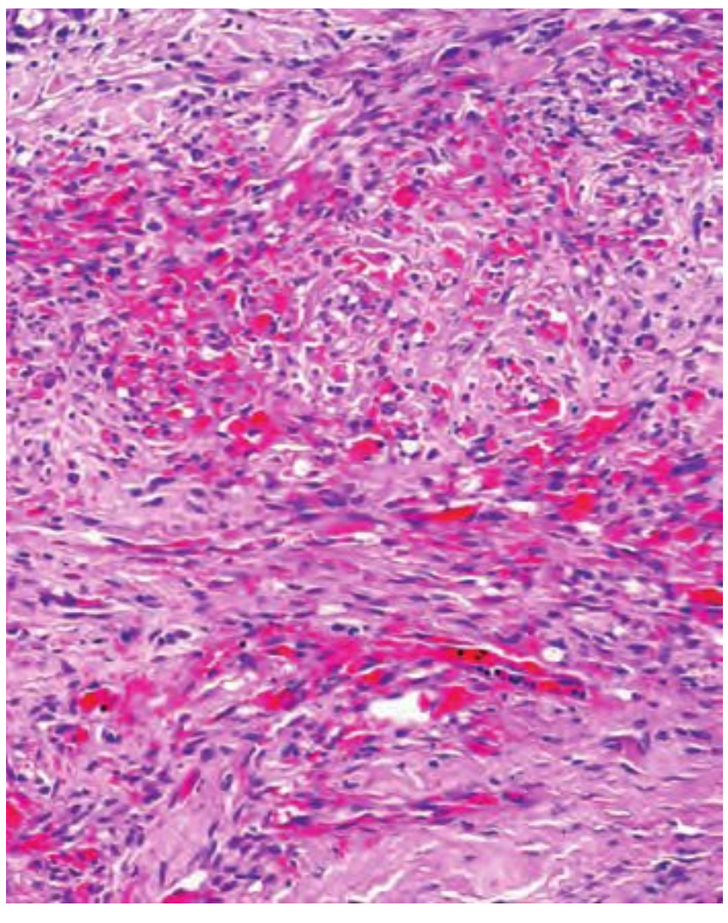


FIGURE 33-61. Plaque-stage Kaposi's sarcoma. Bland spindle-shaped cells with focal formation of cleftlike spaces containing red blood cells.

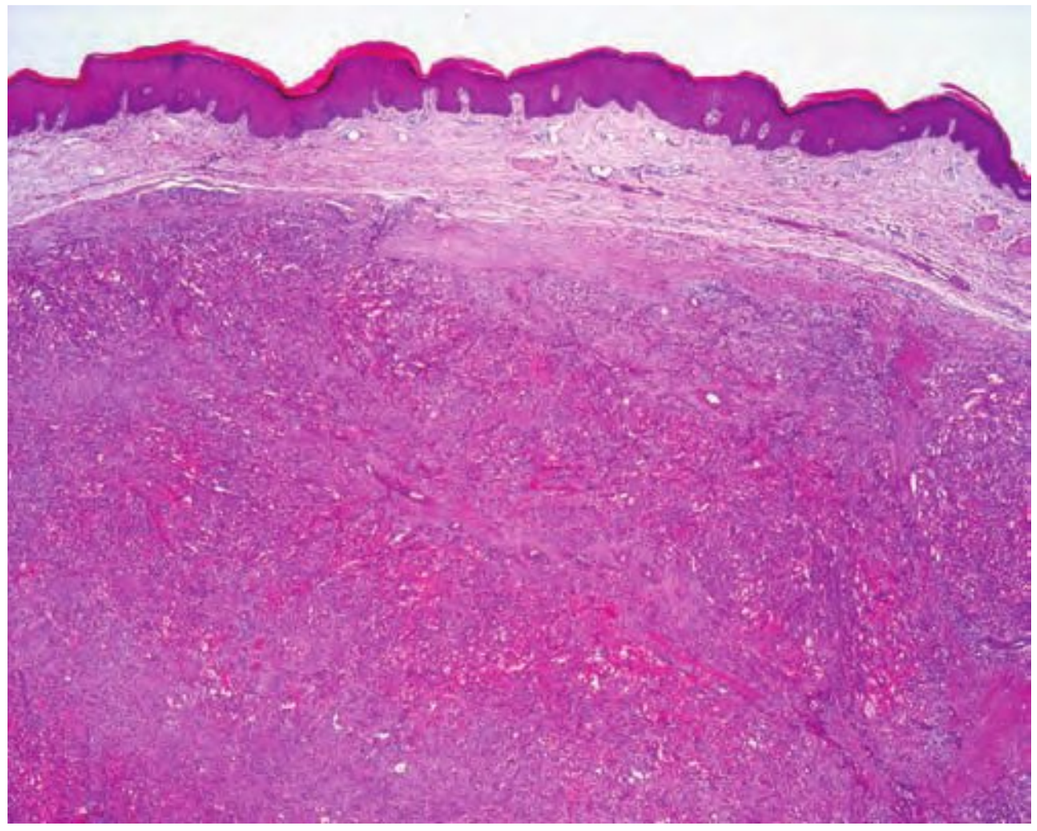


FIGURE 33-62. Nodular-stage Kaposi's sarcoma. Fairly well-circumscribed dermal nodule.

closely set that they lie next to each other in a "back-to-back" arrangement. Delicate, flattened endothelial cells lining the vascular clefts are hardly discernable with routine stains but are easily seen with the immunocytochemical markers CD31 and CD34. The vascular slits in the nodules appear to be in direct contact with spindle cells, leading to the suggestion that they are pseudovascular spaces. The presence of a closely set honeycomb-like pattern of vascular spaces is perhaps the single most important diagnostic feature of Kaposi's sarcoma. In the vascular spaces of pyogenic granuloma and most angiomas, the endothelial cells of the capillary walls are more prominent, and the vessels are set farther apart by intervening stroma. Around the nodules, varying numbers of thicker-walled vessels are encountered that may represent reactive or "feeder" vessels and are not a basic component of the tumor. Blood pigment–containing macrophages are nearly always prominent adjacent to the nodules, especially in lesions at dependent sites.

The spindle cells in the nodules are elongated and fusiform with a well-defined cytoplasm. The nuclei are ovoid and somewhat flattened with finely granular chromatin in the long axis of the cells. The nucleoli are generally inconspicuous, and nuclear atypia is absent or slight. Mitotic figures are not prominent. Prominent and consistent positivity for CD34 is seen in the spindle cell population.

Intra- and extracellular hyaline globules occur more frequently than in plaque-stage lesions. They present in groups as faintly eosinophilic spheres 1 to 7 μm in size and are PAS positive and diastase resistant. The globules probably represent partially digested erythrocytes. Usually, the epidermis and skin appendages remain intact.

Lesions of Kaposi's sarcoma, particularly in the nodular stage, may be partially or completely intravascular (181). The vessels involved are usually veins.

A variant of classic Kaposi's sarcoma presenting with a micronodular pattern has been described (182).

HIV-positive patients presenting with Kaposi's sarcoma in lymphedematous skin may show focal fibroma-like lesions that may represent an early stage in the evolution of Kaposi's sarcoma (183).

4. *Aggressive late-stage lesions.* Mostly in Africans but sometimes with other types of Kaposi's sarcoma, "infiltrating" lesions show a more obviously sarcomatous character with reduction or loss of the vascular component. The spindle cells demonstrate a greater degree of cytologic atypia with regard to size, shape, and nuclear features, with mitosis becoming frequent. In such lesions, phagocytozed erythrocytes and the presence of hyaline globules may provide clues about the tumor's origin. Very rarely, angiosarcoma is mimicked by the development of vascular spaces lined by grossly atypical endothelial cells. This variant of Kaposi's sarcoma is vanishingly rare.

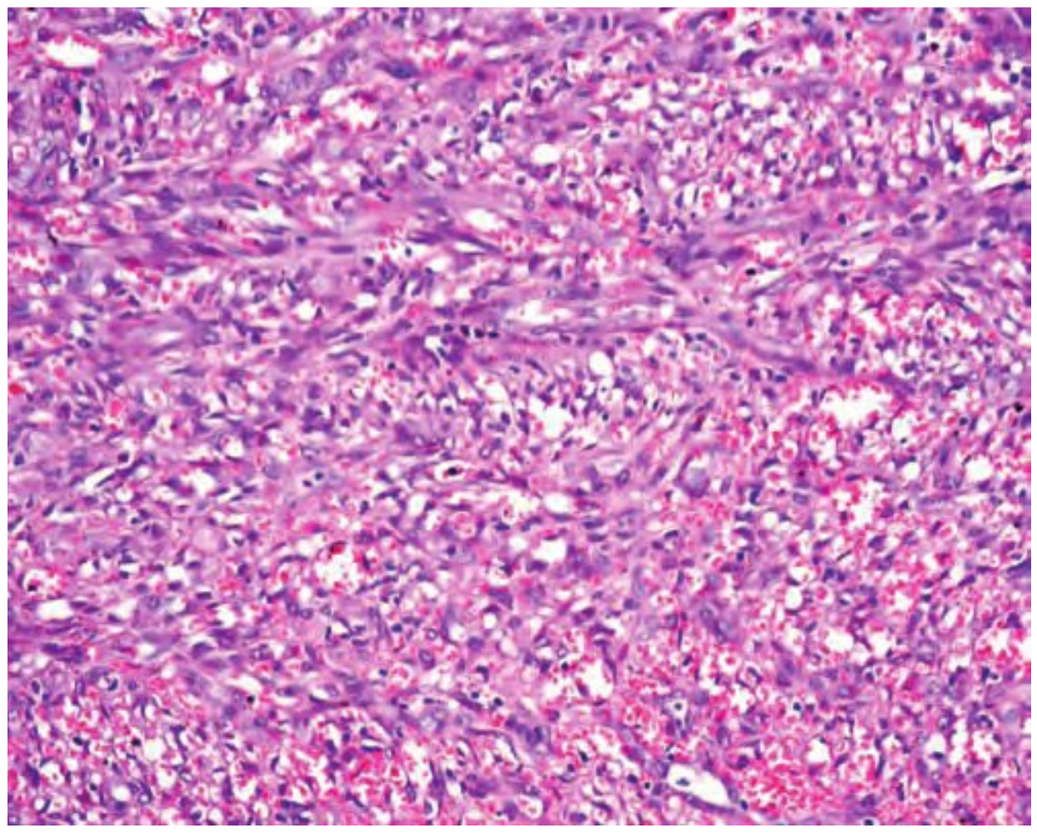


FIGURE 33-63. Nodular Kaposi's sarcoma. Bland spindle cells forming slitlike spaces occupied by red blood cells.

A useful diagnostic tool is the demonstration of HHV-8 in samples from patients with all clinical subsets of Kaposi's sarcoma. All variants of this tumor are etiologically related to this novel virus. Until recently, demonstration of the virus was only possible by *in situ* hybridization. This has been simplified by the development of a commercially available monoclonal antibody against the latent nuclear antigen (LNA-1) of the virus that can be used in routine practice. Positive cases demonstrate granular nuclear staining (184,185) (Fig. 33-64).

The histology of lesions of Kaposi's sarcoma that have regressed after chemotherapy or with angiogenesis inhibitors including Col-3 can be difficult to interpret (186). Regression may be partial or complete. In completely regressed lesions, there is absence of spindle-shaped cells; increase in the number of capillaries in the superficial dermis; a superficial, perivascular

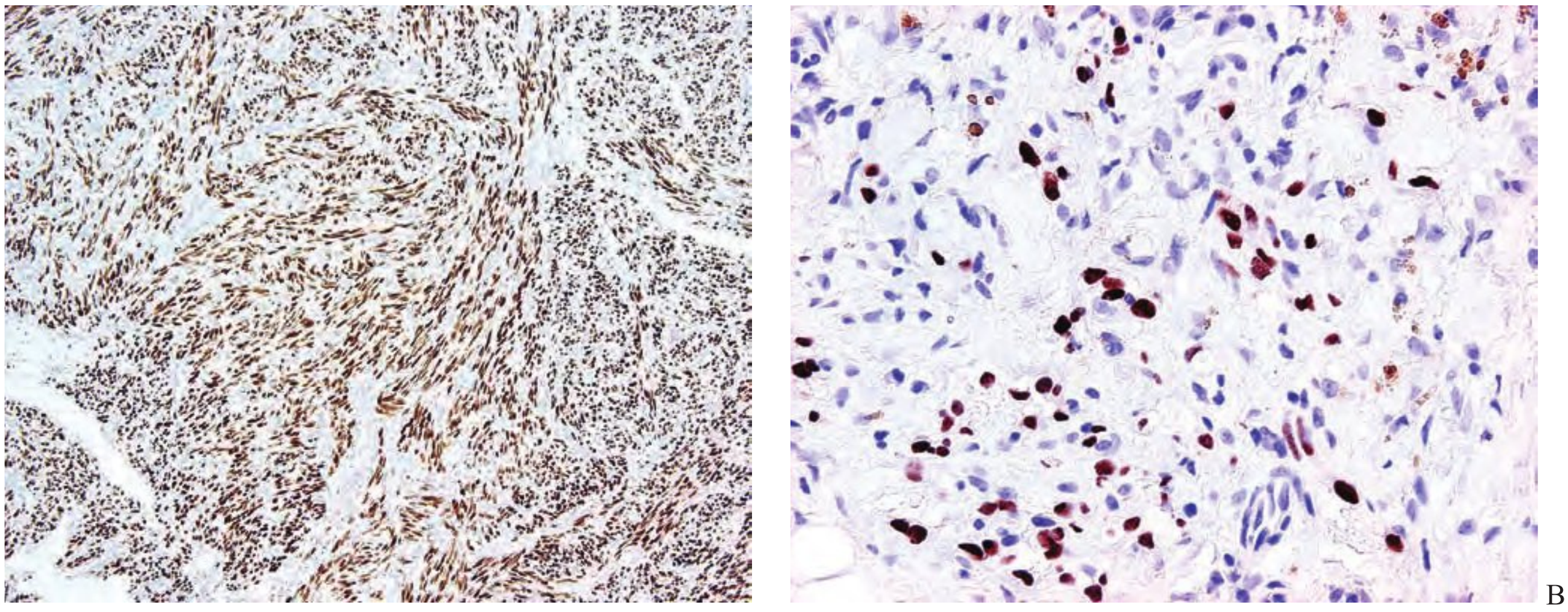


FIGURE 33-64. A: Staining of the nuclei of tumor cells with an antibody against the LAN-1 of HHV-8 using the ABC method. B: High power of another example.

lymphohistiocytic inflammatory cell infiltrate; and variable numbers of siderophages. Partially regressed lesions show prominent decrease in the number of spindle-shaped cells, focal inflammation, and siderophages. The residual spindle-shaped cells tend to be arranged around superficial and mid-dermal capillaries. These changes are correlated with prominent decrease in the expression of LNA-1.

Pathogenesis. The peculiar epidemiologic aspects of Kaposi's sarcoma have stimulated research for many years on whether viruses other than HIV or some other transmissible agent help to induce the disease. Initial studies of the fine structure of tumor cells in Kaposi's sarcoma have revealed tuboreticular structures and cylindrical-confronting cisternae, suggestive of a cellular reaction to a viral infection. In the last decade of the 20th century, the riddle of the association between Kaposi's sarcoma and a virus was resolved. Chang and colleagues (187) described a new human gammaherpesvirus associated with Kaposi's sarcoma. This virus is closely associated to Epstein-Barr virus, has been named *HHV-8*, and it is etiologically associated with Kaposi's sarcoma (188–190). DNA sequences of this virus have been detected consistently in all variants of the disease, including AIDS-related Kaposi's sarcoma, African endemic Kaposi's sarcoma induced by iatrogenic immunosuppresion, and Mediterranean Kaposi's sarcoma. The virus can be found in the blood of patients before lesions of Kaposi's sarcoma develop (191).

For many years, it was suspected that the proliferating cell in Kaposi's sarcoma is lymphatic in origin. This has recently been substantiated by the development of antibodies specific for lymphatic endothelium, including Lyve-1, podoplanin, D2-40, and Prox-1 (192,193).

The multifocal development, slow evolution of the classic form of the disease, regression when immunosuppression is reduced or stopped, and histology of inflammation and cells lacking cytologic atypia have led many to suggest that at least initially Kaposi's sarcoma is a reactive condition and not a neoplastic process (166,169). Initial reports demonstrating the presence of clonality have lended support to the latter (194). However, a number of more recent studies have suggested that the disease starts as a reactive angioproliferative and inflammatory process that progresses to become a monoclonal neoplastic process (195,196). This is a result of close, complex interactions between inflammatory cytokines, angiogenic factors, HHV-8, and, in HIV-positive patients, the HIV virus (197). In the latter setting, it has been demonstrated that the HIV-1 transactivating protein Tat-1 promotes the development of lesions by increasing the activity of different cytokines and angiogenic factors (198).

Differential Diagnosis. The differential diagnosis is wide, with the most difficulties encountered with either early macular or late aggressive lesions. Vascular proliferations in stasis and multinucleate-cell angiohistiocytoma are discussed here in more detail because they are not described elsewhere in this chapter. All of the different lesions described below in this section are usually negative for HHV-8, while Kaposi's sarcoma in all stages should be positive for this marker.

In *early macular lesions*, an inflammatory condition or a cell-poor (atrophic) histiocytoma may be suspected since the vascular nature of vessels with collapsed lumina may not be apparent. Appropiate cell markers may clarify the vascular nature of the underlying lesion. In late macular lesions, the differential diagnosis includes a well-differentiated angiosarcoma, progressive lymphangioma, targetoid hemosiderotic hemangioma, and microvenular hemangioma. Angiosarcoma shows not only a "dissection" of collagen infiltrative pattern but also endothelial cell atypia with hyperchromatism and intraluminal shedding of malignant cells. Histologically, progressive lymphangioma is almost indistinguishable from Kaposi's sarcoma

with prominent lymphangioma-like features, but inflammatory cells, especially plasma cells, tend to be absent in the former. When the clinical features are taken into account, distinction is not difficult. In hobnail hemangioma, lymphangioma-like channels are mainly confined to the upper dermis; in some places, plump "hobnail" endothelial cells invaginate vascular spaces, inflammatory cells are rare, and hemosiderin deposition is prominent, unlike early Kaposi's sarcoma. Microvenular hemangioma differs by showing blood-containing vessels, many of which are surrounded by pericytes or smooth muscle cells (positive for smooth muscle actin) suggestive of venular differentiation.

Spindle cell hemangioma, kaposiform hemangioendothelioma, and moderately differentiated angiosarcomas with spindle cell differentiation are the most important histologic simulants of *nodular Kaposi's lesions*.

Spindle cell hemangioma differs by showing cavernous or widely dilated vascular spaces and collections of epithelioid cells with or without intracytoplasmic lumina.

Kaposiform hemangioendothelioma is mainly a disease of children that usually affects deep soft tissues, although the skin can be affected (199). Histologically, the tumor shows intermediate features of capillary hemangioma and Kaposi's sarcoma and has a lobular growth pattern that is absent in Kaposi's sarcoma. Furthermore, the capillaries at the periphery of tumor lobules in kaposiform hemangioendothelioma often show focal thrombosis, there may be focal epithelioid endothelial cells, and eosinophilic globules are absent.

Sometimes spindle cell differentiation is prominent in angiosarcoma, but usually markedly atypical cells are present, allowing differentiation from Kaposi's sarcoma.

Other acquired vascular conditions that can cause problems from the clinical and histologic point of view are bacillary angiomatosis and pyogenic granuloma, especially if complicated by satellite lesions and tufted angioma. Spindle cell fascicles with a bland cytologic appearance do not feature as a prominent component of any of these entities.

Aneurysmal benign fibrous histiocytoma is a nonvascular, highly cellular spindle cell lesion with pseudovascular spaces and hemosiderin deposition that can be confused with nodular Kaposi's sarcoma (200). The variability of pathology, the presence of peripheral areas similar to common dermal fibrous histiocytoma, and immunohistochemistry should prevent error in diagnosis.

In *aggressive late-stage lesions*, many malignant spindle cell tumors can come into the differential diagnosis, especially if clinical details are unavailable. The most important differential diagnoses are fibrosarcoma, leiomyosarcoma, monophasic synovial sarcoma, malignant cellular blue nevus with sparse melanin deposition, and desmoplastic malignant melanoma. Accurate diagnosis may be impossible unless reliable immunohistochemistry is available. CD31 and CD34 are particularly helpful in suggesting a vascular derivation, even in poorly differentiated Kaposi's lesions.

Hypostasis and high venous pressure gives rise to vascular proliferation (pseudo–Kaposi's sarcoma and acroangiodermatitis). Angiomatous papules and plaques near the ankles that are secondary to high venous pressure result from incompetent veins and are common causes of Kaposi-like lesions (201). Less commonly, high venous pressure can arise due to congenital or acquired arteriovenous anomalies (202). Histologically, there is expansion of the whole capillary bed throughout the dermis. In the papillary dermis, there is reduplication and corkscrewing of thick-walled capillaries, which increase in size and become angiomatous in appearance. Similarly, venules and deeper, vertically small veins become hypertrophied and tortuous. Erythrocyte extravasation, fibrosis with horizontally oriented spindle cells, and numerous siderophages are additional features. The angiomatous capillaries appear separated from each other by an edematous matrix, and they do *not* lie "back-to-back" as in Kaposi's sarcoma. To complicate matters, hypostatic vascular proliferation can coexist with Kaposi's sarcoma. A key difference between Kaposi's sarcoma and pseudo–Kaposi's sarcoma is that in the latter, vascular hyperplasia results from hyperplasia of the preexisting vasculature, whereas in the former, the vascular proliferation is mainly independent.

Multinucleate-cell angiohistiocytoma arises as slowly developing grouped vascular papules usually on the legs (203) but also at other sites including the face and hands (204). Most patients are older women. Histologically, an increased number of capillaries and venules with few inflammatory cells are found throughout the dermis, but the extent of the proliferation does achieve angiomatous proportions. Increased numbers of histiocytes and scattered multinucleate cells are usually found, although not in every biopsy. Blood pigment deposition is generally insignificant.

Immunohistochemical demonstration of HHV-8 is of great help in the histologic differential diagnosis of Kaposi's sarcoma, as all of the vascular and nonvascular entities previously discussed are usually not associated with this virus.

Retiform Hemangioendothelioma

Retiform hemangioendothelioma is a rare variant of low-grade angiosarcoma that is characterized by indolent clinical behavior (115,205,206). There is a predilection for young adults, and it presents as a slowly growing nondistinct tumor with equal gender incidence and a predilection for the extremities, especially the distal lower limbs. Rare cases can be associated with radiotherapy or chronic lymphedema. A single case with multiple primary tumors has been documented (207). Multiple recurrences are common, but metastasis has so far been reported in only two cases. One case metastasized to a regional lymph node, and a second case presented with a soft tissue metastasis close to the primary tumor (207). Retiform hemangioendothelioma is part of the spectrum of a family of vascular tumors that are characterized by endothelial cells with a distinctive hobnail appearance. This includes a benign tumor originally described as targetoid hemosiderotic hemangioma (hobnail hemangioma) and another low-grade malignant lesion, Dabska's tumor.

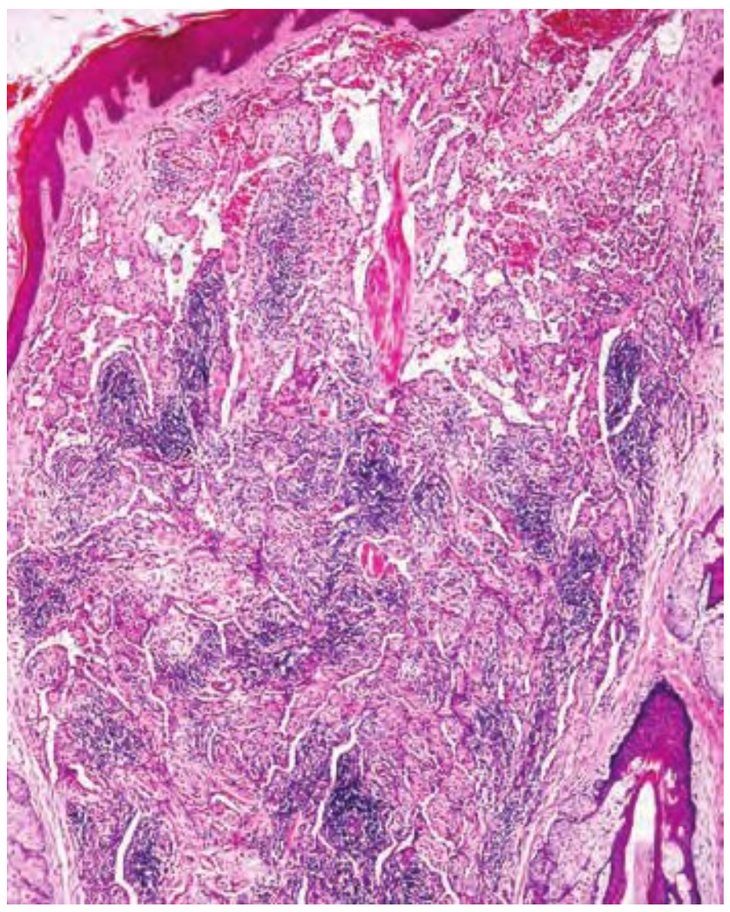


FIGURE 33-65. Retiform hemangioendothelioma. Branching blood vessels and a prominent lymphocytic inflammatory cell infiltrate.

Histopathology. Tumors are ill-defined and involve the reticular dermis with frequent extension into the subcutis. In most cases, there is a striking low-power resemblance to the normal rete testis conferred by the presence of elongated, arborizing blood vessels (Fig. 33-65) lined by monomorphic bland endothelial cells with prominent apical nuclei and scanty cytoplasm. These cells have been described as having a "matchstick" or hobnail appearance (Fig. 33-66). A lymphocytic inflammatory cell infiltrate is frequently seen not only in the stroma but also in the vascular lumina (though not invariably present). The intravascular lymphocytes commonly appear in close contact with the hobnail endothelial cells. Occasional intravascular papillae with hyaline cores can be seen (Fig. 33-66). In most tumors, there are solid areas composed of bland spindle cells or epithelioid cells that stain for endothelial markers. Some lesions present a mini-retiform pattern that may be more difficult to recognize on low-power examination. A sclerotic stroma is seen in some cases.

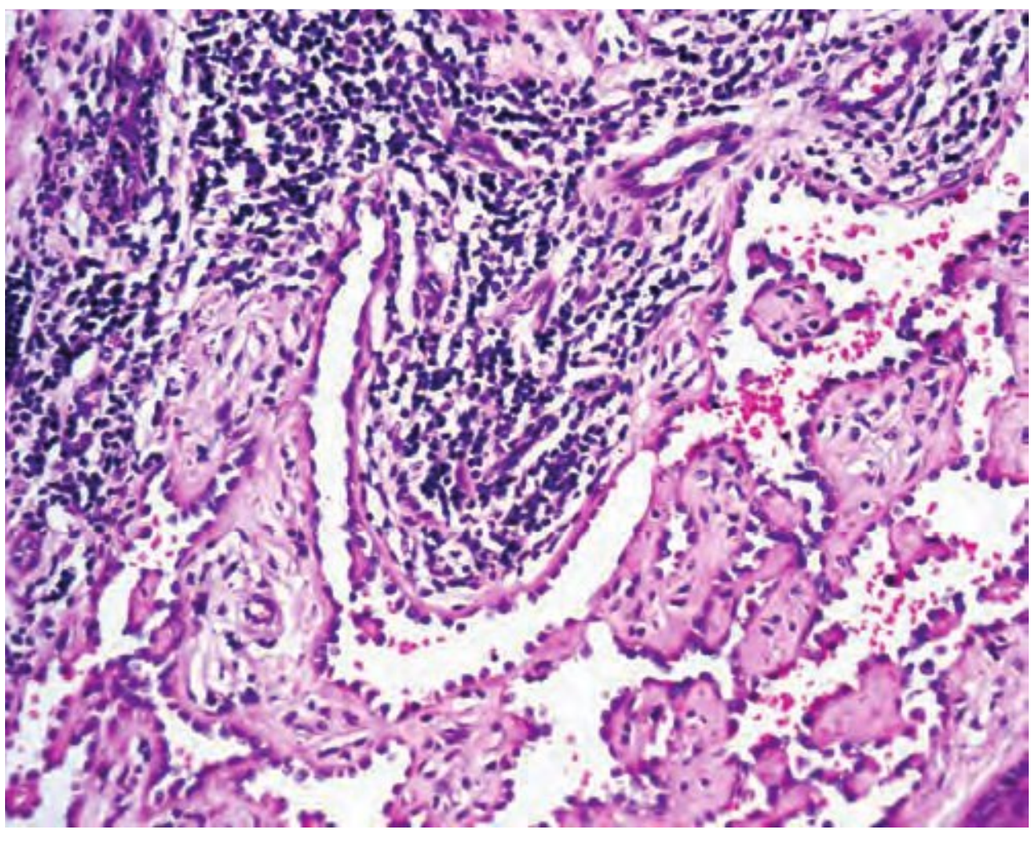


FIGURE 33-66. Retiform hemangioendothelioma. Typical bland hobnail endothelial cells and focal papillary projections.

Differential Diagnosis. Retiform hemangioendothelioma shares clinical and histologic features with Dabska's tumor. However, in Dabska's tumor, cavernous vascular spaces resembling lymphatics predominate, there is no retiform architecture, and intravascular papillae with collagenous cores are a striking feature. Hobnail hemangioma (targetoid hemosiderotic hemangioma) is more superficial, lacks a retiform architecture, and has hobnail endothelial cells that are mainly seen in vessels near the surface. Angiosarcoma often presents in a different clinical setting and shows cytologic atypia, mitoses, and absence of hobnail endothelial cells.

Papillary Intralymphatic Angioendothelioma (Malignant Endothelial Papillary Angioendothelioma, Dabska's Tumor)

Papillary intralymphatic angioendothelioma (PILA) is a very rare tumor that was first described in 1969 as malignant endolymphatic angioendothelioma. Until recently, only very few additional cases had been reported in the literature, and there seemed to be a lack of consensus regarding its specific histologic features. However, a recent series has delineated the histologic features of this tumor more accurately, and the alternative name of PILA has been proposed (208). Tumors present mainly in infants and children, but around 25% of patients are adults. Males and females are equally affected, and most cases involve the limbs. Clinical presentation is that of a slowly growing, solitary, asymptomatic nodule or plaque. This tumor is classified among tumors with low-grade malignant potential based on reports of local recurrence and rare regional lymph node metastasis in the original series. However, follow-up in 8 of the 12 cases recently reported showed no evidence of either local recurrence or distant spread (208). It is therefore likely that these tumors are benign, although confirmation of these findings is required in larger series with longer follow-up. Until this happens, complete excision of these tumors is advised.

Histopathology. Low-power examination reveals a dermal and often subcutaneous tumor composed of markedly dilated, thin-walled vascular channels resembling a cavernous lymphangioma (Fig. 33-67). These vascular channels are lined by bland hobnail endothelial cells with protruding nuclei and very scanty cytoplasm. A prominent intra- and extravascular lymphocytic inflammatory cell infiltrate is often present, and intravascular papillae with collagenous cores are a frequent finding (Fig. 33-68). Commonly, the lymphocytes appear to be in close apposition to the endothelial cells. Tumor cells stain for vascular markers including CD31, CD34, and von Willebrand factor.

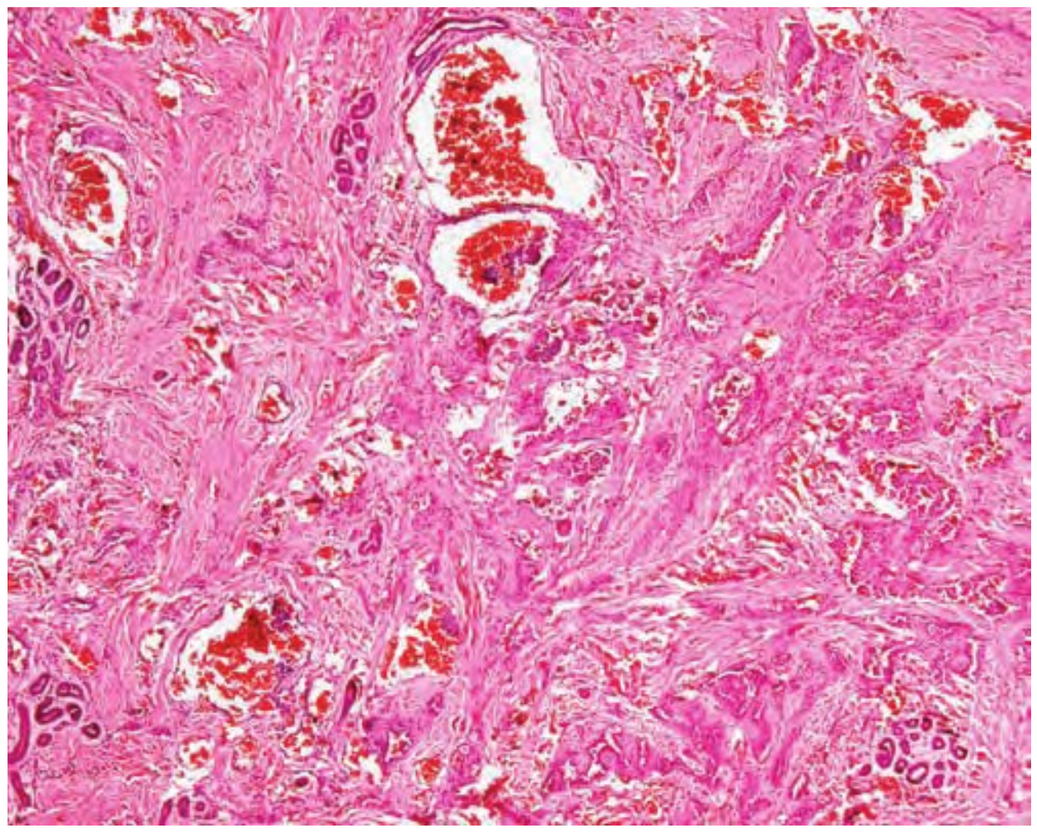


FIGURE 33-67. Papillary intralymphatic angioendothelioma. Cavernous lymphangioma–like vascular spaces and intravascular papillae.

Pathogenesis. Based on the close interaction between lymphocytes and endothelial cells in Dabska's tumor, it has been proposed that the hobnail endothelial cells differentiate toward high endothelial cells, which are normally responsible for the selective homing of lymphocytes in lymphoid organs (209). A similar theory can be proposed for retiform hemangioendothelioma, which shares some histologic features with Dabska's tumor. The strong expression of vascular endothelial growth factor receptor-3 (VEGFR-3) by tumor cells has led to suggestions that these tumors display lymphatic differentiation (209). However, the specificity of this marker as an indicator of lymphatic differentiation is doubtful.

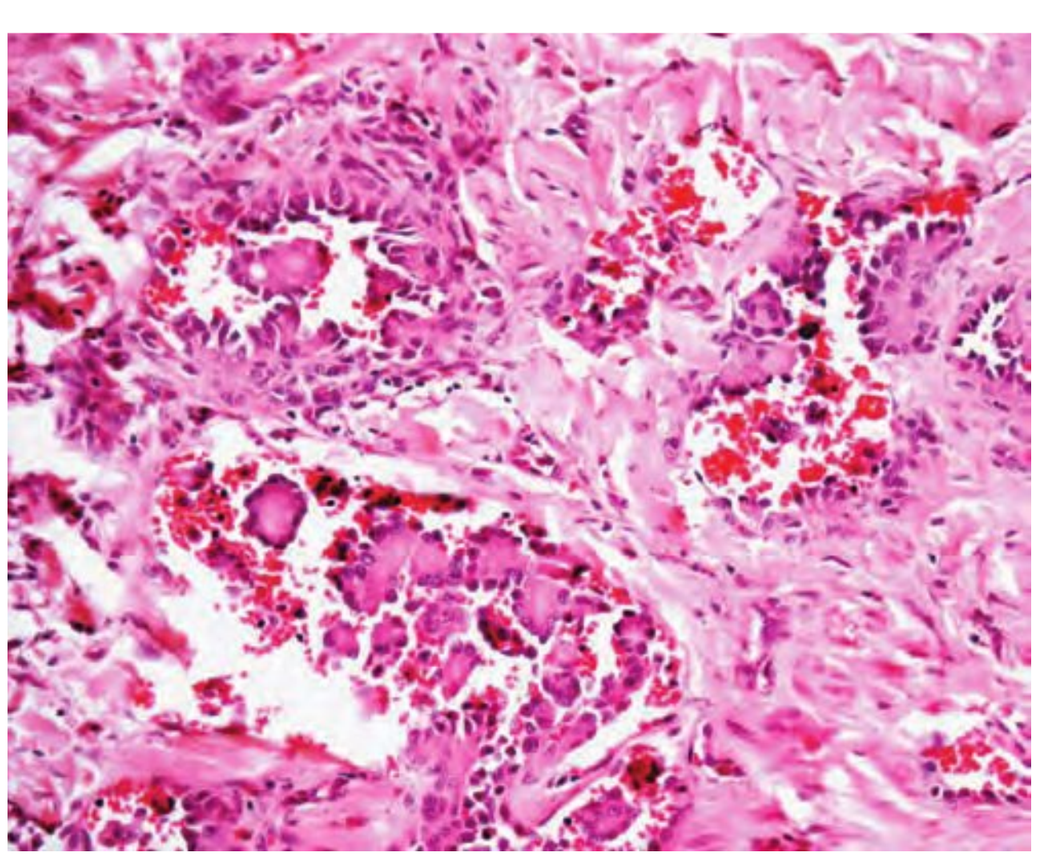


FIGURE 33-68. Papillary intralymphatic angioendothelioma. Bland hobnail endothelial cells and formation of numerous papillary projections with collagenous cores.

Differential Diagnosis. Refer to the differential diagnosis for retiform hemangioendothelioma, previous page.

Composite Hemangioendothelioma

Composite hemangioendothelioma is a recently described low-grade malignant vascular tumor with a tendency for local recurrence but very low metastatic potential. It is defined as a neoplasm containing a mixture of histologic patterns including benign, intermediate, and/or malignant (210). It is a very rare tumor presenting mainly in adults and only exceptionally in children (210–212). There is no sex predilection, and most tumors occur in the extremities with a predilection for the hands and feet. In 25% of patients, tumors arise in association with lymphedema and lesions present as long-standing red-blue nodules or plaques. The rate of local recurrence is around 50%, and this may occur years after excision of the primary tumor. Only a single case originating in the tongue has been reported to metastasize to a regional lymph node and to the soft tissues of the thigh.

Histopathology. Composite hemangioendothelioma is poorly circumscribed, with an infiltrative growth pattern and involvement of the dermis and subcutaneous tissue. The different components vary from tumor to tumor and may include retiform hemangioendothelioma (Fig. 33-69), epithelioid hemangioendothelioma, spindle cell hemangioma, conventional angiosarcoma (low and even high grade), lymphangioma circumscriptum, and areas simulating an arteriovenous malformation. The prognosis is likely to be dictated by the component with the highest histologic grade, but this should be estimated in larger series of cases with adequate follow-up. Immunohistochemistry displays positive staining for vascular markers including CD31, CD34, and von Willebrand factor.

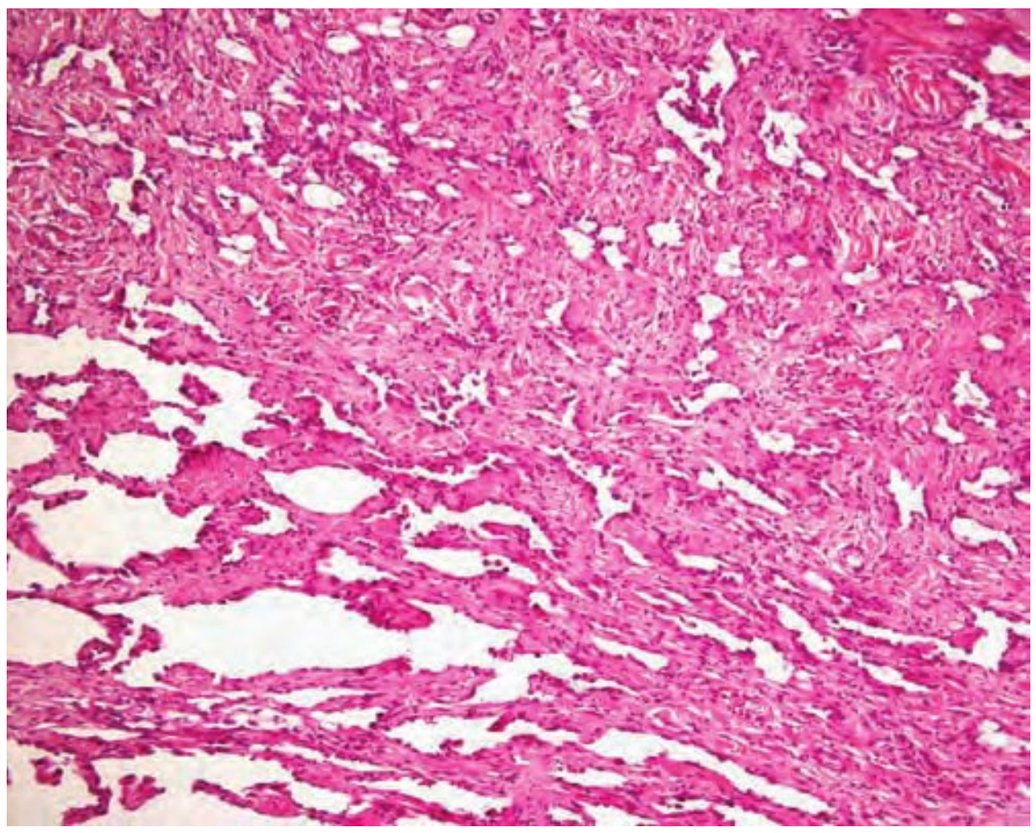


FIGURE 33-69. Composite hemangioendothelioma. Areas of retiform hemangioendothelioma and well-differentiated angiosarcoma. Elsewhere, the tumor contains areas resembling an epitheliod hemangioendothelioma.

Kaposi-like Infantile Hemangioendothelioma

Although Kaposi-like infantile hemangioendothelioma has only been described recently, individual cases of the same condition were reported in the past under different names (199,213–217). It is a rare vascular tumor that usually presents in the retroperitoneum or deep soft tissues of infants. Occasionally, congenital multifocal lesions have been described (218). A high number of cases are associated with Kasabach-Merritt syndrome (up to half of cases or more) or lymphangiomatosis. It is classified as a low-grade malignant vascular tumor because of its locally aggressive growth. Although exceptional regional perinodal soft tissue involvement has been reported, metastases have not been described (214). Cutaneous and superficial soft tissue tumors are relatively rare (219). Lesions with a superficial location tend to behave in a benign fashion except when associated with Kasabach-Merritt syndrome.

Histopathology. Low-power examination shows a tumor with a lobular and focally infiltrative growth pattern (Fig. 33-70). Bands of collagen separate tumor lobules. These lobules are composed of a mixture of congested capillaries surrounded by fascicles of bland spindle-shaped endothelial cells and pericytes (Fig. 33-71). Slitlike vascular spaces are often a feature. Focal areas with epithelioid cells containing abundant pale pink cytoplasm are often seen. In many areas, the tumor resembles a capillary hemangioma. Toward the periphery of the tumor lobules, small vascular channels frequently show intraluminal thrombi (Fig. 33-72). Hemosiderin deposition and hemorrhage are additional findings. It has been suggested that this tumor consists of vascular and lymphatic components. The latter is reflected by the presence of dilated, irregular, lymphatic-like spaces in the stroma between tumor lobules. Some tumors have areas resembling tufted angioma, and it has been suggested that there is an overlap between both entities (220).

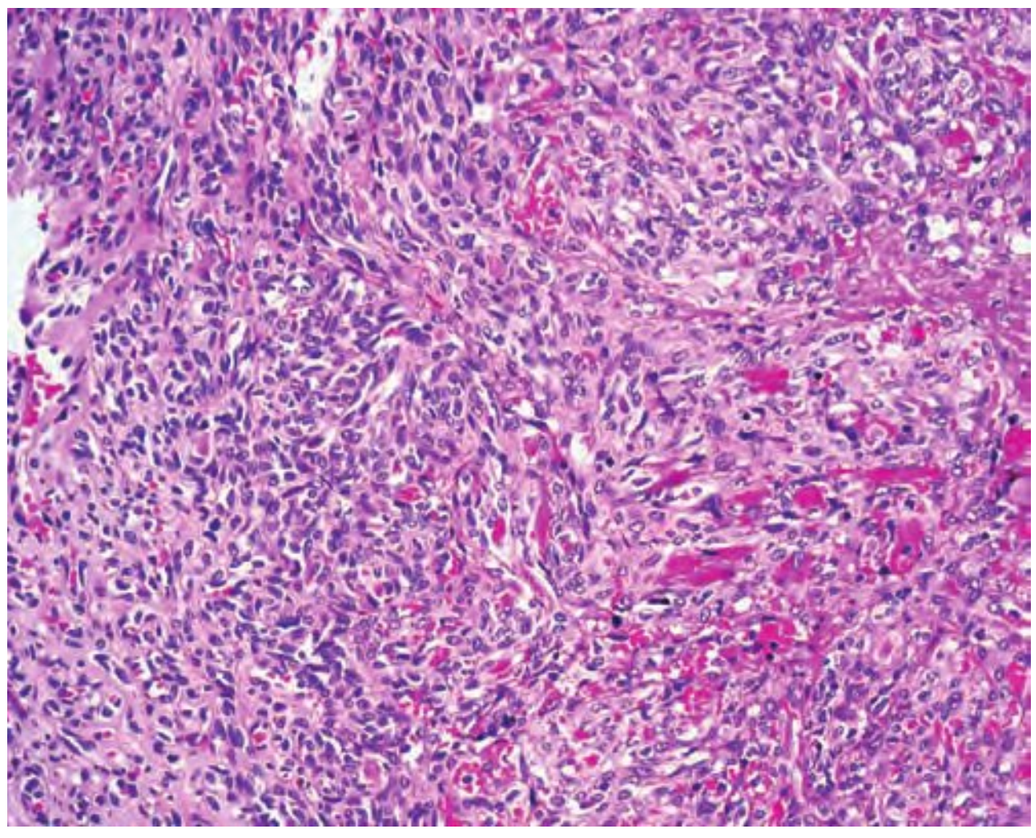


FIGURE 33-71. Kaposiform hemangioendothelioma. Capillaries intermixed with bland spindle-shaped cells.

Lesions are always negative for HHV-8. Regression does not tend to occur in patients who survive the Kasabach-Merritt phenomenon (221).

Distinction from Kaposi's sarcoma is discussed on page 1035.

Giant Cell Angioblastoma

Giant cell angioblastoma (222,223) is very rare, with only a handful of cases reported so far in the literature. Although it is briefly mentioned in the WHO book on classification of tumors of soft tissue and bone (1), it was not formally included in the final classification until more and larger series provide a

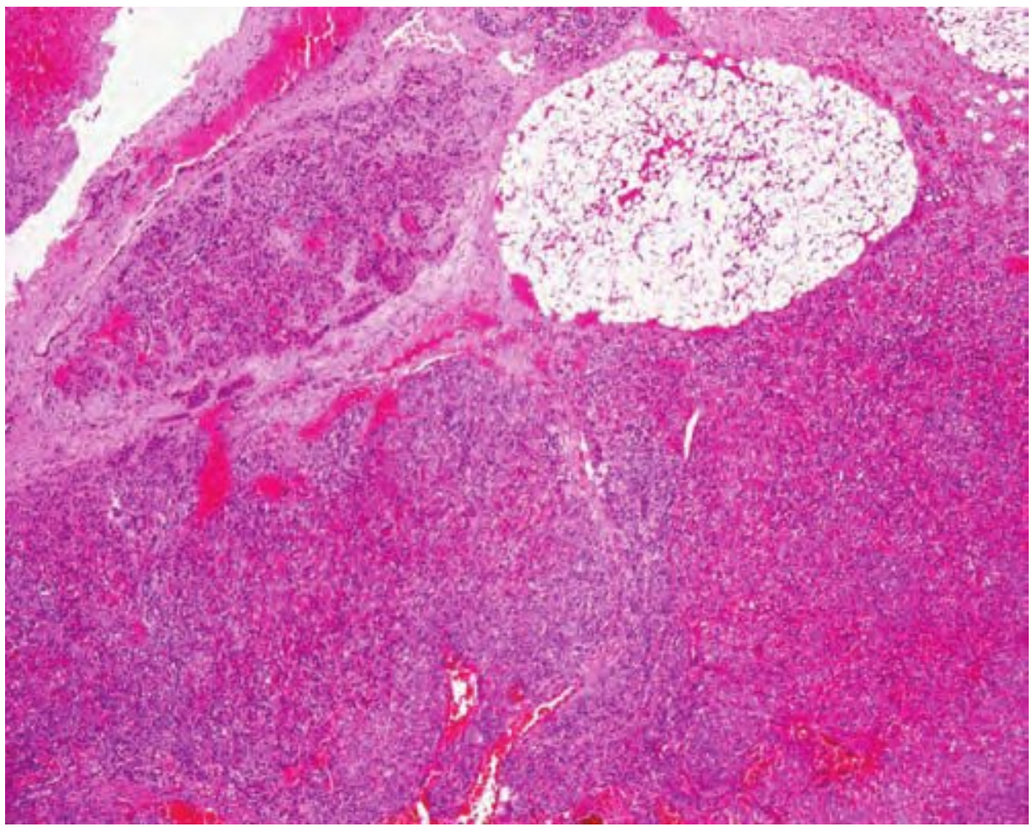


FIGURE 33-70. Kaposiform hemangioendothelioma. Typical lobular and infiltrative growth pattern with replacement of the subcutaneous tissue.

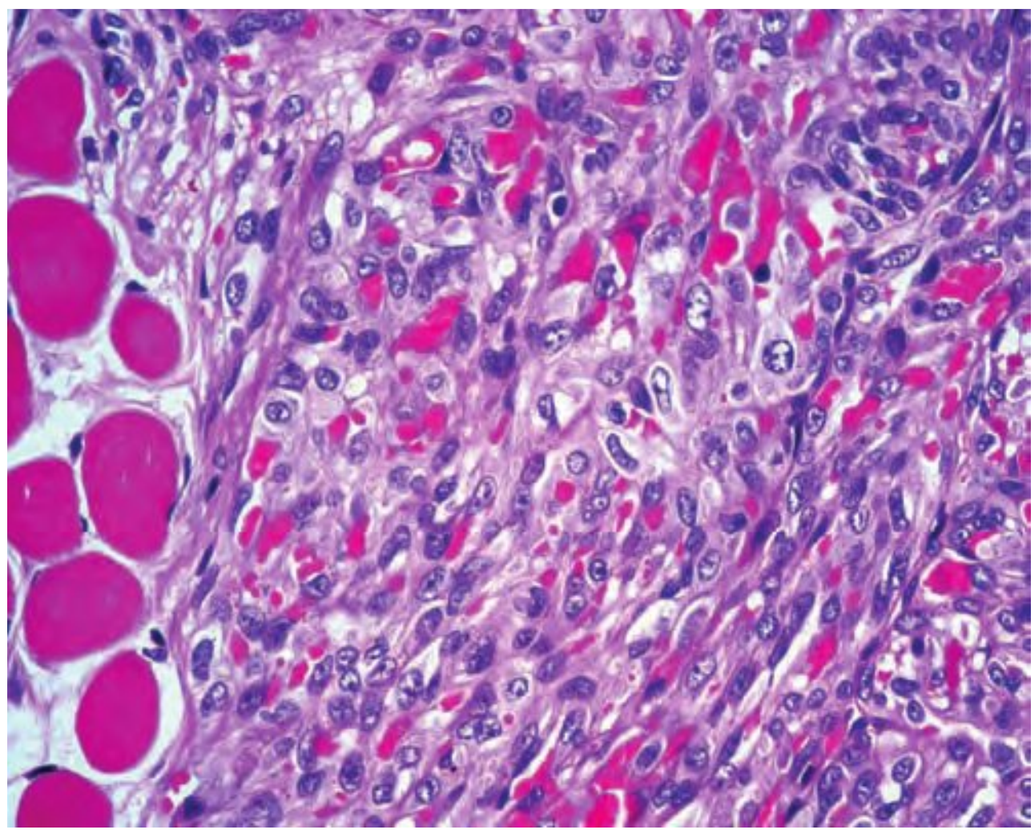


FIGURE 33-72. Kaposiform hemangioendothelioma. Note infiltration of skeletal muscle and frequent microthrombi within the capillaries.

better definition of the entity particularly, as it is not clear whether the line of differentiation of these tumors is truly endothelial.

Tumors are locally destructive and have been described on the hand, forearm, scalp, and palate of infants as hemangioma-like lesions. No metastases have been reported.

Histopathology. Characteristically, tumors display a distorted attempt at producing vascular walls, and many of its features simulate a fibrohistiocytic tumor. There is involvement of the mucosa, dermis, subcutis, and deep soft tissue by nodular, linear, and plexiform granuloma-like aggregates of bland histiocyte-like cells and giant cells with no mitotic activity. These cells are distributed in a concentric onionskin pattern around capillary-sized vessels lined by plump endothelial cells with no atypia. The background shows a loose focally myxoid stroma and a moderate mononuclear inflammatory cell infiltrate. Perineural and intraneural involvement by small vessels can be seen. Smooth muscle actin is strongly positive in most histiocyte-like cells, suggesting a vascular smooth muscle origin while CD68 and KP1 stain the multinucleated giant cells.

Differential Diagnosis. The differential diagnosis includes plexiform fibrous histiocytoma (PFH), myofibroma, and giant cell fibroblastoma (GCF). PFH has a characteristic plexiform biphasic growth pattern with nodules of histiocyte-like cells and small numbers of multinucleated giant cells intermixed with bundles of myofibroblast-like cells. Myofibroma also usually shows a biphasic growth pattern with immature round cells distributed around branching vascular channels in a hemangiopericytoma-like arrangement alternating with bundles of mature myofibroblasts with focal hyalinization. GCF differs in showing CD34-positive, fleurette-type multinucleated cells and pseudoangiomatoid spaces and sinusoidal focally lined by giant cells.

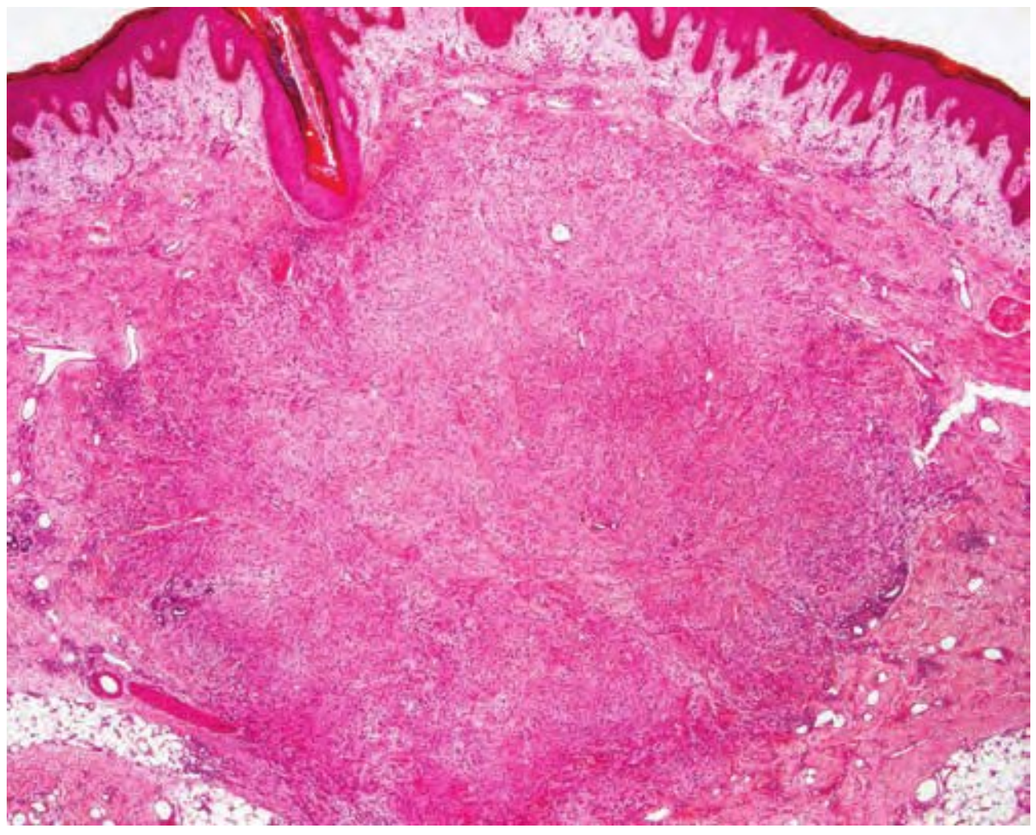


FIGURE 33-73. Epithelioid hemangioendothelioma. Purely cutaneous tumors often present as a fairly circumscribed nodule with hyalinization or myxoid change.

MALIGNANT TUMORS

Epithelioid Hemangioendothelioma

Epitheliod hemangioendothelioma is a neoplasm that was initially described in 1982 as a low-grade tumor of vascular endothelial origin (224). Epithelioid hemangioendothelioma, however, is associated with high morbidity and mortality and should therefore be regarded as a neoplasm with full malignant potential (225). It mainly arises in the superficial and deep soft tissue and muscle of the extremities (226). The tumor can also arise at internal sites and in the viscera (especially the liver, lungs, and bone). Many of such tumors were described previously by different names (224,226). Middle-aged patients, with an equal gender distribution, are mainly affected, but the tumor has a wide age distribution. In about half the cases, the tumor apparently arises from a medium-sized vein or, less often, an artery (224,225). Multicentricity is common in visceral lesions, particularly those affecting the lungs, liver, and bones. Skin involvement is uncommon and usually associated with an underlying soft tissue or bone lesion or with multicentric disease (226–228). Rare cases present with pure cutaneous involvement (229,230). Metastases develop in about 30% of cases involving superficial soft tissues, with a mortality rate of 17% (225). The prognosis is worse for internal sites (226).

Histopathology. Typically, epithelioid hemangioendothelioma shows an infiltrative growth pattern. However, purely cutaneous tumors often consist of a fairly circumscribed dermal tumor (Fig. 33-73). Tumor cells are ovoid, cuboidal, or short and spindle shaped with prominent eosinophilic cytoplasm. The nucleus is vesicular, showing variable or no atypia, and the nucleolus lacks prominence (Fig. 33-74). Cells tend to be

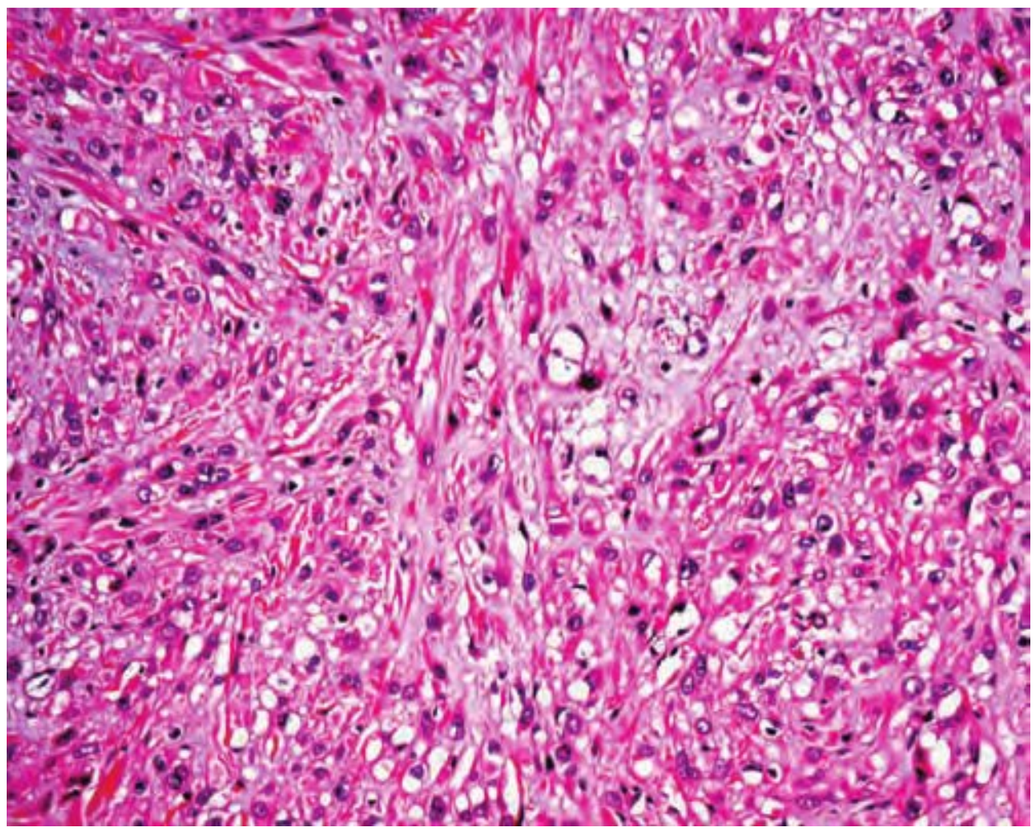


FIGURE 33-74. Epithelioid hemangioendothelioma. Epithelioid cells with variable atypia organized in short strands or individual units. Notice formation of intracytoplasmic lumina.

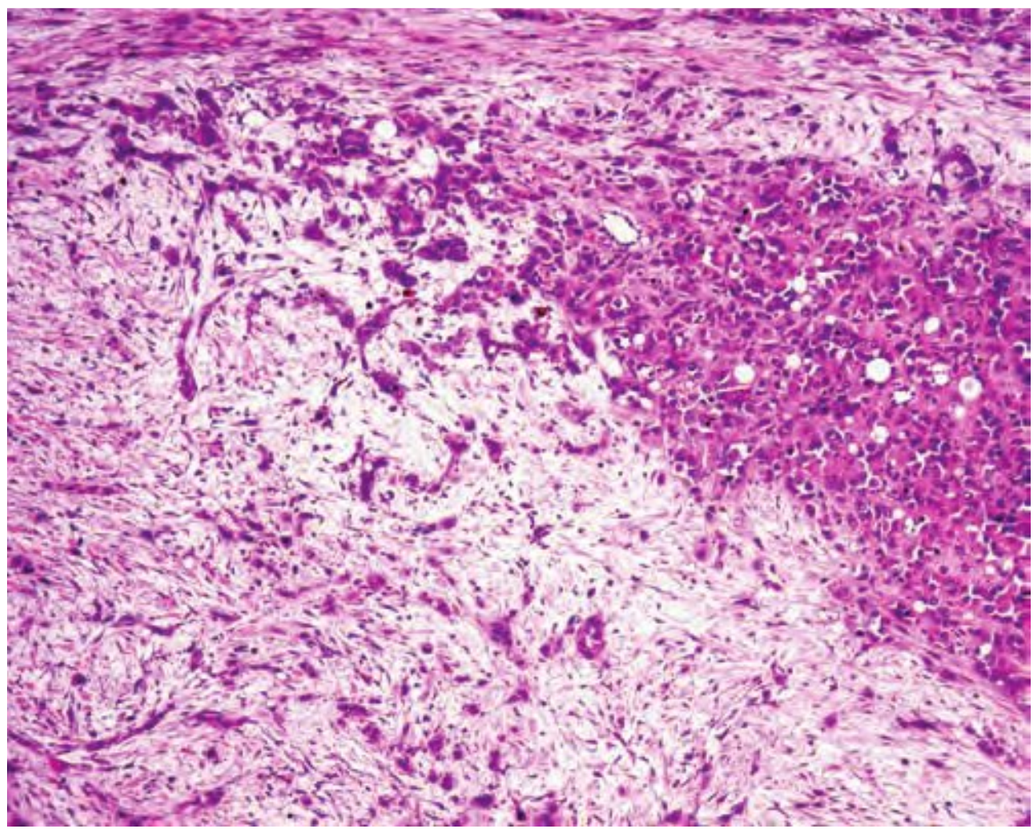


FIGURE 33-75. Epithelioid hemangioendothelioma. Transition between classic epithelioid hemangioendothelioma and solid, more pleomorphic areas with features of an epithelioid angiosarcoma.

arranged in short fascicles, small nests, or in an "Indian file" pattern, often set in a distinctive hyalinized or mucoid stroma rich in sulphated acid mucopolysaccharides. There is often a chondroid appearance. Obvious vascular channels are generally lacking, but intracytoplasmic vacuoles, sometimes containing erythrocytes, are usually present (Fig. 33-74). Infiltration through large-vessel walls and evidence of endothelial origin may be found. A subset of the tumor with a more aggressive clinical course shows prominent cytologic atypia and a high mitotic rate, overlapping histologically with epithelioid angiosarcoma (225) (Fig. 33-75). Some cases are associated with a prominent osteoclast-like giant cell reaction (231,232). Although lesions with cytologic atypia and mitoses are associated with a poorer prognosis, the behavior of tumors with bland morphology is difficult to predict.

Tumor cells often stain for endothelial markers including CD31, CD34, and von Willebrand factor. Positivity for pankeratin can be focally found in up to 20% to 30% of cases (225,233). Staining for epithelial membrane antigen is usually negative.

Cytogenetic analysis in two cases revealed a t(1;3) (p36.3;q25) (234). Analysis of a further case showed a complex translocation 7;22 (235).

Differential Diagnosis. The differential diagnosis includes epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia), which often has a lobular architecture, prominent inflammation, and numerous well-formed blood vessels; metastatic adenocarcinoma, which is negative for endothelial markers and positive for mucin stains; myxoid chondrosarcoma, which has a lobular growth pattern, S-100–positive cells, and absence of intracytoplasmic lumina; and myoepithelioma, which usually lacks intracytoplasmic lumina and has cells that are variably positive for keratin, smooth muscle actin, epithelial membrane antigen, and S-100.

Angiosarcoma

Most angiosarcomas of the skin arise in the following clinical settings: (a) angiosarcoma of the face and scalp in the elderly, (b) angiosarcoma (lymphangiosarcoma) secondary to chronic lymphedema (Stewart-Treves syndrome), and (c) angiosarcoma as a complication of chronic radiodermatitis or arising from the effects of severe skin trauma or ulceration (236).

An aggressive variant known as *epithelioid angiosarcoma* (237) regarded as distinctive from the variants mentioned before has been described. This tumor is difficult to diagnose histologically without the help of immunohistochemistry because of the exclusive epithelioid morphology and the limited formation of vascular channels (see text following).

Apart from these circumstances, cutaneous angiosarcomas are extremely rare. Exceptional case reports include angiosarcoma arising in preceding benign vascular tumors including vascular malformations (238), in a large blood vessel (239), in association with a plexiform neurofibroma in neurofibromatosis (240), in a schwannoma (241), in a malignant peripheral nerve sheath tumor (242,243), in xeroderma pigmentosum (244), in a gouty tofus (245), in association with vinyl chloride exposure (246), in association with immunosuppression in organ transplantation (247), and as the mesenchymal component in a metaplastic carcinoma (248). A case of "cutaneous-type" angiosarcoma has been described arising in a mature teratoma of the ovary (249). Angiosarcoma in children is extremely rare (250). An exceptional case of an angiosarcoma producing granulocyte colony-stimulating factor and inducing a leukemoid reaction has been described (236). With the exception of epithelioid angiosarcoma, the histologic spectrum of angiosarcomas is similar regardless of the clinical setting.

1. *Angiosarcoma of the scalp and face of the elderly.* This is almost invariably a fatal tumor that usually arises innocuously as erythematous or bruiselike lesions on the scalp or middle and upper face with a predilection for men (251–254). Subsequent plaques, nodules, or ulcerations develop (Fig. 33-76); metastasis to nodes or internal organs (mainly lungs, liver, and brain) usually arises as a late complication, with many patients dying as a result of extensive local disease. This sarcoma has only rarely been reported in black patients; the disease mainly affects whites and sometimes Asians. Only a very small percentage of patients, with smaller lesions usually less than between 5 and 10 cm in diameter at presentation, can be successfully treated with radical wide field radiotherapy and surgery (251,254). Combined series of idiopathic angiosarcoma of the face and scalp, other cutaneous angiosarcomas, and angiosarcomas occurring in internal organs report 5-year survival rates varying between 24% and 34% (253–256). The best chance of survival resides in wide surgical excision followed by radiotherapy (257).
2. *Angiosarcoma following lymphedema (postmastectomy lymphangiosarcoma or the Stewart-Treves syndrome).* Typically, the tumor presents in women who have had severe, long-standing lymphedema of the arm following breast surgery (258–260). In most cases, lymphedema is present for about



FIGURE 33-76. Idiopathic angiosarcoma of the face. Hemorrhagic, ulcerated nodule with bruiselike lesions in a multifocal pattern in surrounding skin.

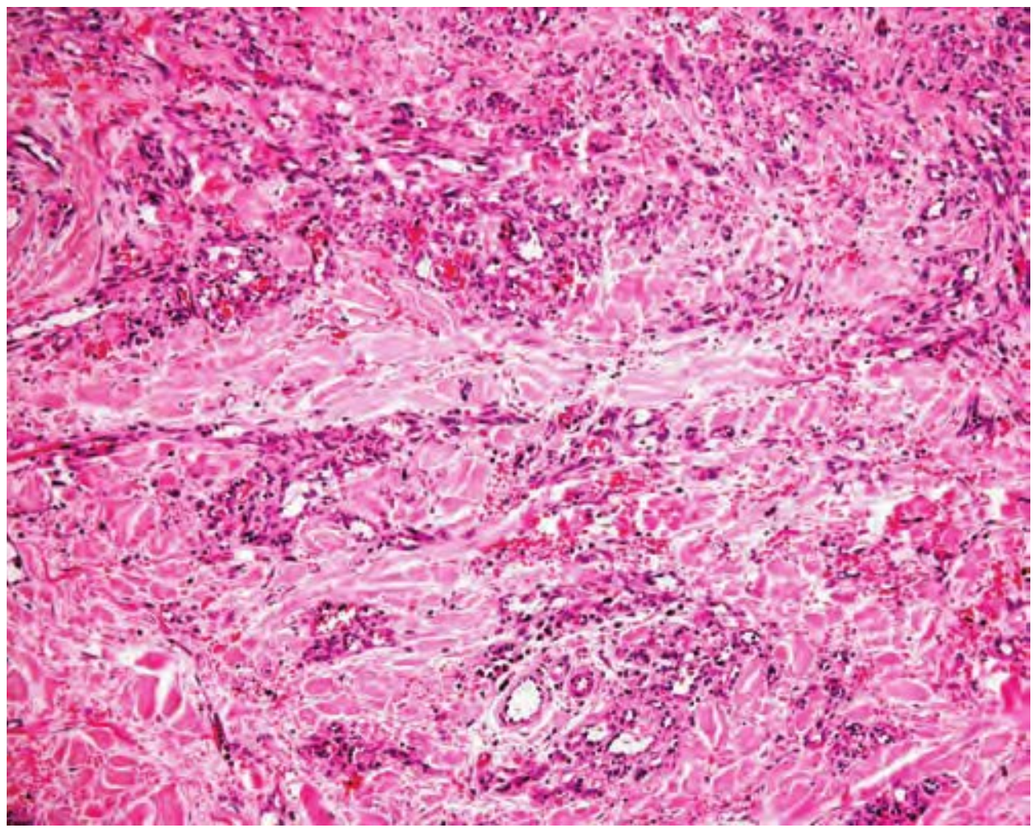


FIGURE 33-78. Well-differentiated angiosarcoma. Irregular and congested vascular channels infiltrating between collagen bundles.

10 years before the tumor arises, usually in the inner portion of the upper arm. Radiotherapy can usually be excluded as an etiologic factor, because the sarcoma nearly always develops beyond the areas of chronic radiodermatitis. Lymphedema-induced angiosarcoma has also been described in men and in a lower extremity (260) from causes other than cancer surgery, including congenital lymphedema (261) and tropical lymphedema due to filarial (262). The prognosis despite radical surgery is extremely poor. Exceptionally, a low-grade angiosarcoma with lesions simulating lymphangioma circumscriptum has been described as complicating chronic lymphedema after surgery (263).

3. *Postirradiation angiosarcoma.* There are many reports of angiosarcoma arising in the skin after radiotherapy for internal cancer. The most common sites are the breast or chest wall (264–268) and the lower abdomen after therapy for breast or gynecologic cancer (268).

Histopathology. Usually, the tumor extends well beyond the limits of the apparent clinical lesion, and multifocality is frequent. As a rule, the tumor shows varied differentiation in different biopsies, even within different fields in a single biopsy (Fig. 33-77). In well-differentiated areas, irregular anastomosing vascular channels lined by a single layer of somewhat enlarged endothelial cells permeate between collagen bundles (Figs. 33-77 and 33-78). Isolation and enclosure of collagen bundles, figuratively referred to as *dissection of collagen* is a characteristic feature (Fig. 33-79). Nuclear atypia is always

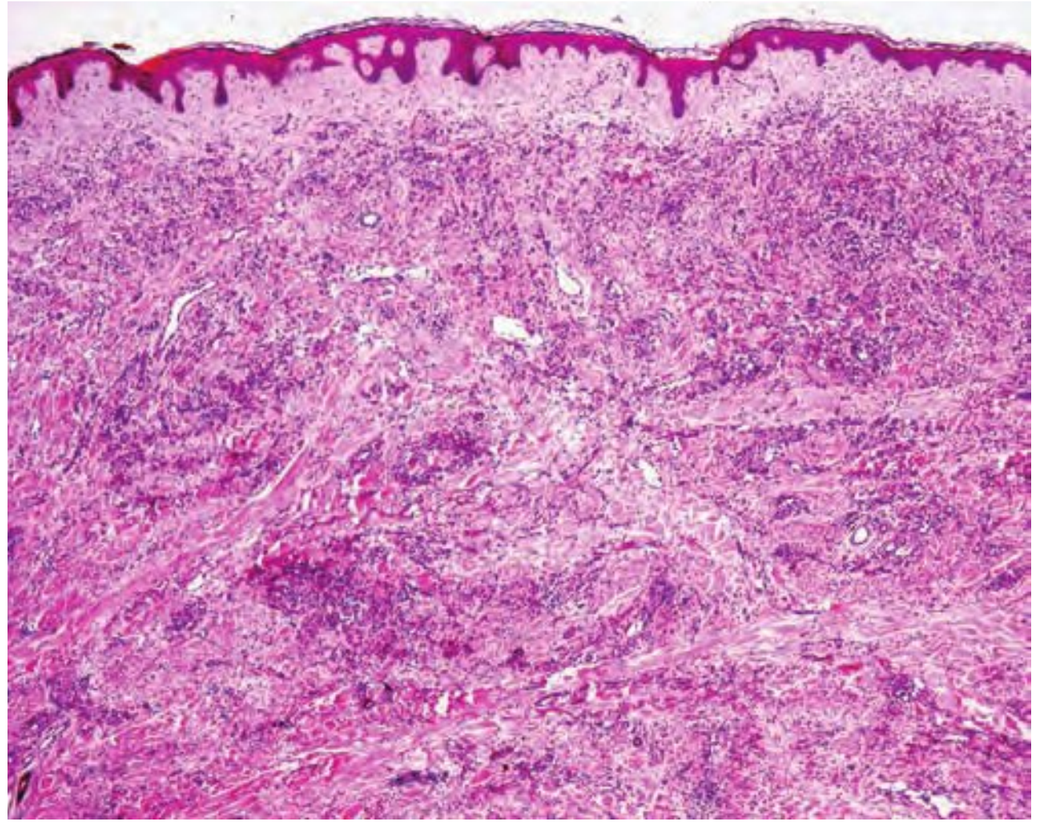


FIGURE 33-77. Well-differentiated angiosarcoma. Low-power view mimicking plaque-stage Kaposi's sarcoma.

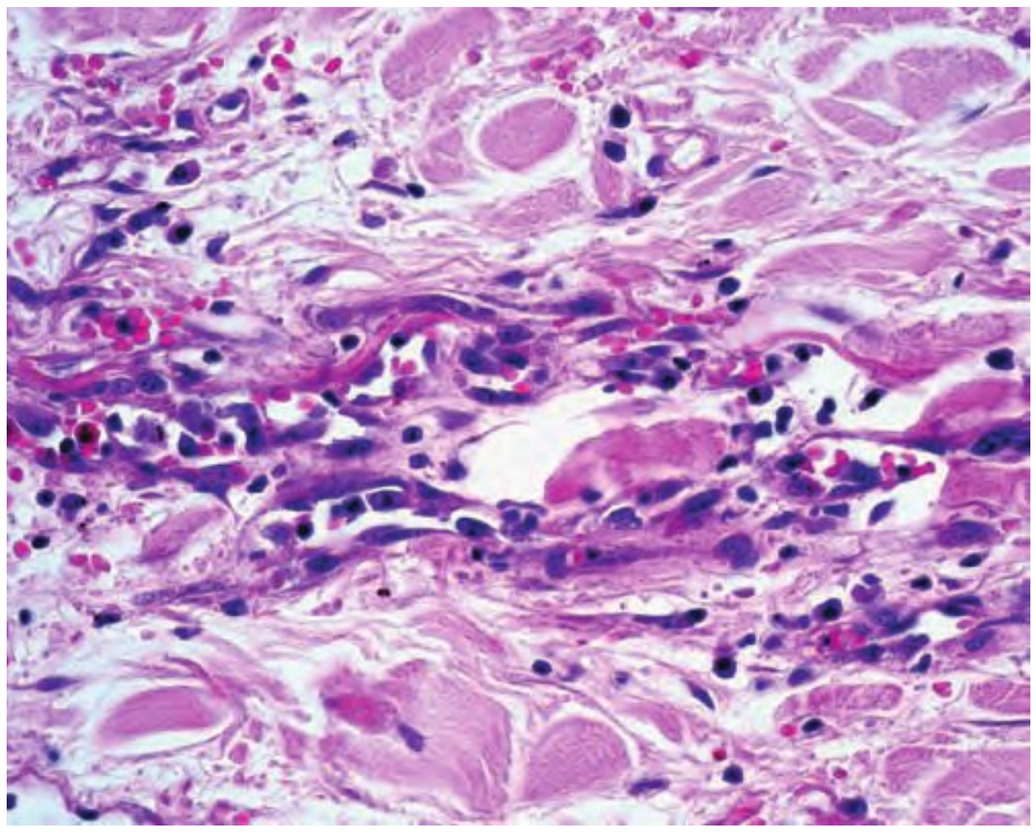


FIGURE 33-79. Well-differentiated angiosarcoma. Dissection of collagen pattern. Marked cytologic atypia and multilayering.

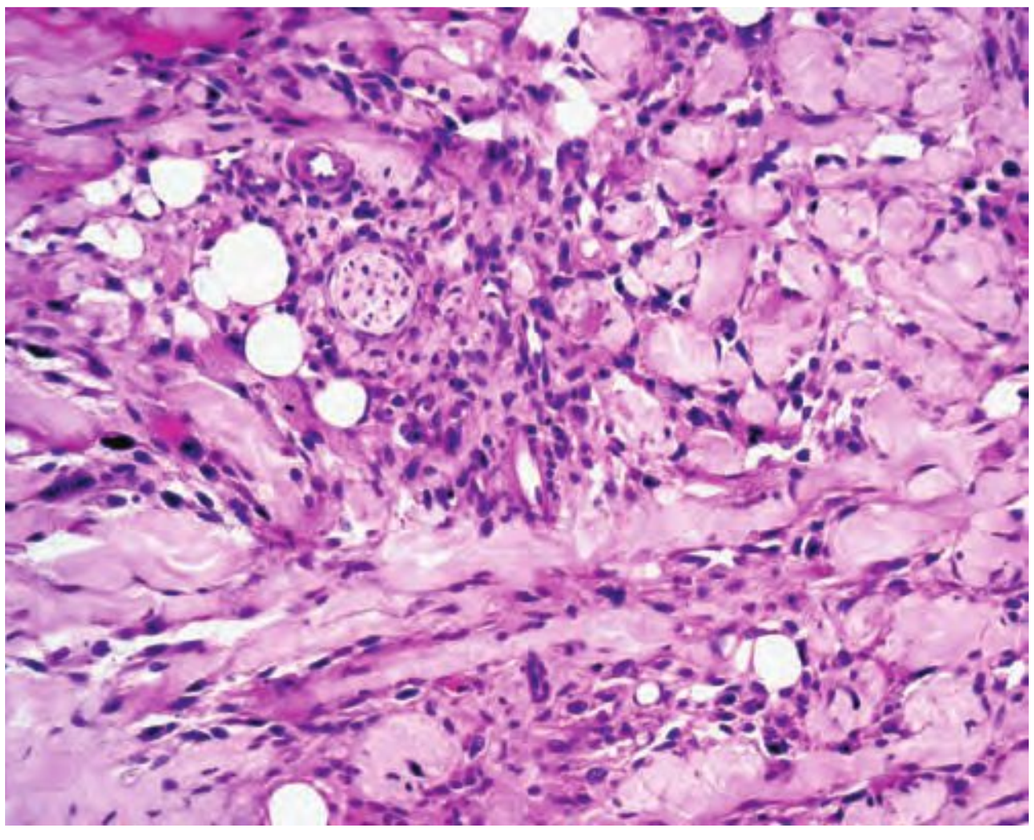


FIGURE 33-80. Moderately differentiated angiosarcoma. More cellular tumor with less evident vascular differentiation and more cytologic atypia.

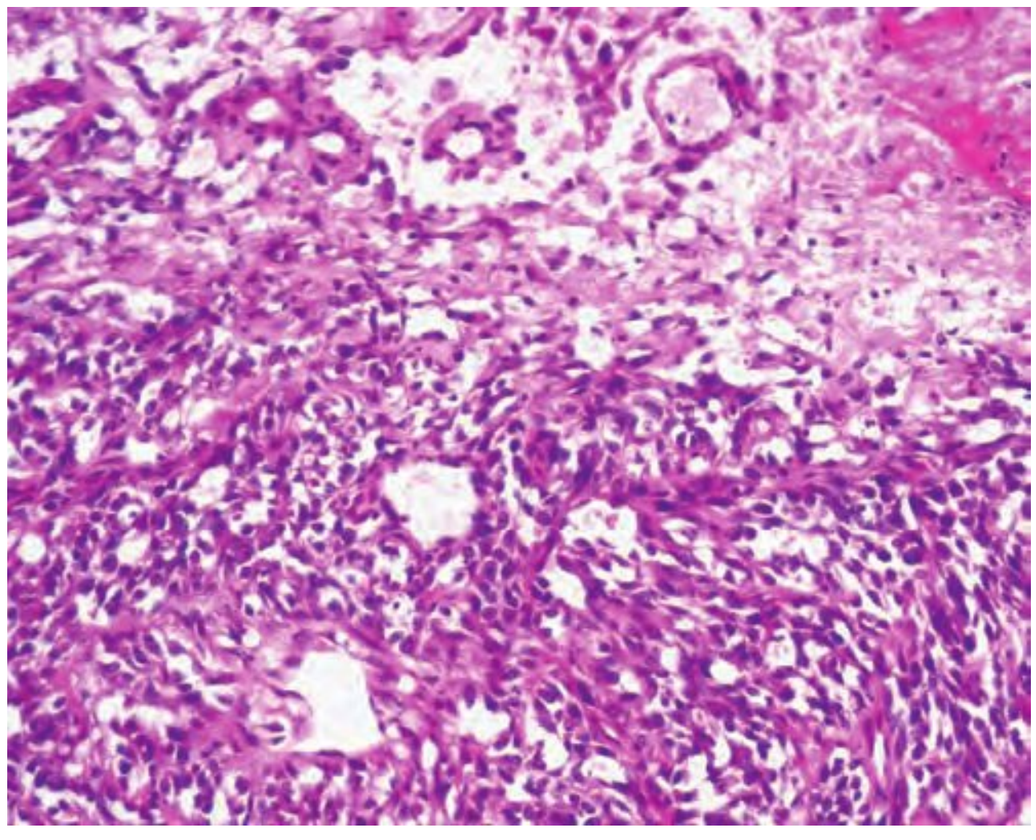


FIGURE 33-81. Poorly differentiated angiosarcoma. Highly cellular tumor composed of pleomorphic spindle-shaped cells and only focal suggestion of vascular differentiation.

present and may be slight to moderate, but occasional large hyperchromatic cells may be encountered. At this stage, the vascular lumens are generally bloodless, but they may contain free-lying shed malignant cells. Mitotic figures are invariably present, and it has been suggested that a high mitotic rate correlates with a poor prognosis (254,269). Other factors that are associated with poor prognosis include depth of invasion and positive tumor margins along with a tumor diameter >5 cm (254).

In less well-differentiated areas, endothelial cells increase in size and number (Fig. 33-80), forming intraluminal papillary projections where there is enhanced mitotic activity. In poorly differentiated areas, solid sheets of large pleomorphic cells with little or no evidence of luminal differentiation can resemble metastatic carcinoma or melanoma. Focally, areas showing epithelioid cells are not uncommon. The presence of an epithelioid component in the three variants of angiosarcoma described herein should not lead to the classification of a tumor, as epithelioid angiosarcoma such as this represents a distinctive variant of angiosarcoma (see next page). Other areas of tumors may simulate a poorly differentiated spindle cell sarcoma (Fig. 33-81). Interstitial hemorrhage and widely dilated blood-filled spaces may sometimes develop. Rare cases are composed of granular cells (270). In exceptional cases, tumors may be extensively infiltrated by lymphocytes or macrophages. In the former setting, distinction from a lymphoma may be difficult (271,272).

The histopathology of angiosarcomas secondary to lymphedema and radiotherapy shows a similar range of well-differentiated to poorly differentiated neoplasms as idiopathic angiosarcoma of the face and scalp. There are no reliable histologic differentiating features, although sometimes evidence of chronic lymphedema or chronic radiation dermatitis may be apparent in the tissue adjacent to the sarcoma.

Histogenesis. Sarcomas of probable lymphatic origin cannot be distinguished histologically from those of presumptive vascular endothelial origin; hence, there is a tendency to disregard the term *lymphangiosarcoma* in favor of *angiosarcoma*. For many years, a number of putative specific markers of lymphatic endothelium have been described, many of which have been a disappointment. However, a few appear to be specific, and these include LYVE-1, podoplanin, D2-40, and Prox-1 (273–276). By using D2-40, it has been shown that a percentage of cases but by no means all angiosarcomas display lymphatic differentiation (275).

von Willebrand factor is the most specific but least sensitive vascular marker, and it is generally negative even in well-differentiated tumors. However, patchy, weak, diffuse staining may be found focally in less well-differentiated tumors that require caution in interpretation. CD34 and especially the more specific CD31 are much more reliable as sensitive markers of tumors of endothelial cell origin for use in routine biopsies. It is important to remember, however, that CD34 is a very poorly specific marker and that CD31 stains macrophages, and this may represent a pitfall in tumors with prominent numbers of macrophages (277). Recently, an antibody against the carboxy terminal of the Fli-1 protein, a nuclear transcription factor member of the ETS family of DNA-binding transcription factors, has been shown to be a fairly specific marker of endothelial cells (278,279). As opposed to other markers of endothelial cell differentiation, the staining with this marker is nuclear. On electron microscopic examination, well-differentiated tumors may show the ovoid laminated organelle-like Weibel-Palade bodies characteristic of vascular endothelial cells, but they are absent in most tumors.

Cytogenetics studies of soft tissue and cutaneous angiosarcoma are limited to a few case reports. Most analyzed cases have shown complex cytogenetic aberrations (280–282). In a

single case of an angiosarcoma arising within a cavernous hemangioma, trisomy 5 and loss of the Y chromosome was the only abnormality demonstrated (283).

Differential Diagnosis. Well-differentiated angiosarcomas, if cell atypia is slight, may closely resemble early macular lesions of Kaposi's sarcoma and benign lymphangioendothelioma, because all of these conditions can demonstrate to a greater or lesser extent a "dissection of collagen" pattern. The major differences in clinical presentation of the disorders (absence of mitosis and the bland appearances of the endothelial cells in macular lesions of Kaposi's sarcoma and benign lymphangioendothelioma) should prevent any difficulties. Focal dissection of collagen pattern is also mimicked in intravascular papillary endothelial hyperplasia by new vessels invading thrombotic material. In poorly differentiated angiosarcomas, it is usually possible to find evidence of channel formation in peripheral areas that allows diagnosis. However, the use of endothelial markers, especially CD31, is an important aid in diagnosis. CD31 is the most specific and sensitive marker of endothelial cell differentiation, but it is important to remember that this marker also stains macrophages, and this may represent a diagnostic pitfall. Finally, occasionally adenoid squamous carcinomas or sarcomatoid squamous cell carcinoma, with or without intratumor hemorrhage, can simulate angiosarcoma (284–286). Immunohistochemistry is useful in these cases, since only angiosarcomas with epithelioid morphology are usually positive for cytokeratin, but these also show staining for CD31 and CD34. Angiosarcomas are consistently negative for HHV-8 (287).

Epithelioid Angiosarcoma

Epithelioid angiosarcoma is a rare form of angiosarcoma that usually arises in deep soft tissues (237) but may also occur in the skin and internal organs, including the thyroid and adrenal gland (288,289). Personal experience indicates that cutaneous lesions are more common than previously thought, and it is likely that such lesions were diagnosed in the past as epithelial or melanocytic neoplasms. There is wide anatomic distribution, and cases present in adults with a slight predilection for males. Some examples are multifocal, and it is difficult to establish the source of the primary tumor. Epithelioid angiosarcoma occurring in internal organs may rarely metastasize to the skin (290). Rare examples have been associated with radiation therapy (237), an arteriovenous fistula (291), and a foreign body (292). The outlook is extremely poor, although a slow course has been described for some skin tumors (289). However, the latter is based on a small number of cases with short follow-up, and cutaneous tumors appear to be aggressive.

Histopathology. Tumors are composed of sheets of pleomorphic large cells with prominent eosinophilic cytoplasm, a large nucleus, and an eosinophilic nucleolus, usually with little evidence of vascular differentiation other than the occasional presence of intracytoplasmic vacuoles sometimes containing red blood cells (Fig. 33-82). This angiosarcoma can easily be mistaken for a carcinoma deposit or even malignant melanoma (Fig. 33-83). Usually, the tumor cells demonstrate consistent

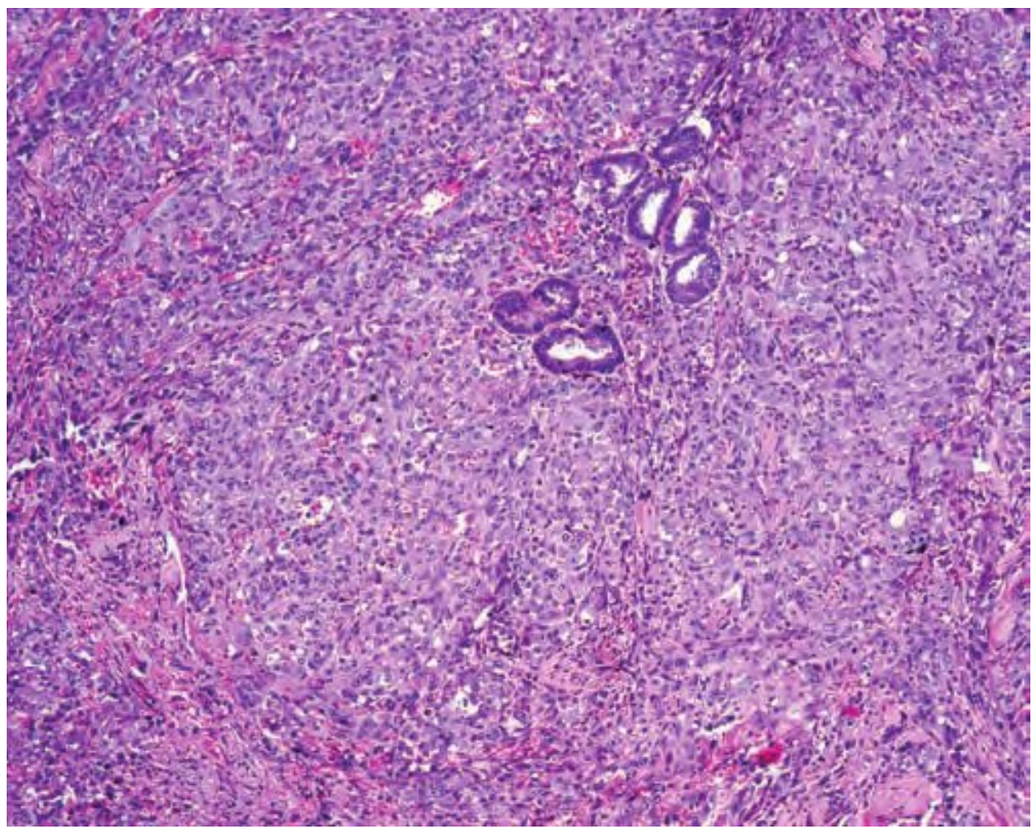


FIGURE 33-82. Epithelioid angiosarcoma. Solid proliferation of atypical epithelioid cells replacing the dermis.

positivity for von Willebrand factor, CD34, Fli-1, and CD31. However, cytokeratin positivity is present in up to 50% of cases, and rare cases are focally positive for epithelial membrane antigen; this might be a source of confusion with metastatic carcinoma and epithelioid sarcoma, which are negative for endothelial markers. However, epithelioid sarcoma is positive for CD34 in up to 60% of cases.

TUMORS OF LYMPHATIC VESSELS

Lymphangiomas constitute only about 4% of all vascular tumors and about 26% of benign vascular tumors in children (59).

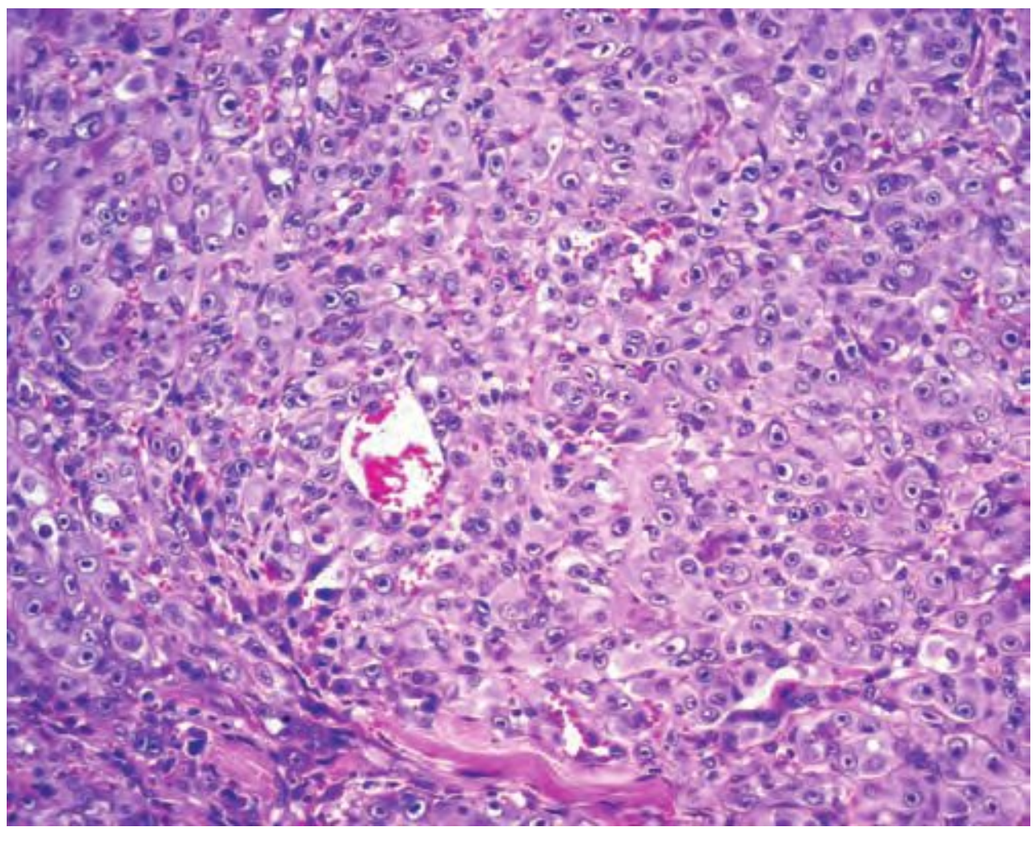


FIGURE 33-83. Epithelioid angiosarcoma. Large epithelioid cells with abundant pink cytoplasm, vesicular nuclei, and a single prominent eosinophilic nucleolus. Note the resemblance to melanoma cells and the hemorrhage in the background.

They can be classified into four types: (a) cavernous lymphangioma, (b) cystic hygroma, (c) lymphangioma circumscriptum (293), and (d) acquired progressive lymphangioma or benign lymphangioendothelioma (294–296). In addition, lesions of lymphangiectasia, which are indistinguishable from classic lymphangioma circumscriptum, may occur, although rarely, in association with congenital or acquired lymphedema (297). Although traditionally cavernous lymphangioma and cystic hygroma have been considered independent entities, it is likely that the latter is an ectatic variant of the former, which arises in areas of loose connective tissue; therefore, they will be discussed under the same heading (298). The existence of capillary lymphangioma is doubtful and will not be considered further.

Histogenesis. The great majority of tumors of lymphatic vessels are benign, and most of them appear to represent developmental abnormalities rather than true neoplasms. Although in hemangiomas the endothelial cells stain positively for factor VIII–related antigen, the endothelial cells in lymphangiomas are for the most part negative for this marker (299). The presence of fragmented basal lamina and anchoring filaments in hemangiomas is a more reliable ultrastructural feature to use to distinguish lymphatics and blood vessels. However, distinction between angiomas and lymphangiomas is not always clear even when light microscopy is combined with immunohistochemistry and electron microscopy (300).

Cavernous Lymphangioma and Cystic Hygroma

Cavernous lymphangioma usually presents at birth or during the first 2 years of life with an equal gender incidence (301,302). The most common locations are the head and neck area (particularly the oral cavity) and, less often, the extremities. It presents as a large, diffuse, subcutaneous, often fluctuant soft mass. Recurrences are common after limited excision.

Cystic hygroma has a similar age and gender distribution, and lesions tend to affect the neck, axillae, and groin (301). Tumors tend to be better circumscribed than cavernous lymphangiomas, but there is also a tendency for local recurrence unless a wide excision is performed. Cystic hygroma of the neck is commonly associated with Turner's syndrome (301,303).

Histopathology. Cavernous lymphangioma shows large, irregularly shaped spaces in the dermis and subcutaneous tissue lined by a single layer of bland endothelial cells (Fig. 33-84). The surrounding stroma can be loose or fibrotic and shows a lymphocytic inflammatory cell infiltrate with scattered lymphoid follicles. An incomplete layer of smooth muscle can be seen in the walls of some vessels. The vascular lumina show pink proteinaceous fluid with lymphocytes, but erythrocytes can also be seen. Large cavernous lymphangiomas, particularly in areas of the lip or tongue, may extend between the muscle bundles, separating them from one another (293).

In cystic hygroma, microscopic features are similar to those of cavernous lymphangioma except for the presence of numerous cystically dilated thin-walled lymphatic spaces.

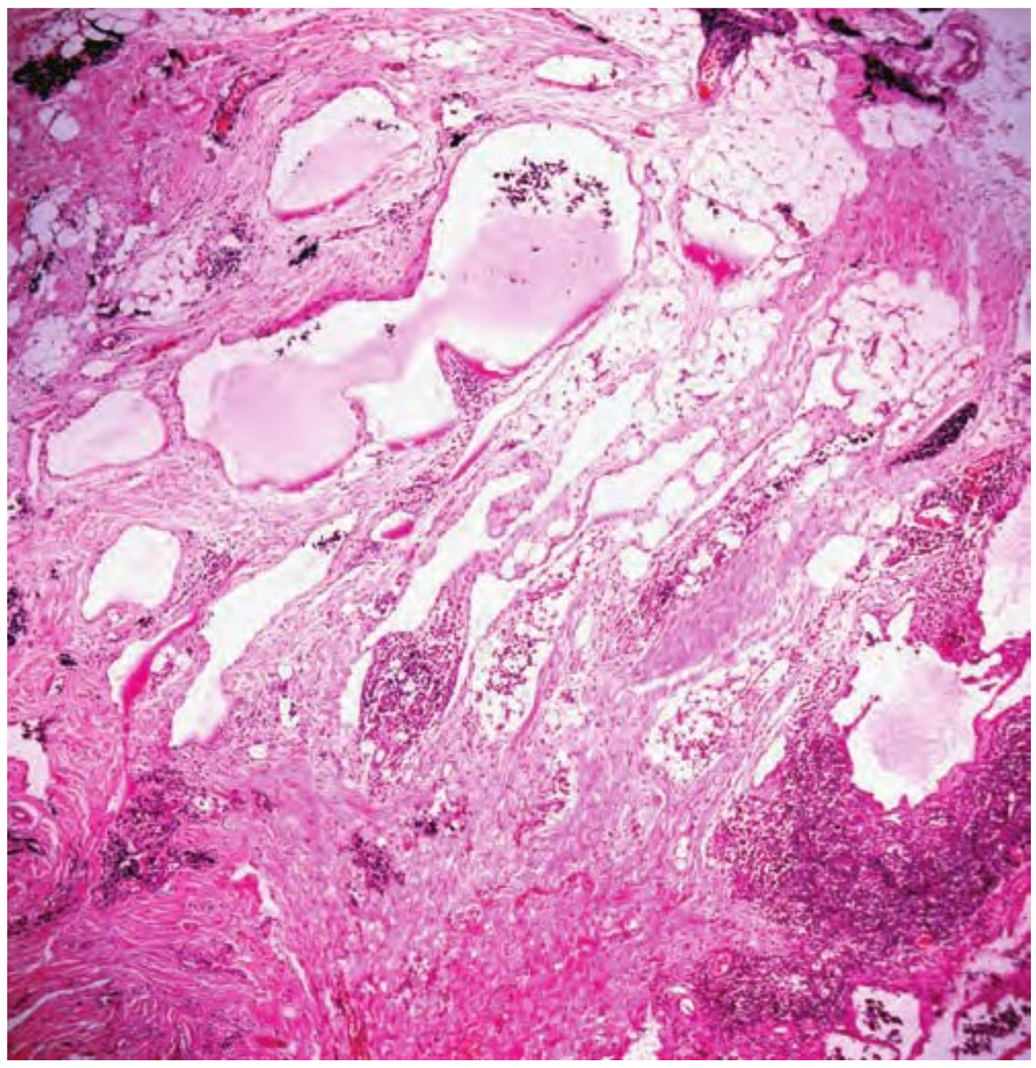


FIGURE 33-84. Cavernous lymphangioma. Dilated lymphatic channels and aggregates of lymphocytes in the stroma.

Differential Diagnosis. Distinction from cavernous hemangioma can be impossible, since the vascular channels in both conditions can show red blood cells in their lumina. The presence of lymphoid aggregates in the stroma tends to favor the diagnosis of lymphangioma.

Lymphangioma Circumscriptum

Lymphangioma circumscriptum is predominantly a developmental malformation of infancy with an equal gender incidence, but it may arise at any age (294,304). Similar acquired lesions arising in adults in relation to chronic lymphedema or radiotherapy are best regarded as *lymphangiectasia* (298). The anatomic distribution is wide, but the proximal portions of the limbs and limb girdle are most frequently affected. Association with cavernous lymphangioma, cystic hygroma, and even lymphangiomatosis is common. A typical lesion consists of collections of numerous papules with vesicle-like lesions containing clear fluid and, less commonly, blood (Fig. 33-85). Due to the presence of a deep component (see text following), lesions arising in infancy tend to recur after simple excision.

Histopathology. Lymphangioma circumscriptum is composed of numerous dilated lymphatics in the superficial and papillary dermis (Fig. 33-86). There is clear fluid and, less frequently, red blood cells in their lumina. In the overlying epidermis, there is some degree of acanthosis and hyperkeratosis. The surrounding stroma shows scattered lymphocytes. Lesions developing in infancy often show a large-caliber, muscular lymphatic space in the subcutaneous tissue, which



FIGURE 33-85. Lymphangioma circumscriptum. Localized, plaque-like lesion with multiple slightly warty papules.

has to be ligated at the time of excision to avoid recurrence (Fig. 33-87).

Progressive Lymphangioma (Benign Lymphangioendothelioma)

Progressive lymphangioma (benign lymphangioendothelioma) is a benign rare tumor that has a tendency to present in middle-aged to elderly adults and evolve slowly over years. Males and females are equally affected, and although the anatomic distribution is wide, there is preferential involvement of the limbs (295–297). Clinically, a typical lesion is a solitary well-circumscribed erythematous macule or plaque. Recurrence after simple excision is exceptional, and occasional lesions can show focal or complete spontaneous regression (305). A case has been described after femoral arteriography (306).

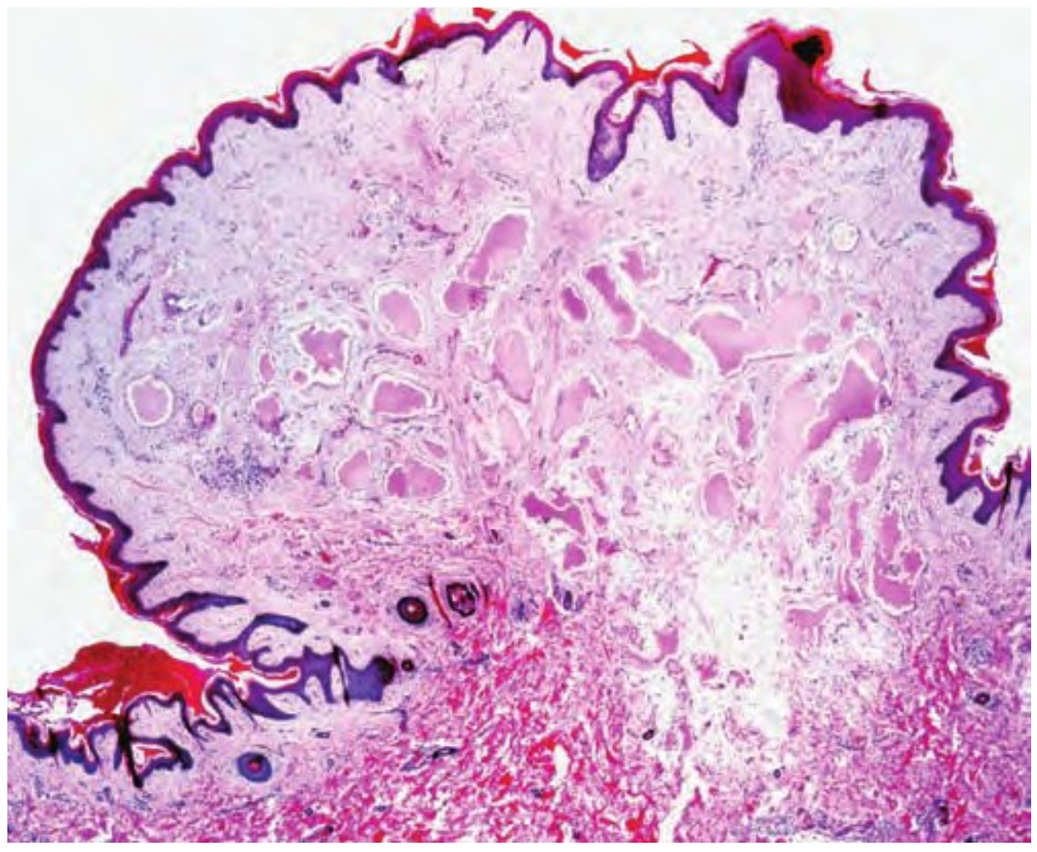


FIGURE 33-86. Lymphangioma circumscriptum. Numerous dilated lymphatic channels expand the papillary dermis.

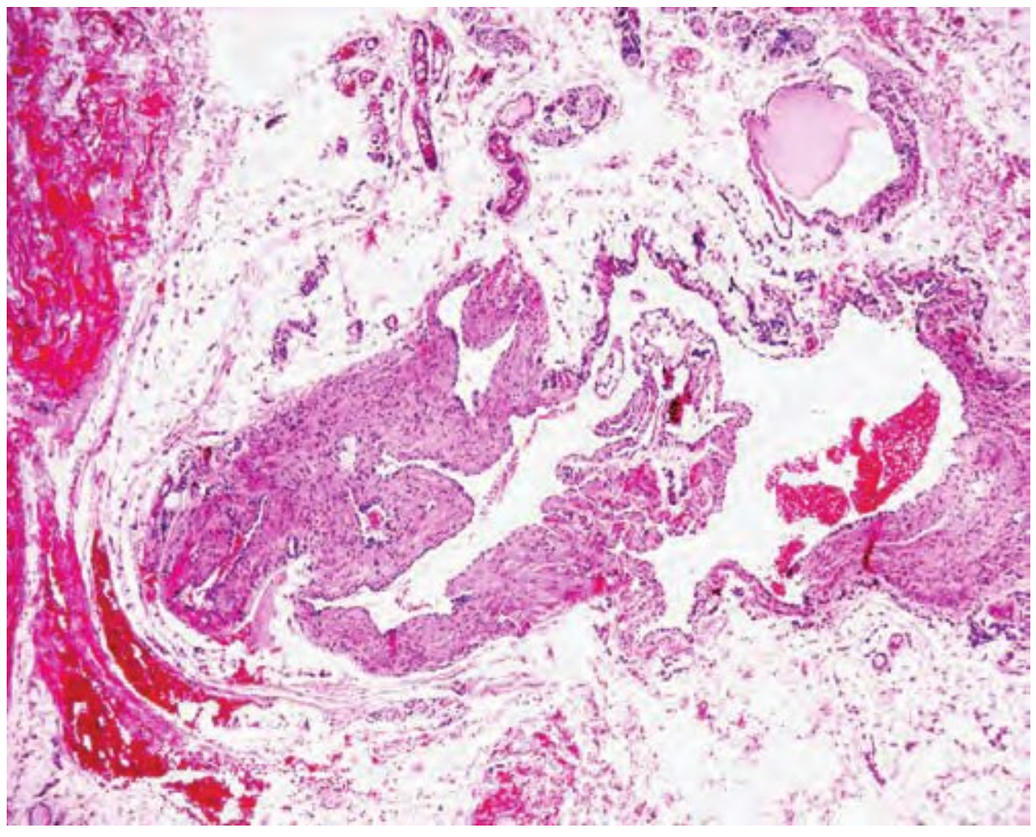


FIGURE 33-87. Lymphangioma circumscriptum. Deep muscular lymphatic. If this vessel is not ligated, the lesion will recur.

Histopathology. Most lesions predominantly involve the superficial dermis, but extension into the dermis and subcutis can be present (295,297). Irregular, horizontal, thin-walled vascular channels lined by a single layer of bland endothelial cells are seen dissecting collagen bundles (Fig. 33-88). Endothelial cell atypia and mitotic figures are absent. The vascular channels appear empty or have scanty proteinaceous material and/or a few red blood cells.

Differential Diagnosis. The main differential diagnosis is with well-differentiated angiosarcoma and patch-stage Kaposi's sarcoma. Although sharing with angiosarcoma the presence of extensive dissection of collagen bundles, the latter conditions occur in completely different settings, and in angiosarcoma, there is usually, at least focally, cytologic atypia and mitotic figures. Patch-stage Kaposi's sarcoma often presents clinically with multiple lesions, and histologically, the abnormal blood vessels tend to cluster around normal preexisting blood vessels. There is hemosiderin deposition with an inflammatory cell infiltrate with lymphocytes and plasma cells.

Lymphangiomatosis

Lymphangiomatosis is a rare developmental abnormality that affects children with an equal gender incidence. Although most cases appear to be congenital, the disease is often not diagnosed until childhood. The majority of cases involve soft tissues, skin, bone, and parenchymal organs. When vital organs are affected, the prognosis is very poor (307,308). Cases with involvement limited to skin and soft tissues of a limb (with or without bone involvement) have been described and are associated with a better prognosis (308). Rare cases can present in association with kaposiform hemangioendothelioma of

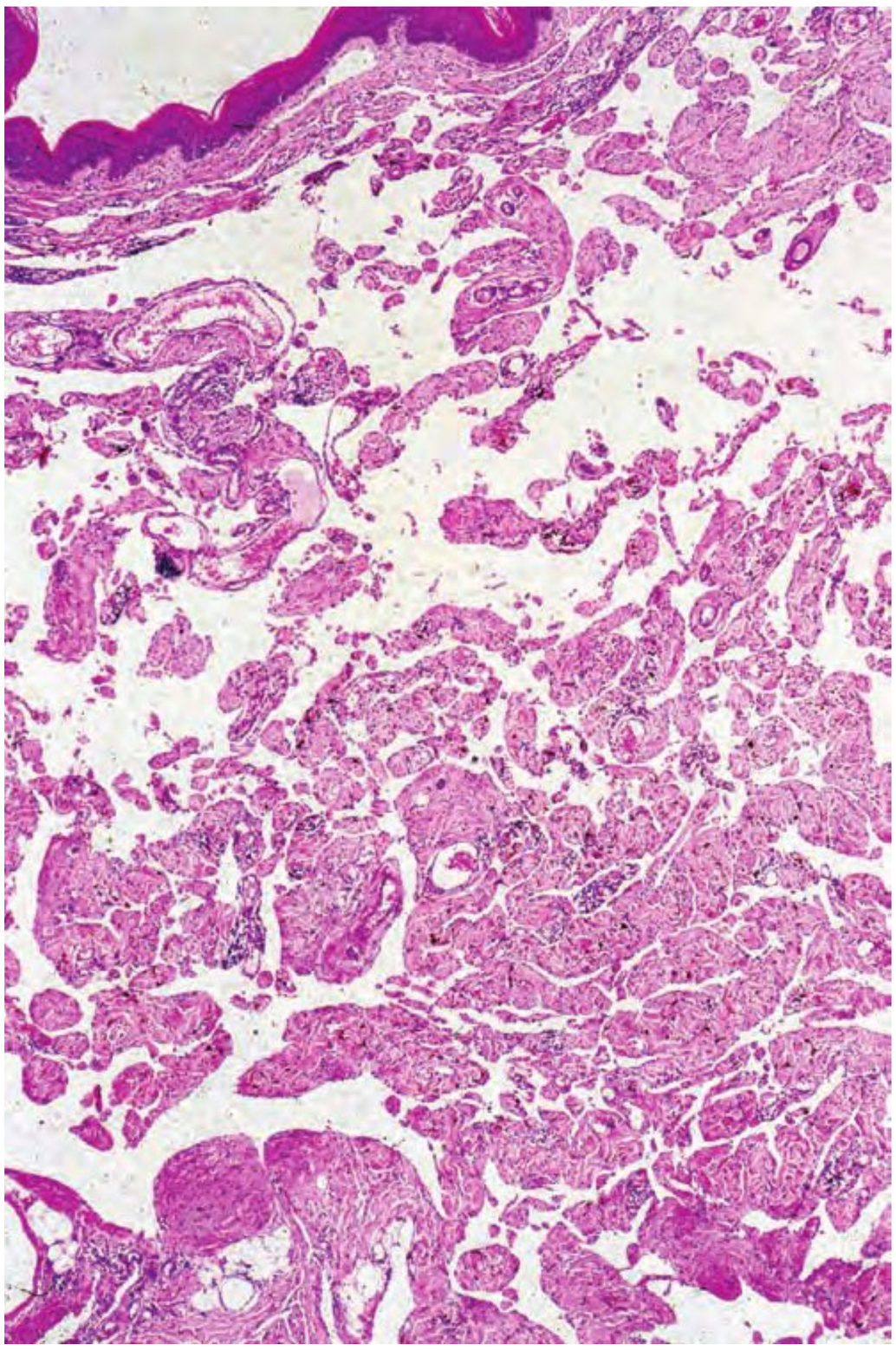


FIGURE 33-88. Progressive lymphangioma. Extensive dissection of collagen bundles by irregular vascular channels lined by bland, flat endothelial cells.

infancy and childhood. Lymphangiomatosis is the lymphatic counterpart of angiomatosis. In some instances, distinction between them can be difficult, although lymphangiographic studies can be very helpful in establishing the difference.

Histopathology. The appearance of lymphangiomatosis is very similar to that of progressive lymphangioma, but the changes in lymphangiomatosis are more extensive and diffuse with involvement of deeper soft tissues, fibrosis in long-standing cases, and stromal hemosiderin deposition.

Atypical Vascular Proliferation After Radiotherapy

Lesions related to atypical vascular proliferation usually develop a few months or years after radiotherapy for breast cancer, but they may also appear in irradiated skin after treatment for ovarian and endometrial carcinoma (309–313). The clinical presentation is not distinctive and varies from skin-colored to red macules and papules. Occasional cases may mimic

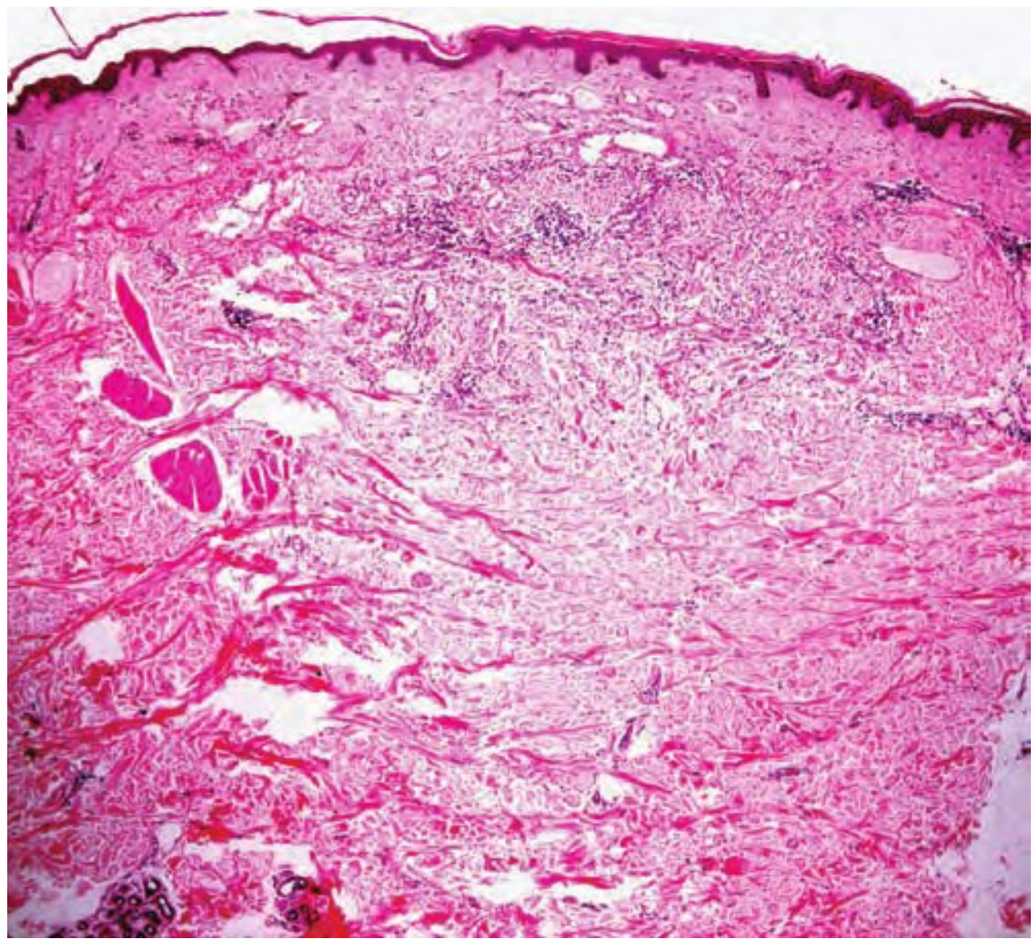


FIGURE 33-89. Atypical vascular proliferation after radiotherapy. Fairly localized superficial dermal vascular proliferation.

lymphangioma circumscriptum. The behavior appears to be benign, with occasional local recurrences. However, it has been suggested that there is a spectrum between these proliferations and postradiation angiosarcoma (312,313). This contention has been challenged by a recent study from the French Sarcoma Group, but unfortunately, the follow-up in their reported cases is limited (314). In view of the controversy and also due to the fact that histologic diagnosis may be difficult, these lesions should therefore be treated with complete excision, and patients should be followed-up closely.

Histopathology. Irregular lymphatic-like vascular channels lined by a single layer of endothelial cells are present focally in the superficial and/or deep dermis. An infiltrative growth pattern is lacking, and lesions are usually fairly circumscribed (Fig. 33-89). The cells lining the channels often have a hobnail appearance, and papillary projections may occasionally be seen. There is no cytologic atypia, multilayering, or mitotic figures (Fig. 33-90). Interestingly, dermal changes secondary to radiotherapy are not usually seen.

Differential Diagnosis. The differential diagnosis includes a well-differentiated angiosarcoma, hobnail hemangioma, and Kaposi's sarcoma. As opposed to hobnail hemangioma, the lesion is not symmetrical, and the vascular channels do not have a predominant superficial dermal location. The clinical setting, the absence of inflammation, and the presence of hobnail endothelial cells with focal papillary projections should allow distinction from Kaposi's sarcoma. Careful examination of multiple sections is recommended to make sure that there are no mitotic figures and cytologic atypia to distinguish it from a well-differentiated angiosarcoma. This distinction can be very difficult, especially in small biopsies.

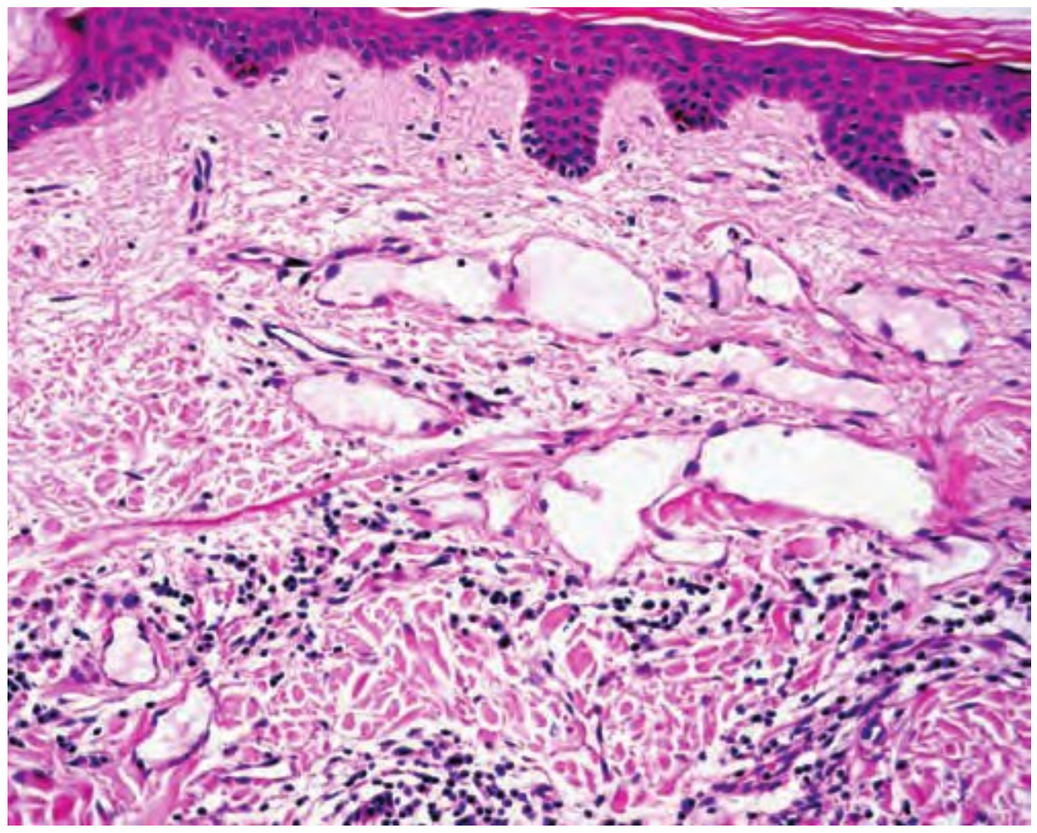


FIGURE 33-90. Atypical vascular proliferation after radiotherapy. Irregular vascular channels lined by slightly hyperchromatic endothelial cells, some of which have a hobnail appearance.



FIGURE 33-91. Glomangiomas. Multiple bluish dermal lesions.

TUMORS OF PERIVASCULAR CELLS

Glomus Tumor

Glomus tumors are relatively rare lesions that usually present in young adults between the third and fourth decade of life with no gender predilection except for subungual tumors, which have a marked female predilection (315). The hand (particularly subungual region and palm) is the most commonly affected site, followed by the foot and forearm. Lesions, however, can occur with a wide anatomic distribution, not only on the skin but also rarely in mucosa and internal organs. The latter include the stomach (316), lung (317), trachea (318), bone (319), small bowel (320), pterygoid fossa (321), and mediastinum (322). Most tumors classically present as solitary, small (<1 cm), blue-red nodules that are characteristically associated with paroxysmal pain often elicited by changes in temperature (especially cold) or pressure. Subungual glomus tumors have been associated with neurofibromatosis type I (323–325).

A very small proportion of glomus tumors are multiple (in up to 10% of patients) (Fig. 33-91). As opposed to solitary glomus tumors, the latter usually arise in children, tend to be asymptomatic, are rarely subungual, and are thought to be inherited in an autosomal dominant fashion (326). The gene for multiple inhereted glomangiomas (also known as *glomuvenus malformations*) has been linked to chromosome 1p21-22 (327–330). Clinically, multiple glomangiomas can be confused with lesions of the blue rubber bleb nevus syndrome, and it is likely that cases of this condition reported in the past represented examples of multiple glomangiomas or glomangiomyomas. They can also be confused with venous malformations (331). Histologically, multiple glomus tumors are predominantly glomangiomas (see text following).

The glomus coccygeum is a prominent glomus body measuring up to several millimeters and located near the tip of the coccyx. Awareness of its existence is important, because when found incidentally in biopsies, it may be confused with a neoplasm (332).

Local recurrence is uncommon and when seen is usually in deep-seated tumors with an infiltrative growth pattern (so-called infiltrating glomus tumor; see text following) (333). Glomangiomatosis is defined as lesions with clinical features of angiomatosis displaying histologic evidence of glomus cells around the vascular channels (334). Exceptionally, glomus tumors originate within a blood vessel (335,336) or nerve (337). Malignant glomus tumor or glomangiosarcoma is very rare and usually arises in deep soft tissues. It comprises around 1% of all glomus tumors (338). Glomangiosarcoma appears to be an aggressive tumor with a metastasis rate of 40% (338). Exceptionally, a glomangiosarcoma arising in an internal organ may present with metastases to the skin (339).

Histopathology. Glomus tumors show varying proportions of glomus cells, blood vessels, and smooth muscle and are classified accordingly into *solid glomus tumor* (25% of cases), *glomangioma* (60% of cases), and *glomangiomyoma* (15% of cases). Most cases of glomus tumor are well circumscribed, and a classic solid lesion (Fig. 33-92) is composed of sheets of uniform cells with pale or eosinophilic cytoplasm, well-defined cell margins (highlighted distinctively by PAS stain), and round or ovoid punched-out central nuclei (Fig. 33-93). Small blood vessels are uniformly distributed in the tumor but may not be apparent without the use of special stains. The stroma is

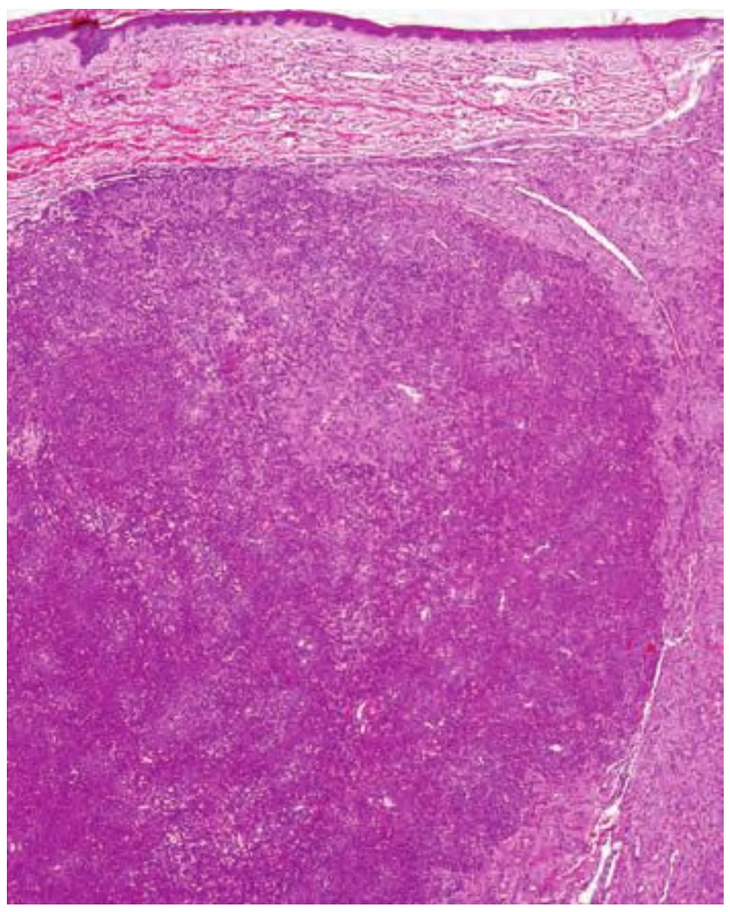


FIGURE 33-92. Solid glomus tumor. Well-circumscribed dermal nodule with only tiny vascular channels in the background.

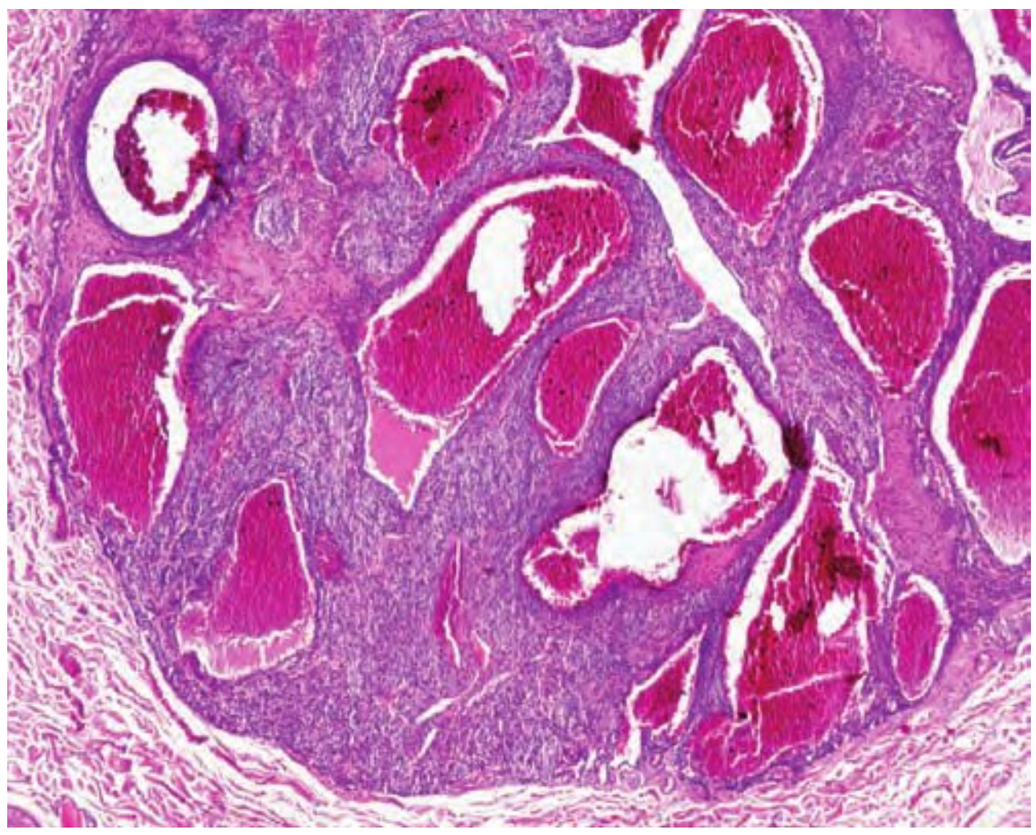


FIGURE 33-94. Glomangioma. Cavernous vascular spaces surrounded by layers of glomus cells.

often edematous, and extensive myxoid change may be present. Normal mitotic figures may be conspicuous in some cases, but cytologic atypia is usually absent. Numerous stromal nerve fibers may be highlighted with special stains. Exceptional cases show extensive oncocytic change (340). Tumor cells with epithelioid morphology have also been described (341). In glomangioma, there are numerous dilated, cavernous-like, thin-walled vascular spaces surrounded by one or a few layers of glomus cells (Fig. 33-94). In glomangiomyoma, there is an important number of spindle-shaped smooth muscle cells, which tend to be distributed near the vascular spaces and blend with the adjacent collections of glomus cells (Fig. 33-95).

Infiltrating glomus tumor is a very rare variant that occurs in deep soft tissues and is characterized by solid nests of glomus cells with an infiltrative growth pattern (333). It is associated with a high recurrence rate.

The histologic diagnosis of glomangiosarcoma is difficult because of the few cases reported in the literature (333,338). Only recently, criteria for the histologic diagnosis of glomangiosarcoma have been delineated and include (338) (a) size >2 cm and subfascial or visceral location, (b) atypical mitotic figures, or (c) moderate to marked nuclear atypia and five or more mitotic figures per 50 high-power fields. A preexisting benign component is common but not invariably present.

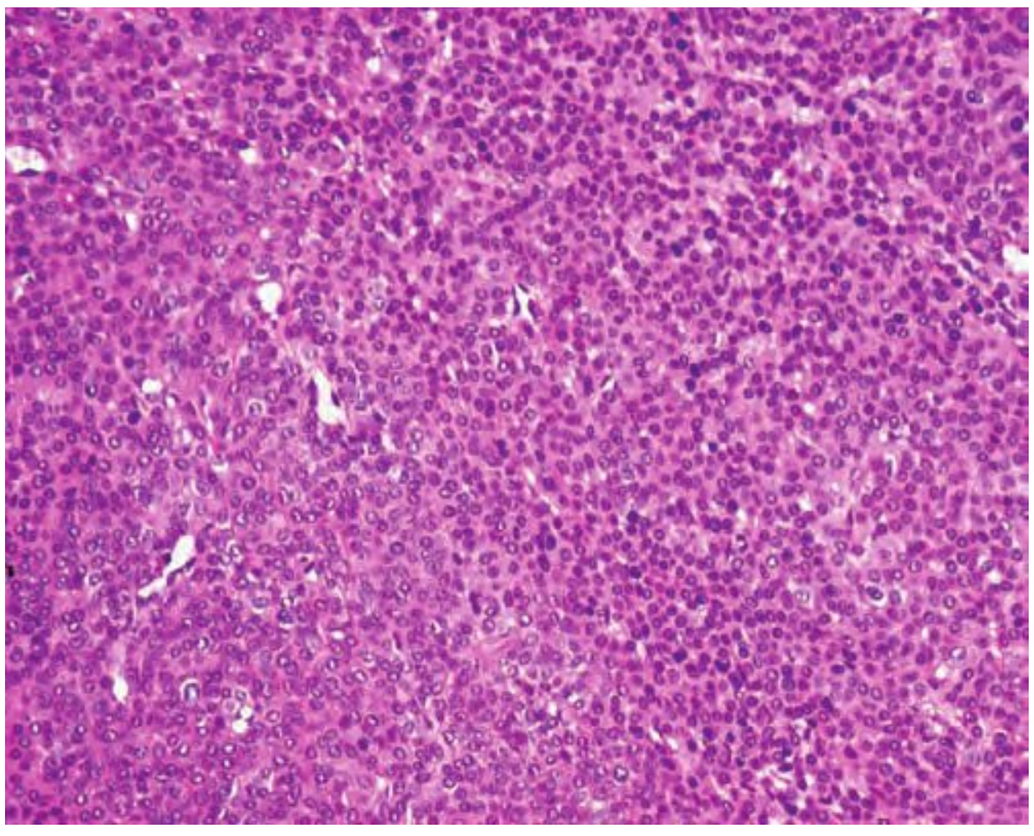


FIGURE 33-93. Solid glomus tumor. Monomorphic round cells with eosinophilic cytoplasm and central punched-out nuclei.

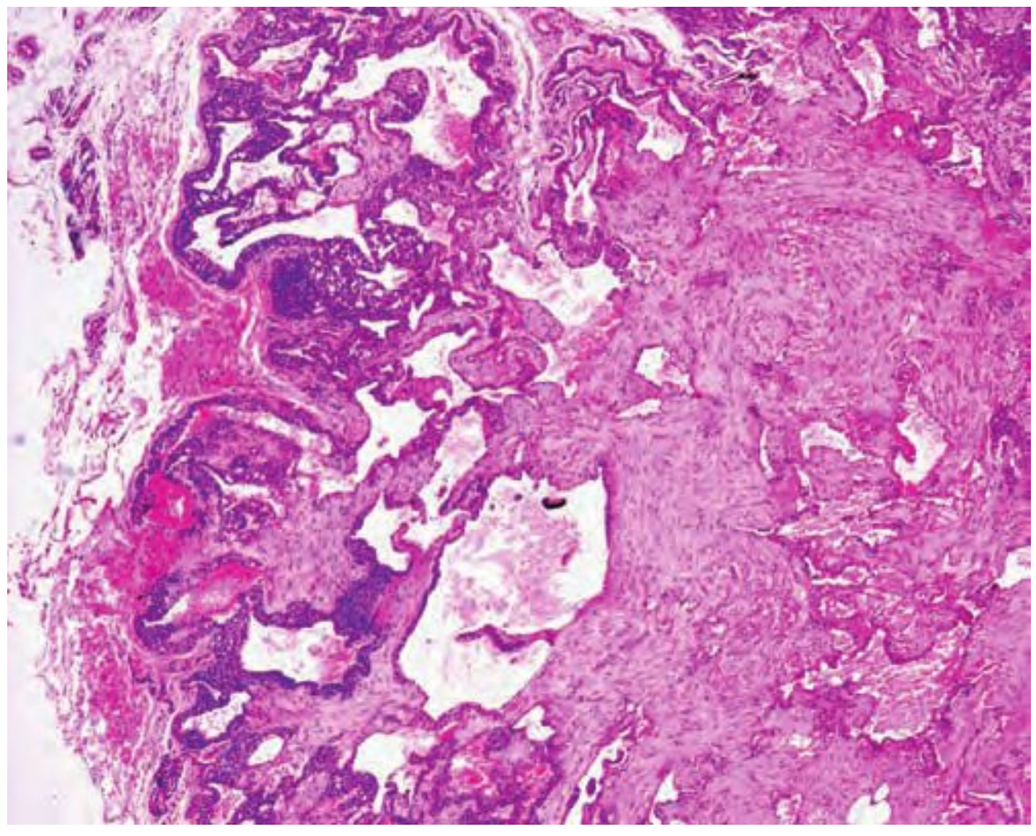


FIGURE 33-95. Glomangiomyoma. Spindle-shaped cells with pink cytoplasm combined with glomus cells.

Tumors arising *de novo* have architectural features resembling a glomus but consist of cells with prominent atypia. In such cases, the diagnosis should be confirmed by positive immunohistochemical stain for smooth muscle actin and for collagen type IV (in a pericellular distribution) (338). Tumors with focal cytologic atypia but no evidence of other features suggestive of malignancy are classified as symplastic glomus tumors. Glomus tumors of uncertain malignant potential are regarded as those that do not fulfill the criteria for the diagnostics of malignant glomus tumor or symplastic glomus tumor but have frequent mitotic activity and superficial location only, deep location only, or large size only.

Histogenesis. Glomus tumors closely resemble the modified smooth muscle cells of a segment of a specialized arteriovenous anastomoses (Sucquet-Hoyer canal) that is involved in the regulation of temperature, the *glomus body*. Glomus bodies are usually found in acral skin, particularly on the hands. However, many glomus tumors arise from sites where glomus bodies are not known to exist. In view of this, it is likely that some glomus tumors arise from differentiation of pluripotential mesenchymal cells or ordinary smooth muscle cells. On immunohistochemical examination, glomus tumor cells stain for smooth muscle actin, H-caldesmon, muscle-specific actin, and myosin (342,343). Staining for collagen type IV shows prominent pericellular positivity. Staining for desmin is only occasionally focally positive. CD34 may also be positive in glomus tumors (344).

Differential Diagnosis. Solid glomus tumor can be distinguished from eccrine spiradenoma by the presence in the latter of two populations of cells, focal ductal differentiation, and positivity for epithelial markers. Occasionally, intradermal nevus with pseudovascular spaces resembles a glomus tumor, but in the former, there is always evidence of nesting, maturation, and positivity of lesional cells for S-100 (345).

Multiple glomus tumors differ from lesions of the blue rubber bleb nevus by the presence of glomus cells in nearly all tumors. It is likely that some, if not all, previously reported cases of blue rubber bleb nevus have actually represented examples of multiple glomangiomas.

Myopericytoma

Traditionally, tumors thought to differentiate toward perivascular myoid cells or pericytes have been divided into two main categories: infantile hemangiopericytoma and adult hemangiopericytoma. Both variants, however, appear to have very little in common except for the histologic presence of a pericytomatous vascular pattern. Moreover, with the combination of immunohistochemistry and electron microscopy, most tumors classified as adult hemangiopericytoma on light microscopy show other lines of differentiation (346). These include synovial sarcoma, mesenchymal chondrosarcoma, solitary fibrous tumor, and deep benign fibrous histiocytoma. The few cases for which the line of differentiation remains obscure are the "true" adult hemangiopericytomas, but it is likely that they arise from an undifferentiated mesenchymal cell. These rare examples of "true" adult hemangiopericytomas do not usually occur in the skin and will not be discussed further in this chapter.

In recent years, the concept of myopericytoma has been introduced to describe a spectrum of tumors composed of short, oval- to spindle-shaped cells with a myoid appearance and a distinctive concentric perivascular growth (347). These tumors tend to occur mainly in the deep dermis and subcutaneous tissue and include lesions classified in the past as glomangiopericytoma, myopericytoma, myofibroma, and myofibromatosis in adults. Infantile hemangiopericytoma and infantile myofibromatosis represent identical entities, and the only term used now to denote the entity is the latter (347–349).

Infantile myofibroma/myofibromatosis usually presents at birth or in the first years of life as single or multiple dermal or subcutaneous nodules. Local recurrence is common, and distant spread has been described, but it is likely that spread represents multicentricity rather than true metastasis (350,351).

Myopericytoma most commonly occurs in middle-aged adults with a predilection for the limbs, especially the distal lower limb. Lesions are small (<2 cm in diameter), long-standing, usually asymptomatic, and may be single or, less frequently, multiple. Tumors rarely are painful. In the setting of multiple myopericytomas, these often develop simultaneously with a predilection for a single anatomic site. Recurrence is rare and frequently represents either persistence or the development of a new tumor. Very rare malignant examples of myopericytoma have been described (352).

Histopathology. Infantile myofibroma/myofibromatosis lesions are multinodular and show, at least focally, a biphasic growth pattern (Fig. 33-96). Hemangiopericytomatous areas composed of small, round hyperchromatic cells blend with areas composed of bundles and nodules of more mature spindle-shaped cells with eosinophilic cytoplasm resembling myofibroblasts

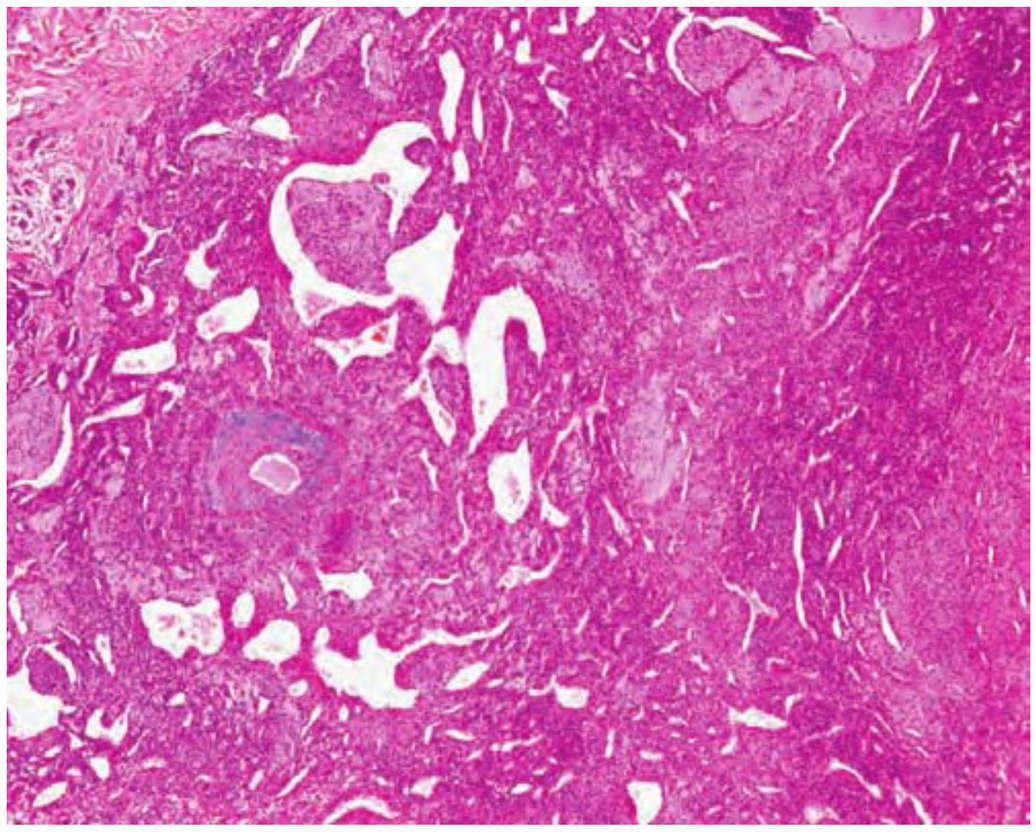


FIGURE 33-96. Infantile myofibroma. Biphasic tumor with numerous branching blood vessels.

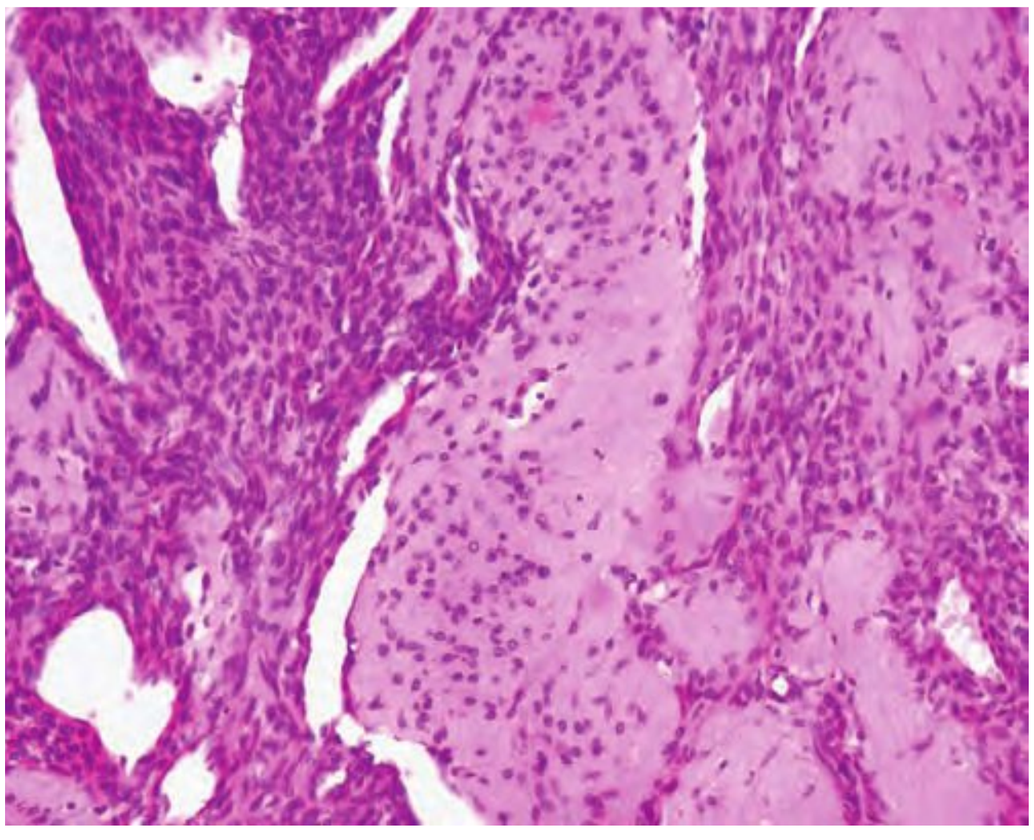


FIGURE 33-97. Infantile myofibroma. Typical biphasic pattern showing immature round cells with scanty cytoplasm (left) alternating with bundles of spindle cells with a myofibroblastic appearance (right).

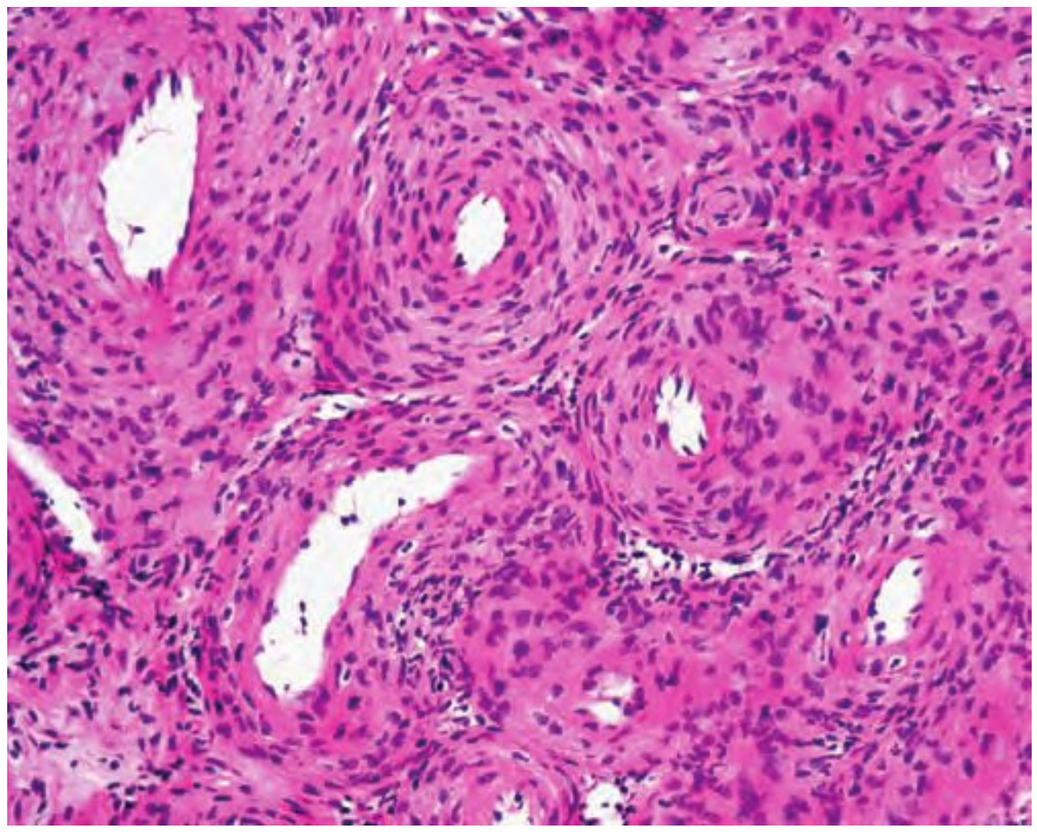


FIGURE 33-99. Myopericytoma. Bland spindle-shaped pericytes arranged in a concentric manner.

(Fig. 33-97). This zoning phenomenon is identical to, although less pronounced than, that seen in infantile myofibromatosis (see Chapter 32, page 984). Mitosis, necrosis, and vascular invasion are common features.

In infantile hemangiopericytoma, the darker, less mature cells in the pericytomatous areas usually do not stain for any markers, whereas the more mature spindle-shaped cells resembling myofibroblasts stain for alpha-smooth muscle actin. Identical features are seen in infantile myofibromatosis, and it is believed that the two entities are part of the same spectrum.

The histologic spectrum of myopericytoma is very wide and varies from lesions that are very similar to myofibromatosis to tumors that closely resemble glomus tumors and even an angioleiomyoma. Tumors are well circumscribed and composed of a mixture of solid cellular areas intermixed with variable numbers of vascular channels (Fig. 33-98). The latter are often elongated and display prominent branching resulting in a stag-horn appearance (hemangiopericytoma like). The cells in the solid areas are round or short and spindle shaped with eosinophilic or amphophilic cytoplasm and vesicular nuclei. Cytologic atypia is not usually a feature, and mitotic figures are very rare. A common and striking feature is the presence of concentric layers of tumor cells around vascular channels resulting in a typical onion ring appearance (Fig. 33-99). Myxoid change may be focally

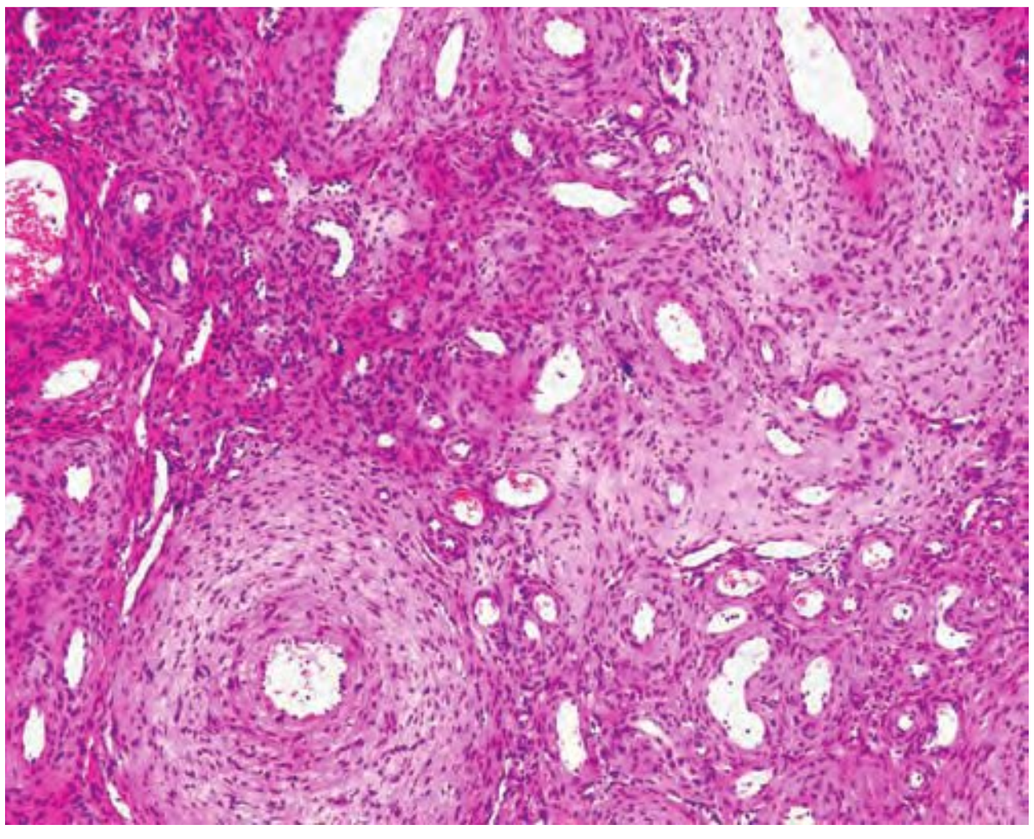


FIGURE 33-98. Myopericytoma. Biphasic pattern and prominent whirling of tumor cells around blood vessels.

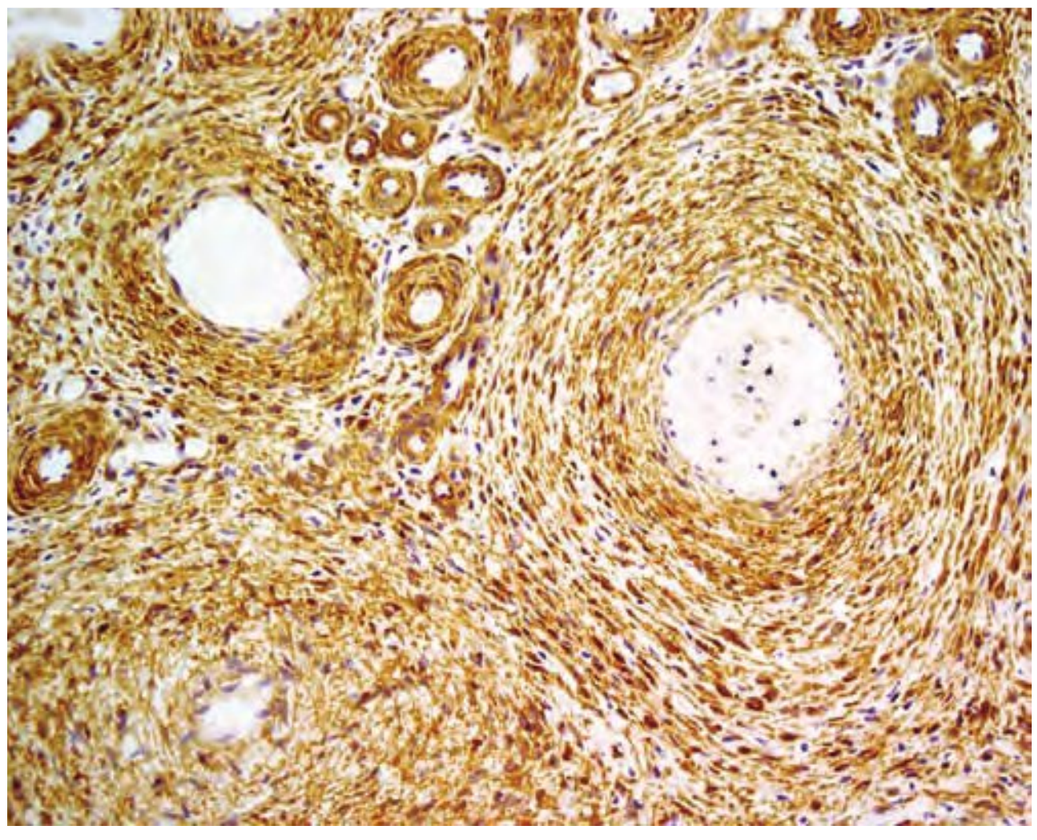


FIGURE 33-100. Myopericytoma. Diffuse staining of tumor cells with alpha-smooth muscle actin by the ABC method.

prominent. Occasional findings include hyalinization, cystic degeneration, and bone formation. Nodules of tumor cells may protrude into the lumina of vascular channels. Rare examples are entirely intravascular (353). In some cases, tumor cells closely resemble glomus cells and are characterized by round punched-out central nuclei and pale eosinophilic cytoplasm. These cases are referred to as *glomangiopericytomas*.

Glomangiopericytoma cells stain diffusely for smooth muscle actin (Fig. 33-100) and are only very rarely focally positive for desmin. Focal staining for CD34 may also be seen.

Differential Diagnosis. Some authors regard angioleiomyoma as part of the spectrum of myopericytoma. Angioleiomyoma, however, is composed of uniform smooth muscle cells, which stain diffusely for both smooth muscle actin and desmin. Furthermore, concentric arrangement of tumor cells around vascular channels is not present.

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CHAPTER 34

Bruce D. Ragsdale

Tumors With Fatty, Muscular, Osseous, and/or Cartilaginous Differentiation

INTRODUCTION

Dermatoradiology

It is axiomatic in dermatopathology that correlation of histopathology with the clinical configuration of skin lesions is the surest route to an accurate and therapeutically relevant diagnosis. However, lesions covered in this chapter often appear merely as dome-shaped elevations of otherwise normal skin. For these, the best "clinical photo" is a radiologic study. These will depict location that bears on origin and adjacent structures at risk, size, character of margins that predicts biologic potential and the necessary extent of surgery, and the presence or absence of mineralization to judge adequacy of the biopsy. Magnetic resonance imaging (MRI) predicts composition (fat vs. other soft tissue +/– cystic change and necrosis). There are many syndromes with simultaneous skin and bone expression. Correlation with available films can avoid misdiagnosis. Radiology contributes to dermatopathology in these and other ways (Table 34-1).

Differentiation

In tumors, clonality does not always translate into morphologic uniformity. While most sarcomas exhibit only one line of histologic differentiation, a minority may display a strikingly diverse phenotype in addition to the main lineage. This phenomenon not only presents a diagnostic problem but also raises questions about the commitment of tumor cells toward a specific phenotype. Diagnostically, it is crucial to recognize the "primary" sarcoma in such tumors correctly and distinguish it from the "secondary" divergent elements. Even though it may be difficult to explain the pathogenesis of divergent differentiation, divergence still illustrates that the phenotype of a tumor cell is not set in stone but can be modulated or switched by a number of factors (1), particularly body location and character of the vascular supply.

Modifiers

The usual bewildering array of uniquely pathologic adjectives are applied to the tumors discussed in this chapter, such as myxoid, histiocytoid, epithelioid, angiomatoid, atypical, bizarre, pleomorphic, giant cell, pseudosarcomatous, dedifferentiated, plexiform, storiform, inflammatory, desmoplastic, round cell, clear cell, granular cell, lipomatous, and the like, and their use is a sure route to acceptance of a case report.

THE BASIC SCIENCE OF FAT RELEVANT TO LIPOCYTIC TUMORS

Adipose tissue can be divided into two types: brown and white. In adults, most fat is the white, univesicular variety. White fat serves as the depot for stored lipid, which is an efficient energy reserve, and protects against external trauma. Obesity, formerly a status symbol of wealth, is now known to be detrimental to health and associated with a wide variety of dermatologic conditions (2).

With hematoxylin and eosin (H&E) staining, only the cell membrane and possibly an eccentric nucleus with or without vacuoles or pseudoinclusions of cytoplasmic fat (*lochkern*, German for "hole in the nucleus") are seen. The red-brown to tan color of brown adipose tissue results from cytochrome pigment in the numerous mitochondria of its finely vacuolated cells. Brown fat has been considered an immature or fetal stage in the development of white fat, but most evidence now substantiates the unique identity of brown fat and its role in basal metabolism and nonshivering thermogesis. In humans, brown fat is more prevalent in the newborn period than later in life, but it persists throughout adulthood in the neck, axilla, and mediastinum, as well as elsewhere, embedded within the common white fat that, over time, tends to replace it.

Most investigators agree that perivascular cells resembling pericytes and fibroblasts play an important transition role in the development of benign and malignant lipoblasts. Both white and brown fat cells modulate (Fig. 34-1A) from these primitive fat organ precursors through multivesicular stages easily mistaken for histiocytes, to preadipocytes in which lipid inclusions coalesce and glycogen decreases, and finally to univacuolar adipocytes (3) (Fig. 34-1B) that are variably S-100 positive. The multivacuolar stage is observed in various tumors and is likely to reappear with involution following fat injury. In these settings, the cells with foamy cytoplasm are commonly mistaken for histiocytes—for example, the CD68-negative foam cells in the subcutis following biopsy. This is the source of much nosologic confusion, particularly with regard to some of the lesions termed *histiocytomas* (4).

TABLE 34-1 Utility of Radiologic Studies in Dermatopathology ("Dermatoradiology")

1. Serves as the "clinical photo" for subsurface lesions that are otherwise merely dome-shaped elevations.
   - Dermal, subcutaneous, and deeper lesions
2. To unequivocally demonstrate site of origin and extent.
   - Subungual exostosis versus fibro-osseous pseudotumor (myositis ossificans) versus osteochondroma in a digit
   - Calvarial osteoma versus mineralized/ossified subcutaneous cyst and others
   - Intracranial extension of occult meningoceles and encephaloceles
   - Scalp hemangioma versus sinus pericranii
3. A cross-check on adequacy of biopsy sampling or removal.
   - Diagnostic mineralized portions of soft tissue masses
   - MRI predicts tissue composition and degree of cystic change
4. To detect recurrence.
   - Subcutaneous metastasis beneath a surgical site versus hematoma, foreign body, etc.
5. Ancillary evidence for diagnosis.
   - Sarcoidosis (chest film), psoriasis (hip arthritis), congenital syphilis (periostitis)
   - Pachydermoperiostosis (thickened corticies), metastatic renal cell carcinoma (kidney tumor)
   - Sterile lytic bone lesions with palmoplantar pustulosis, acne fulminans, and Sweet's syndrome
6. To diagnose syndromic associations.
   - Maffucci's syndrome
   - McCune-Albright syndrome
   - POEMS syndrome
   - Buschke-Ollendorff syndrome
7. An aesthetic dimension and confirmation of early cases.
   - Calciphylaxis
   - Dystrophic mineralization in scleroderma

Normal fat has scattered CD34-positive dendritic cells and small factor XIIIa–positive dendritic cells, more numerous near vessels and within fibrovascular septae. Subsets of them proliferate together in mesenchymal areas of spindle cell lipomas, pleomorphic lipomas, myxoid lipomas, and atypical lipoma/well-differentiated liposarcomas (5).

Fatty tumors of dermatologic interest are common and are generally situated in subcutaneous position (6). Purely *cutaneous* lipogenic tumors are exceptionally rare and have different specific clinicopathologic features in comparison with more deeply located tumors (7). This fact, as with many other subsets of soft tissue tumors, makes correlation of histopathologic opinions with history and radiologic studies the surest route to accurate diagnoses.

NEVUS LIPOMATOSUS SUPERFICIALIS

Nevus lipomatosus superficialis is a fairly uncommon lesion showing groups of soft, flattened papules or nodules that have smooth or wrinkled surfaces and are skin colored or pale yellow. Characteristically, the lesions are linearly distributed on one hip or buttock (nevus lipomatosus superficialis of Hoffman and Zurhelle) (8) (Fig. 34-2), from where they may overlap onto the adjacent skin of the back or the upper thigh. Other areas, such as the thorax or the abdomen, are only rarely affected. The lesions may be present at birth or may begin in infancy (nevus angiolipomatosus of Howell) (9), in which case the replacement of hypoplastic dermis may cause pseudotumorous yellow protrusions and be associated with skeletal and other malformations, but they develop most commonly during the first two decades of life and occasionally later. Multiple lesions may coalesce.

Solitary lesions that may not appear until after the fifth decade predilect the trunk and have been diagnosed as nevus lipomatosus superficialis, but it seems preferable to regard them instead as solitary, baglike, soft fibromas (see Chapter 33), polypoid fibrolipomas, or pedunculated lipofibromas (10).

Histopathology. Groups and strands of fat cells are found embedded among the collagen bundles of the dermis, often as high as the papillary dermis (Fig. 34-2B). The proportion of fatty tissue varies greatly, from >50% of the dermis to <10%. In cases with only small deposits, the fat cells are apt to be situated in small foci around the subpapillary vessels. In instances with relatively large amounts of fat, the fat lobules are irregularly distributed throughout the dermis, and the boundary between the dermis and the hypoderm is ill-defined or lost. The fat cells may all be mature, but in some instances an occasional small, incompletely lipidized cell may be observed.

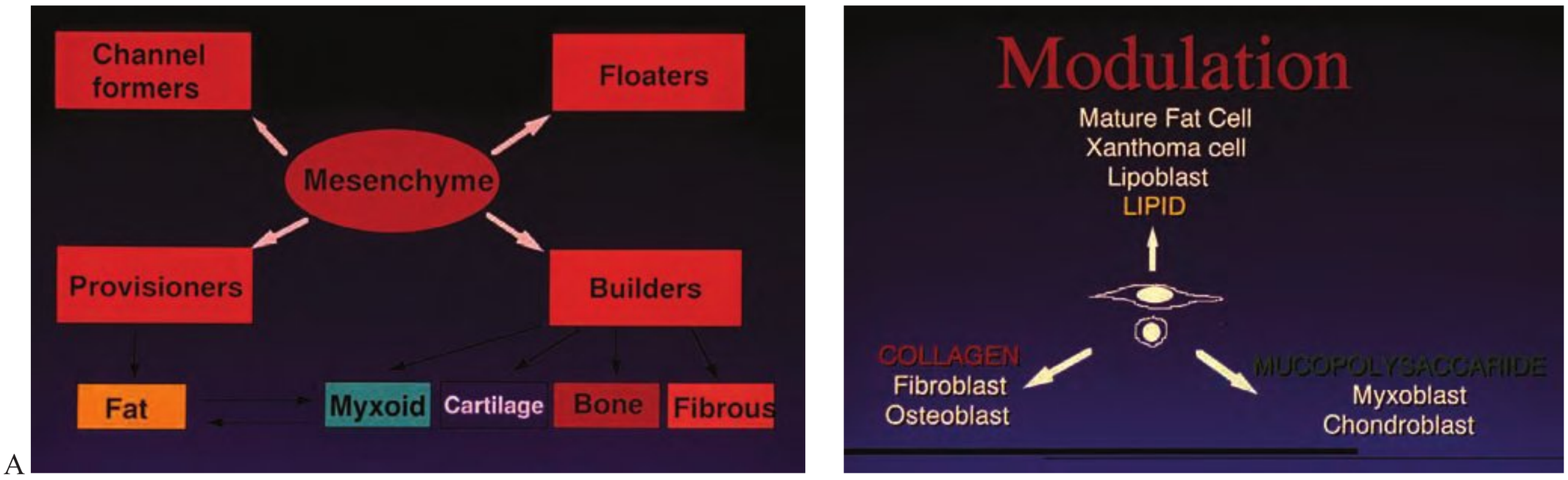
Aside from the presence of fat cells, the dermis may be entirely normal, but in some instances the density of the collagen bundles, number of fibroblasts, and vascularity are greater than in normal skin (8).

Pathogenesis. It is generally agreed that nevus lipomatosus represents, as the name implies, a nevoid anomaly. The ectopic fat cells in the dermis are derived from the perivascular mesenchymal tissue. This view has found support in electron microscopic studies of nevus lipomatosus superficialis, which in some instances showed, in the vicinity of capillaries, immature lipocytes containing numerous small lipid droplets and a centrally located nucleus (11).

Differential Diagnosis. In focal dermal hypoplasia, fat cells are also present in the dermis, often in close proximity to the epidermis but with concomitant extreme attenuation of collagen (see Chapter 6). The rather common presence of fat cells within long-standing intradermal melanocytic nevi represents an involutionary phenomenon rather than an association of a nevus lipomatosus with a melanocytic nevus (see Chapter 28).

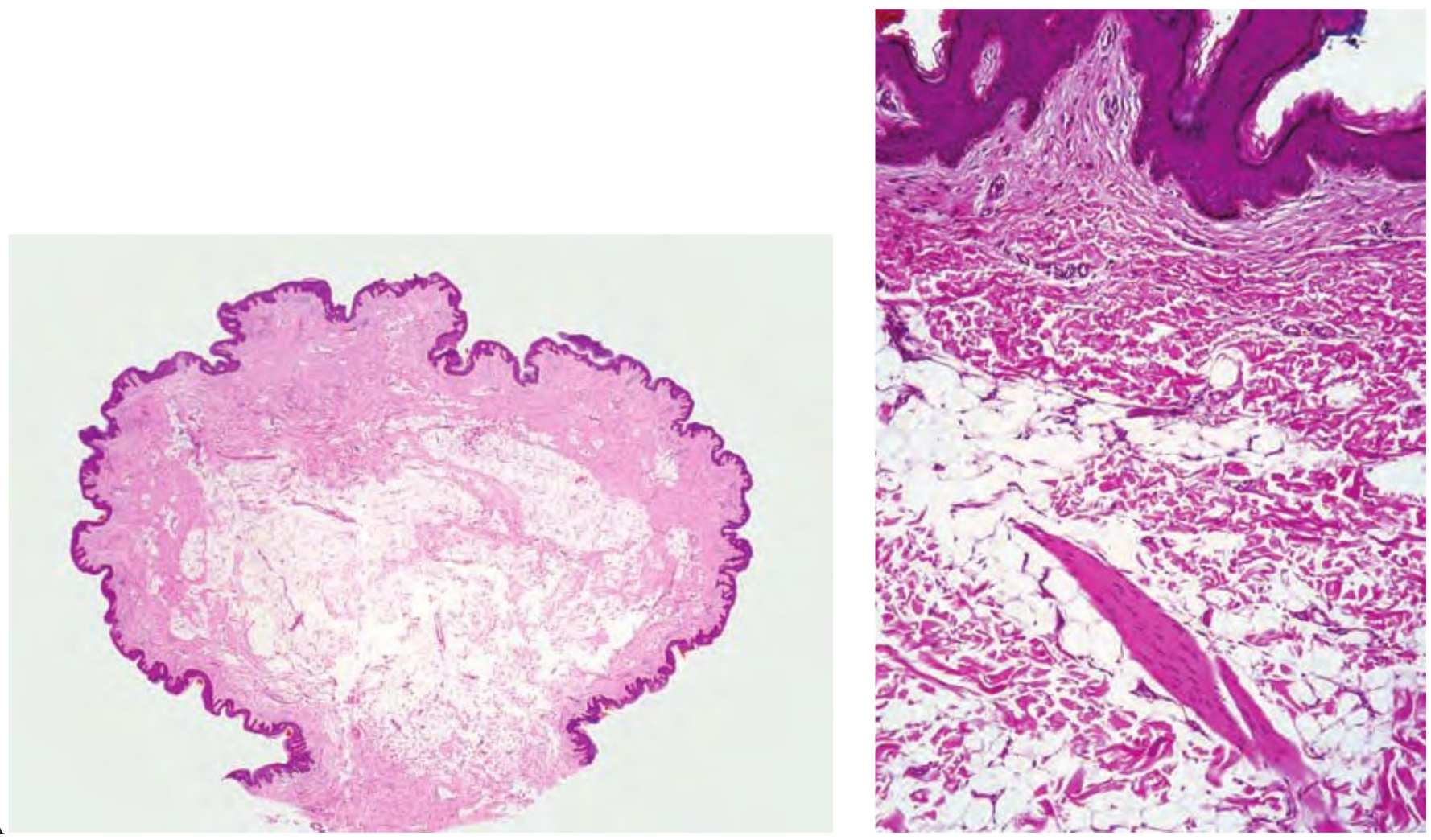
FOLDED SKIN WITH LIPOMATOUS NEVI

Multiple, symmetric, deep, gyrate skin folds involving trunk and similar circumferential lesions on extremities since birth



A B

FIGURE 34-1. Mesenchymal modulation diagrams. A: Uncommitted mesenchyme is the product of differentiation, distinct from ectoderm and endoderm. Further adoption of specific function and corresponding cell structure (phenotype) is modulation, resulting in components of the circulatory system ("channel formers"), lymphohematopoietic cells ("floaters"), structural connective tissue ("builders"), and fat-storing cells ("provisioners"). This normal panoply has its frequent neoplastic parallel in the multiple tissue types that can be found in mesenchymal tumors. B: Extracellular matrix products can be collagen dominant (fibrous or osseous) or mucopolysaccharide dominant (chondroid or myxoid). A signet-ring fat cell represents the end result of internal product storage rather than export (i.e., accumulation of cytoplasmic fat), a process that begins as multiple small vacuoles. The structure and function of some fully modulated mesenchymal cells can change with altered systemic or local influences in the realms of metabolic, mechanical (e.g., trauma, friction, etc.), and/or circulatory (increased arterial flow vs. venous congestion) factors. Initially, in this process, regression leads to spindle or round cells that can be easily mistaken for fibroblasts or lymphocytes. This is followed by cytoplasmic reorganization and acquisition, making possible new functions. Also, more than one modulational potential may be seen in mesenchymal tumors as they grow (e.g., Figs. 34-8 and 34-9). (11a) (After Lent C. Johnson, AFIP, Washington, DC.)



A B

FIGURE 34-2. Nevus lipomatosus (45-year-old man; 2-cm lesion from buttock). A: A polypoidal projection of crenated epidermis has a fatty core. B: Mature signet-ring fat cells displace dermal collagen. A pilar muscle is surrounded by lesional fat.

are seen in the Michelin tire baby syndrome. Look for the characteristic round face with hypertelorism; depressed nasal bridge; thin, down-turned vermillion border of upper lip; and short neck (12).

Newborns, phenotypically likened to the "Michelin man" of tire fame (13), have excessive symmetric, circumferential folds of skin with underlying nevus lipomatosus affecting the neck, forearms, and lower legs and resolving spontaneously in childhood (14). Smooth muscle hamartoma (15) and multiple anomalies may coexist (16).

Histopathology. In some areas, hypertrophic fat lobules extend close to the epidermis, as in nevus lipomatosus superficialis, and surround adnexal structures (17). In other areas, the dermis is of normal thickness, but excessive amounts of adipose tissue are beneath the dermis and around adnexal structures. Several bands of fibrous tissue penetrate the subcutaneous fat. An increase in smooth muscle fibers of the deeper dermis is reported (18) as well as fragmented elastic fibers (19).

Differential Diagnosis. Folded skin has also been reported overlying smooth muscle hamartoma (14).

PIEZOGENIC PAPULES

Fat pad thickness and septal integrity are both important to the mechanical characteristics of the heel fat pad. In various diseases (e.g., rheumatoid arthritis and diabetes) and aging, the load-carrying ability of the heel pad is impaired (20). Septal wall fragmentation and increased width is noted in atrophic heel fat pads from patients with peripheral neuropathies (21). Nonneoplastic *piezogenic papules* due to the herniation of fat into the dermis present as multiple small papulonodules on the heels (22) or wrist (23), with or without pain. Piezogenic papules are primarily a problem of athletes (24) and tend to retract when unburdened. They can be seen in the Ehlers-Danlos syndrome, possibly due to structural defects in the connective tissue with resultant poor compartmentalization of the fat (25).

Histopathology. The normally small fat compartments in lower dermis and subcutis coalesce due to loss of thin fibrous septations (23).

Differential Diagnosis. In bilateral congenital adipose plantar nodules (or congenital fibrolipomatous hamartoma) (26), well-defined lobules of mature fat occur in the mid and deep dermis, mostly around adnexa (27).

LIPOMAS

Common lipomas consist of mature fat cells throughout (Fig. 34-3) and are the most common neoplasms of mesenchyme. Lipomas are subclassified according to the anatomic site into dermal, subcutaneous, and subfascial, also inter- or intramuscular, or tumors directly related to bone, synovium, or nerve. Most lipomas (98%) occur as single or multiple subcutaneous growths that are soft, rounded or lobulated, and movable against the overlying skin. They often grow insidiously, displaying an initial growth phase followed by a period of quiescence. They come to clinical attention only if they reach inordinate size (Fig. 34-3A) or are perceived as blemishes in need of cosmetic removal. Approximately 6% of all cases are multifocal. The patient commonly presents with an asymptomatic, slowly growing round mass having a gelatinous or cystic consistency. Well-circumscribed lipomas are easily "shelled out" and only rarely regrow, generally when initially incompletely encapsulated or infiltrative. Deep-seated variants of ordinary lipomas tend to be less well circumscribed than their superficial counterparts, often sending out pseudopod-like processes within fascial planes, engulfing aponeuroses, and potentially compressing local structures. Large, even giant size, defined as >10 cm diameter in at least one dimension (28), rapid growth, deep location, fixation, pain, and thigh or retroperitoneal location are features that suggest the wisdom of preoperative radiographic characterization and a cautious surgical approach to exclude a more significant lesion before enucleation that could preclude limb-sparing surgery for a more aggressive lesion.

Some lipomas are characterized by specific clinical presentation and location. Location on the forehead (29) (Fig. 34-3B) is a rather common dermatologic specimen. *Perineural lipoma* involves the median nerve in 9 out of 10 cases and may be associated with macrodactyly. *Lumbosacral lipomas* frequently occur in conjunction with spina bifida and intraspinal lipoma. *Lipomas of tendon sheath and joint synovium* are centered on the named structures. *Lipoma arborescens (diffuse articular lipomatosis, synovial lipomatosis, Hoffa disease)* is a rare intra-articular lesion of unknown etiology where benign papillomatous intra-articular fatty expansions usually in the knee joint have a tendency for repeated regrowth (30).

Intramuscular lipomas, in contrast to *intermuscular lipomas*, infiltrate muscle and tend to recur unless completely excised (31). *Myolipomas of soft tissue* are rarely subcutaneous (32).

The *cutaneous angiomyolipoma*, also known as *cutaneous angiolipoleiomyoma*, is seen most often in adult male patients and in an acral location. Like its more common renal counterpart, it is composed of an admixture of blood vessels, smooth muscle, and adipose tissue. While the renal lesions are often seen in the setting of tuberous sclerosis and its pulmonary lymphangiomyomatosis, not those in skin, work-up for tuberous sclerosis should not be pursued (33). Smooth muscle cells in cutaneous angiomyolipomas stain negatively for HMB-45, in contrast to renal and extrarenal angiomyolipoma (7,34). It is proposed that cutaneous angiomyolipomas should be termed *angioleiomyoma with fat* to avoid confusion with unrelated noncutaneous angiomyolipomas that are HMB-45 negative and require investigation for tuberous sclerosis (35).

The *adenolipoma* is a dermal or subcutaneous variant of the common lipoma that does not deviate appreciably in presentation or gross appearance but microscopically has inclusions of sweat gland apparatus (7), likely passively enveloped as in "glandular" neurofibroma.

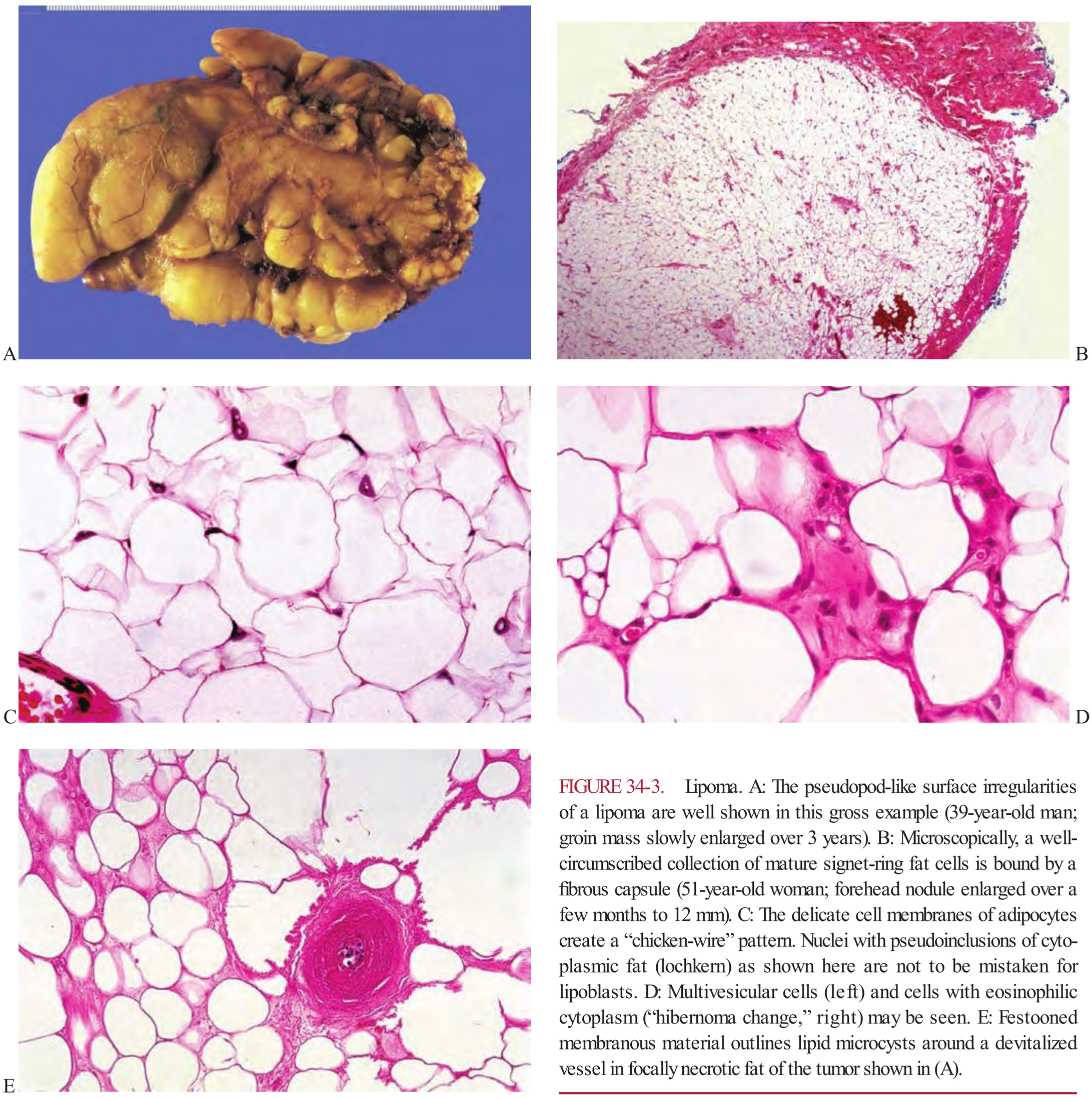


FIGURE 34-3. Lipoma. A: The pseudopod-like surface irregularities of a lipoma are well shown in this gross example (39-year-old man; groin mass slowly enlarged over 3 years). B: Microscopically, a well-circumscribed collection of mature signet-ring fat cells is bound by a fibrous capsule (51-year-old woman; forehead nodule enlarged over a few months to 12 mm). C: The delicate cell membranes of adipocytes create a "chicken-wire" pattern. Nuclei with pseudoinclusions of cytoplasmic fat (lochkern) as shown here are not to be mistaken for lipoblasts. D: Multivesicular cells (left) and cells with eosinophilic cytoplasm ("hibernoma change," right) may be seen. E: Festooned membranous material outlines lipid microcysts around a devitalized vessel in focally necrotic fat of the tumor shown in (A).

Instances of malignant transformation of ordinary lipomas are anecdotal at best.

In two rare conditions, multiple lipomas composed of mature fat cells arise in adult life. In Dercum's disease (adiposis dolorosa, lipomatosis dolorosa morbus Dercum) (36), there are tender, circumscribed, or diffuse fatty deposits, with a predilection for the upper arms, legs, abdomen, and buttocks (37). Postmenopausal women are selectively affected. Paresthesia in the overlying skin is common. Lipomas about the joints cause mechanical arthralgia. The diagnosis, which is often delayed, rests on ultrasonography and, above all, MRI. The portrait painted of Dercum's disease is very complicated, with many other disorders seen associated with the disease. There are no clear pathologic mechanisms known, although it is suspected that there is either a metabolic or autoimmune component involved. A combination of medications, surgery, and psychiatric care is usually needed. The treatment aims at relieving the pain and restoring a normal appearance.

Multiple or *benign symmetric lipomatosis (Madelung's disease)* is a rare disease of undetermined cause characterized by symmetric deposits of painless, diffuse, subcutaneous adipose tissue on the suboccipital area, cheeks, neck (in "horse collar"

distribution), shoulders, and upper trunk. Lipomas are present especially on the back and upper trunk (38). It is most common in countries bordering the Mediterranean. The patients are usually middle-aged male alcoholics (39). Although lesions can initially mimic a head and neck malignancy, management is essentially symptomatic, with conservative removals done as indicated clinically or for cosmesis.

Familial multiple lipomatosis has hundreds of slowly growing subcutaneous (forearm, trunk, and thigh) masses and deep or visceral lipomas that appear in the third decade (40,41). This as well as Dercum's disease can be inherited as an autosomal dominant trait. Children presenting with lipomas need a complete physical examination to look for other signs of Bannayan-Riley-Ruvalcaba syndrome, which is a dominant autosomal disorder characterized by cutaneous lipomas, intestinal polyps, developmental delay associated with PTEN gene mutations and in some instances hemangiomas, and macrocephaly, because they may need further follow-up for tumor screening in adulthood (42).

Diffuse lipomatosis features infiltrating masses of mature adipose tissue in part of an extremity or the trunk before age 2 years, possibly with concurrent tuberous sclerosis (43). *Nevus psiloliparus* (44) is the cutaneous component of subcutaneous scalp lipomas with overlying alopecia in *encephalocraniocutaneous lipomatosis* (45). Similarly, hamartomatous, *infiltrating lipoma of the face* (46) is another variant of it. A thickened and soft scalp that may present as alopecia, *lipedematous scalp*, is a thickening of the subcutaneous fat (47). Multiple lipomas and hemangiomas occur in *Cowden's syndrome*. *Fröhlich's syndrome* exhibits multiple lipomas, obesity, and sexual infantilism. The *Proteus syndrome* features multiple lipomatous lesions, including pelvic lipomatosis and fibroplasia of the feet and hands, skeletal hypertrophy, exostoses and scoliosis, and pigmented skin lesions. This rare overgrowth disorder is generally progressive, with subcutaneous lipomas and cerebriform connective tissue nevi progressively increasing in size, and in most patients, additional lesions developed at new locations (48).

Use of protease inhibitors for HIV-1 can be associated with fat abnormalities including subcutaneous lipomas (49), angiolipomas (50), peripheral lipodystrophy, and benign symmetrical lipomatosis (51).

Histopathology. By definition, lipomas contain mature adipocytes as a principal component. They tend to be surrounded by a thin connective tissue capsule and are composed, often entirely, of normal fat cells that are indistinguishable from the fat cells in the subcutaneous tissue (Fig. 34-3C). Occasional "hibernoma-like" cells or multivesicular cells (Fig. 34-3D) around foci of necrosis should not be misinterpreted as lipoblasts, which differ in having coarse vacuoles and irregular nuclei. Membranous fat necrosis is a rare occurrence in lipomas of larger size (Fig. 34-3E) and has the typical staining reactions of ceroid pigment. Traumatic or ischemic causation is postulated (52).

Intramuscular (infiltrating) lipomas consist of mature fat cells that infiltrate muscle, splaying fibers but showing no nuclear atypia (Fig. 34-4). Be skeptical of this diagnosis on the face where mature fat is normally admixed with facial muscles of expression (Fig. 34-5). In some lipomas, what is found is more or less of a connective tissue framework than in the normal subcutaneous fat. Those containing considerable proportions of fibrous connective tissue are called *fibrolipomas* (Fig. 35-6) or *sclerotic lipoma* if a prominent sclerotic stroma is in a storiform arrangement (53). Substantial basophilic mucopolysaccharide may fill regions of the tumor and the term *myxolipoma* is recommended (Fig. 34-7). Focal chondroid (Fig. 34-8) and/or osteoid production (Fig. 34-9) have no significance other than underscoring the modulational potential of functional mesenchymal cells (see below).

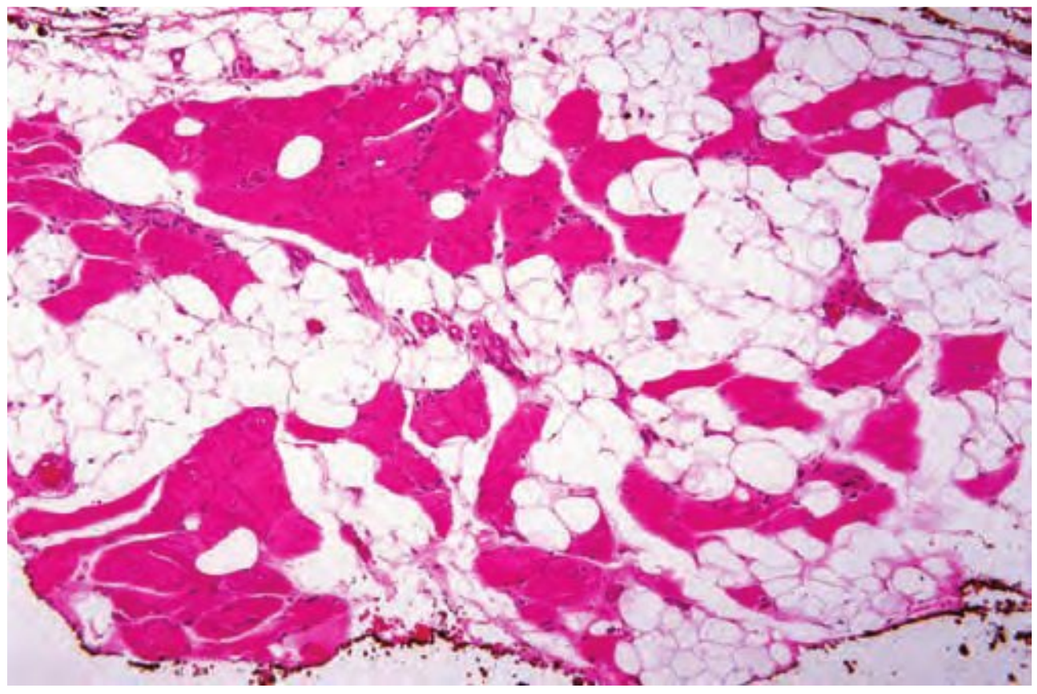


FIGURE 34-4. Intramuscular (infiltrating) lipoma (28-year-old woman; 11-month history of a 1.5-cm shin nodule). Mature fat cells splay individual skeletal muscle fibers.

Myolipomas are comprised of variable amounts of benign smooth muscle and mature adipose tissue. The smooth muscle component of a cutaneous *angiomyolipoma* comprised of mature adipose tissue, smooth muscle fascicles, and medium-

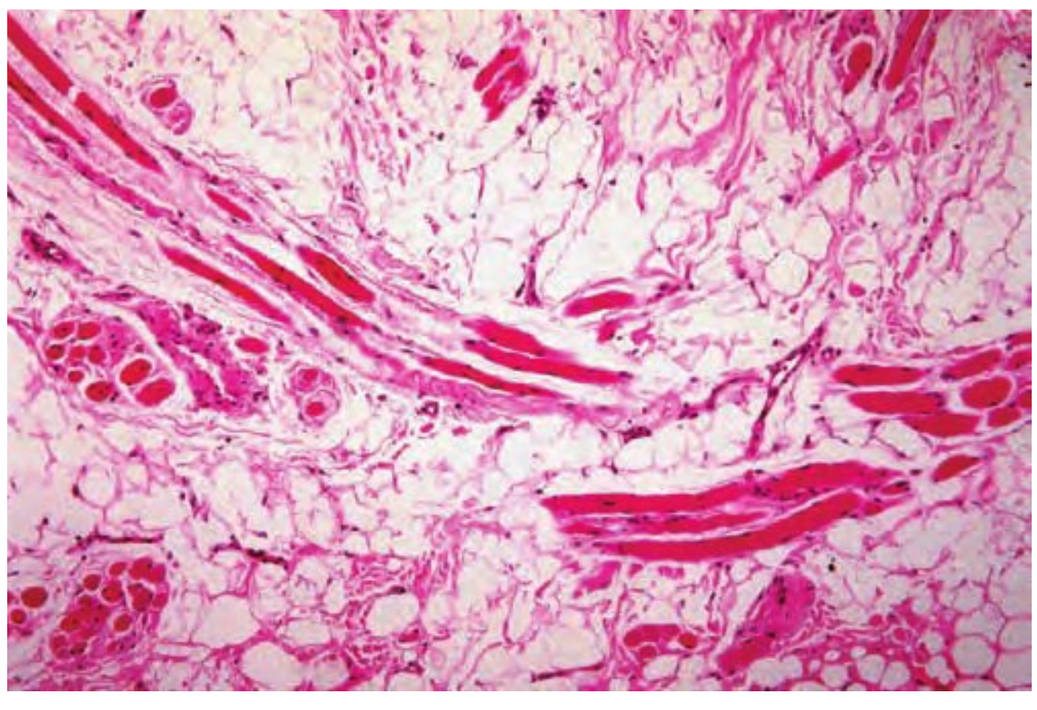


FIGURE 34-5. Normal subcutaneum, face. Skeletal muscle bundles are normally surrounded by mature fat on the face, and this is not to be mistaken for infiltrating lipoma.

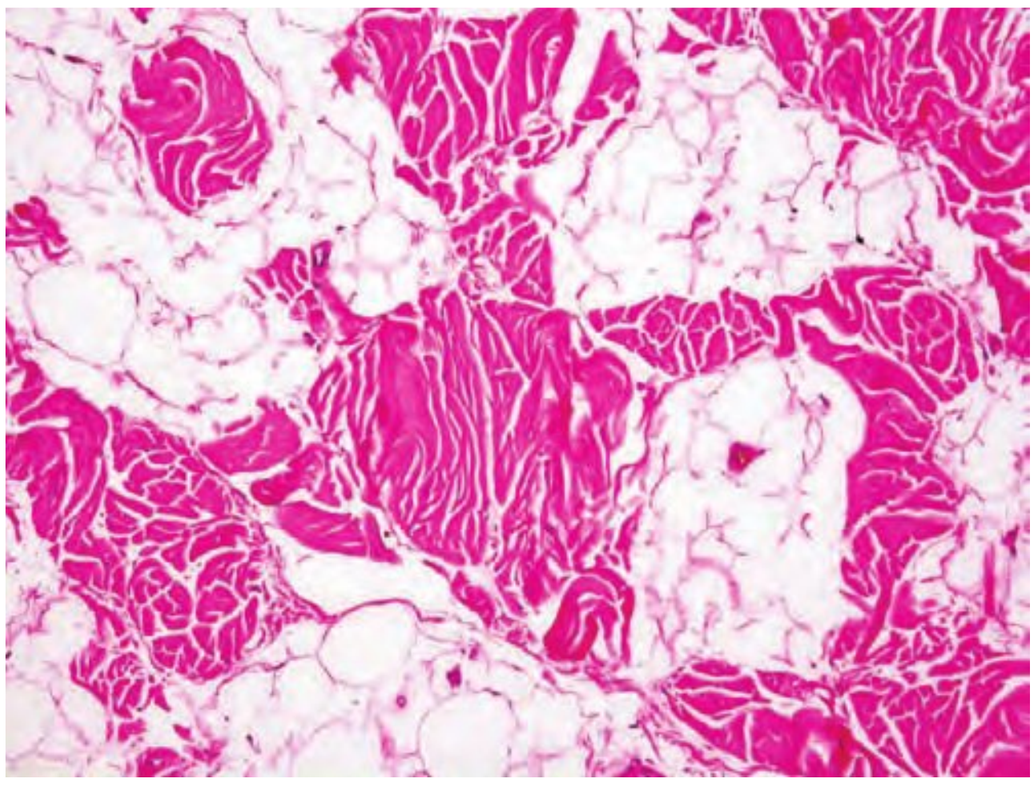


FIGURE 34-6. Fibrolipoma. Strands of collagenous, fibrous connective tissue can be seen within a tumor composed of mature adipocytes. In other cases, the nodule may be predominantly fibrous with little fat.

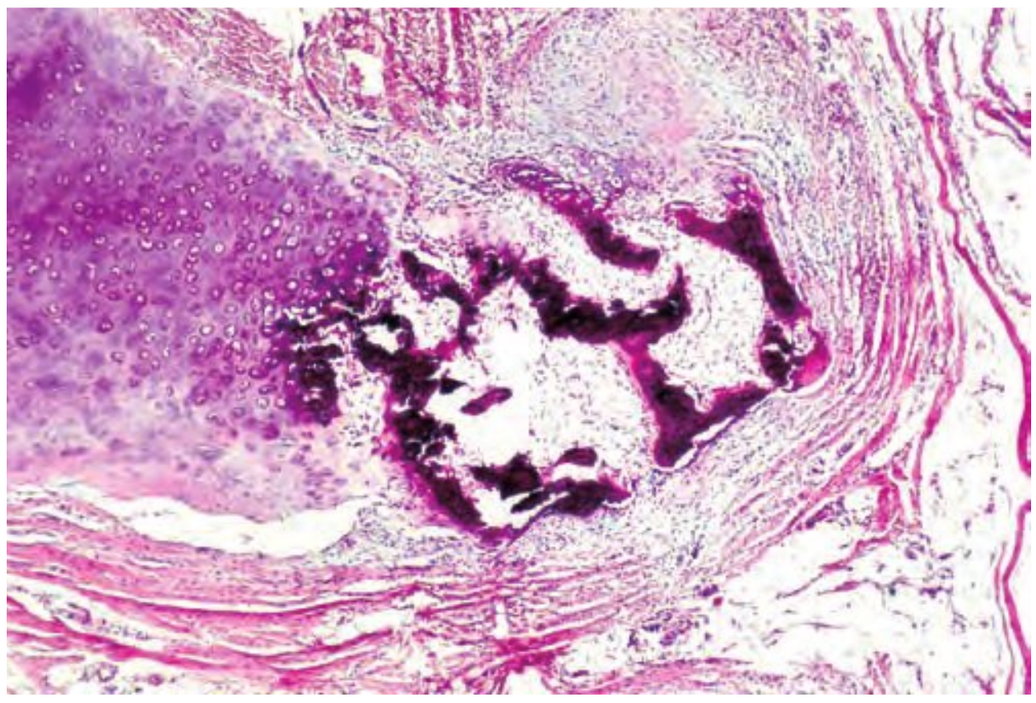


FIGURE 34-8. Ossifying chondromyxoid lipoma. Within a fatty and myxoid background are areas of chondrification (right) and ossification (center). The contact between the bone and cartilage to the left of center indicates that part of the bone was formed through the enchondral mechanism, analogous to longitudinal bone growth at the growth plate. A portion of the bone has formed directly from the fibrous background (intramembranous ossification). This lesion manifests all three directions of modulation outlined in Figure 34-1B.

sized blood vessels (Fig. 34-10) may show pronounced cellular and nuclear pleomorphism and hyperchromatism, as is common in the renal tumor of the same name (54). The distinctive feature of an *adenolipoma* (Fig. 34-11) is an admixture of displaced and distorted sweat glands within the fatty background.

In *adiposis dolorosa* (Dercum's disease), most authors have found the lipomas to be indistinguishable histologically from ordinary lipomas. In some cases, the histologic appearance is that of an angiolipoma, a tumor that is often painful (see text following). In other cases, granulomas of the foreign body type have been noted within the fatty tissue. In *benign symmetric lipomatosis* (Madelung's disease), the lipomas have the histologic appearance characteristic of ordinary lipomas.

Metaplastic formation of cartilage and bone is only rarely seen in lipomas. Ossifying lipomas, independent of bone tissue and with concurrent cartilage in about half, is rarely reported in the dermatopathologic literature (55). It has the same excellent prognosis as simple lipoma after excision. Focal chondroid (Fig. 34-8) and/or osteoid production (Fig. 34-9) have no significance other than underscoring the modulational potential of functional mesenchymal cells. Mechanical stress, trophic disturbances, character of local vascular flow, the conspicuously frequent contact with periosteum, and still unknown factors may be the causes for the metaplastic transformations (56).

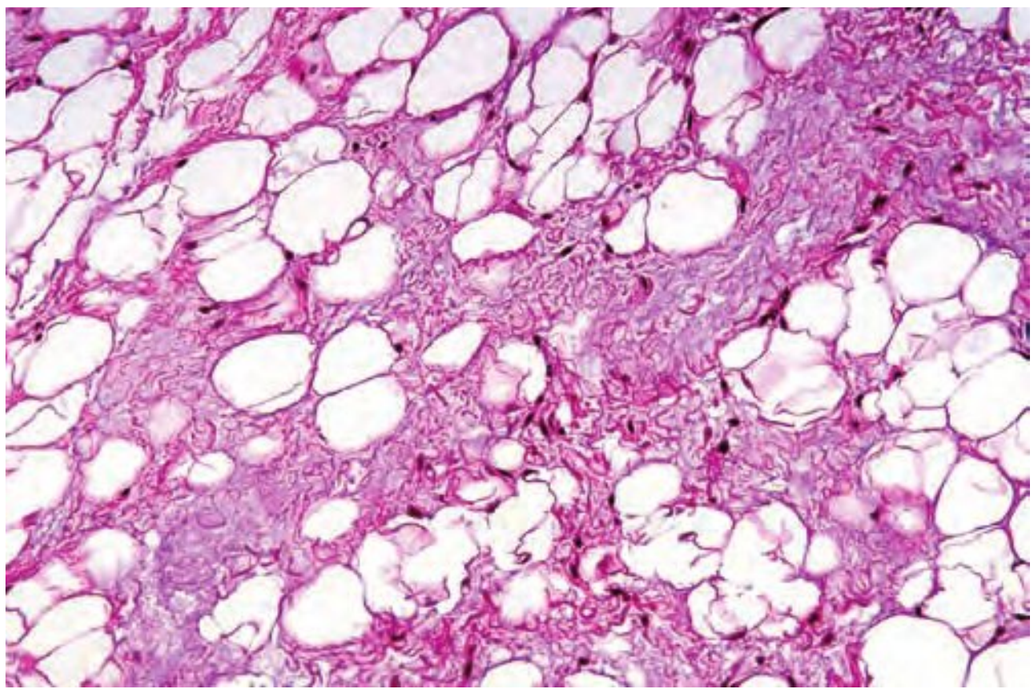


FIGURE 34-7. Myxolipoma (65-year-old woman; small dorsal hand mass for 7 years, enlarging in the last several months to 2.8 cm). Basophilic myxoid substance between mature adipocytes is sparcely populated by nonatypical stellate- and spindle-shaped cells.

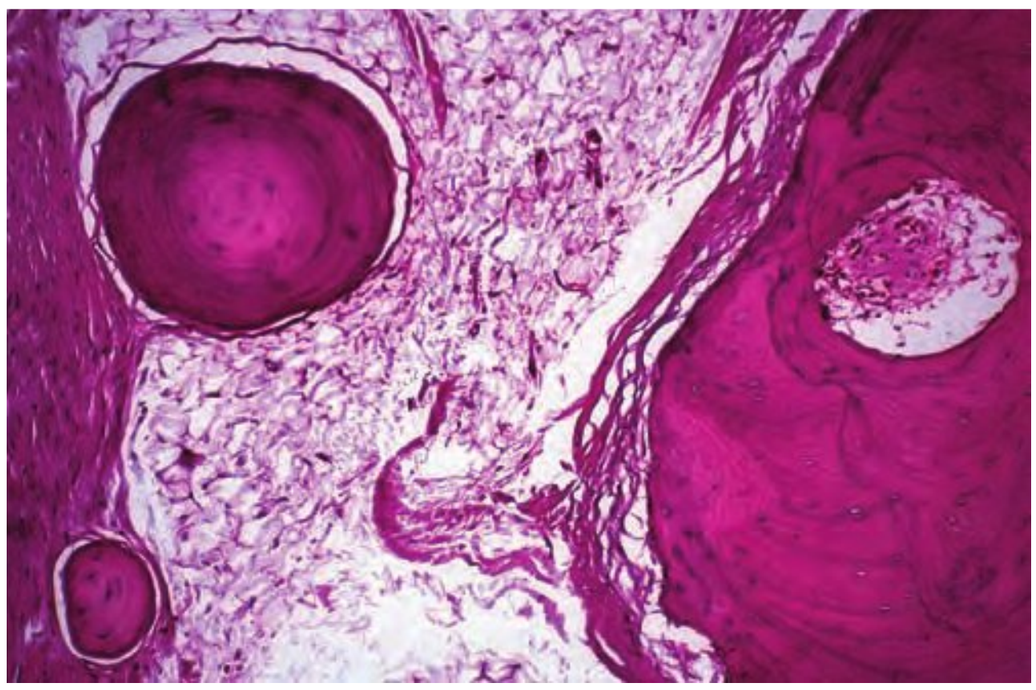


FIGURE 34-9. Osteolipoma (63-year-old man with "cyst" on forehead for many years). Rounded islands of bone are visible within a fibrofatty background in this mass. The largest ossicle (right) is undergoing haversianization.

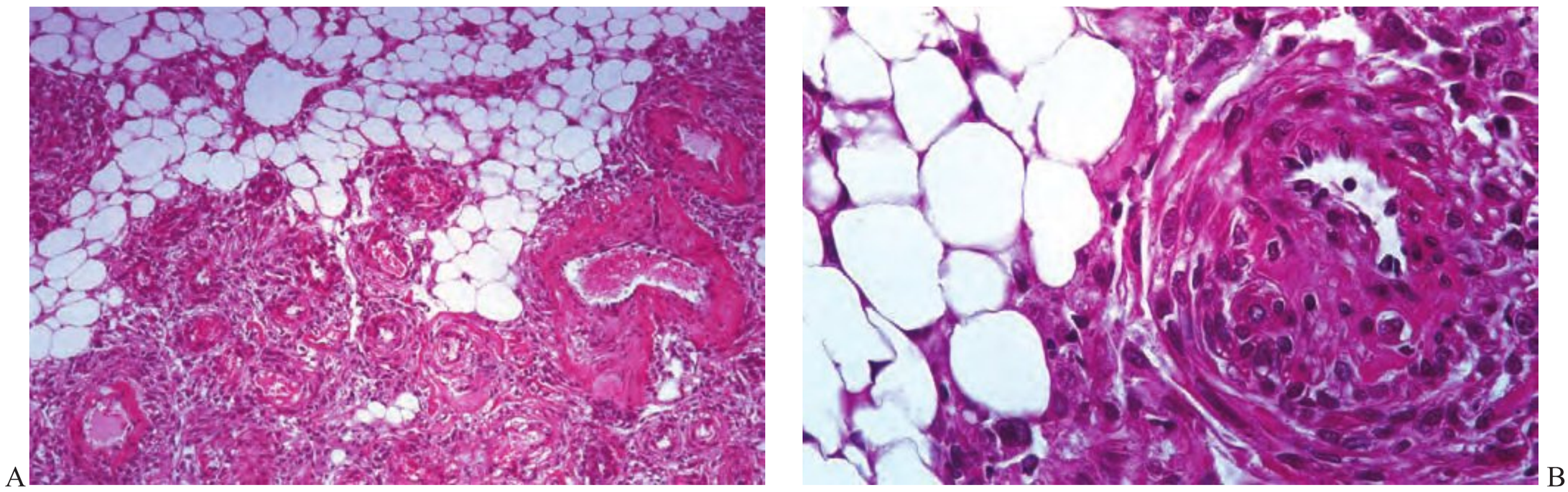


FIGURE 34-10. Angiomyolipoma. A: The basic components of this tumor are mature adipose tissue and thick-walled, medium-sized vascular channels from which sheets of plump, smooth muscle cells appear to be derived. B: Plump cells with features of smooth muscle appear to derive from the wall of a vessel within a fatty background. Moderate pleomorphism of the fatty and smooth muscle components is expected and does not connote malignancy.

Efforts to distinguish true adipocyte neoplasms from lipomatous hamartomas and localized overgrowth of fat have been limited by the lack of reproducible markers for adipose neoplasms. Identification of a (12:16)(q13p11) translocation in myxoid liposarcomas, and of a similar translocation in lipomas with breakpoints at 12q14 (57), makes future prospects of resolving these issues of pathogenesis seem bright. For the present, lipomatous tumors are still classified morphologically (Table 34-2).

Differential Diagnosis. Growth pattern and size may suggest well-differentiated liposarcoma, but superficial (dermal or subcutaneous) liposarcomas are extremely rare. Lipomas do not contain diagnostic lipoblasts. This fact and the absence of the characteristic delicate capillary network distinguish lipomas with focal or substantial basophilic mucopolysaccharide from myxoid liposarcomas. Intramuscular (infiltrating) lipoma lacks the lipoblasts of well differentiated (lipoma-like) liposarcoma and the lobulation and multiple muscle involvement of the pediatric lipoblastoma. Deeply situated myolipomas can be confused with well-differentiated liposarcomas (32).

ANGIOLIPOMA

Angiolipomas usually occur as encapsulated subcutaneous lesions. As a rule, they arise in young adults. The forearm is the single most common location for this tumor, which comprises 10% of tumors of fat (58). Clinically, angiolipomas resemble lipomas, although they have a greater tendency to be multiple. Size of these yellow to yellow-red, circumscribed lesions is from 0.5 to 4.0 cm. They are often tender or painful when pressured or moved (59).

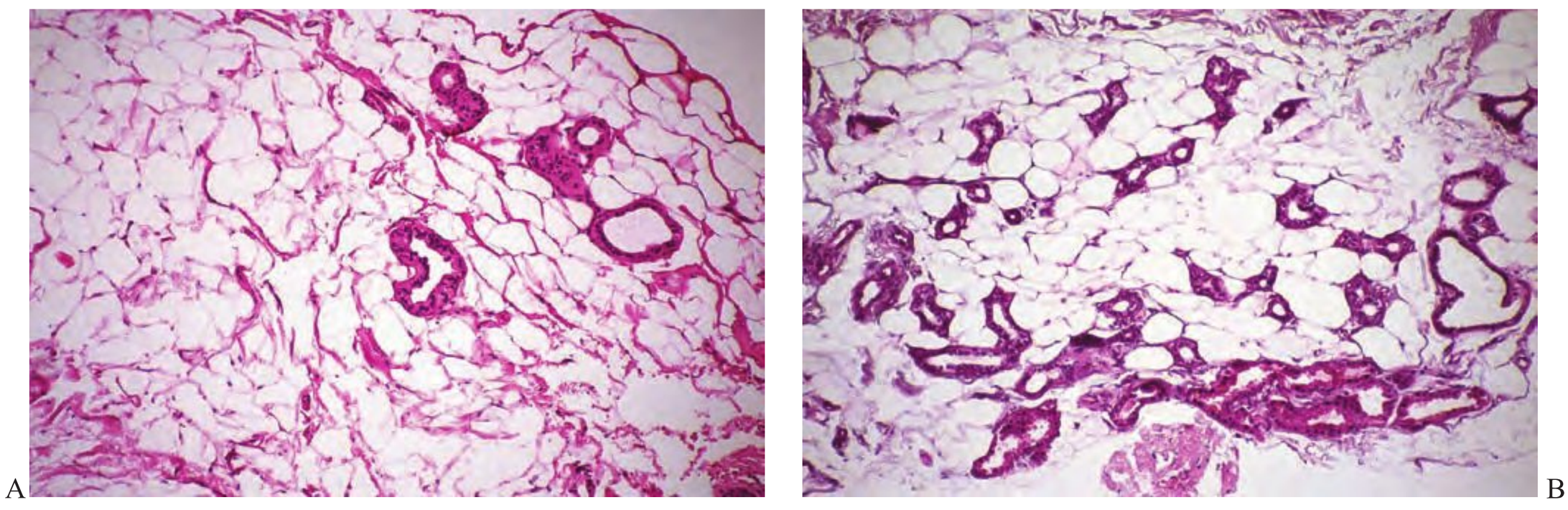


FIGURE 34-11. Adenolipoma. A: Excess mature fat in this medium-magnification view surrounds sweat gland coils and tubules (52-year-old man; 2-cm left neck nodule). B: Apocrine glandular elements (bottom) can be seen with sweat gland elements in a background of mature fat (62-year-old woman; small axillary mass).

TABLE 34-2 Benign Lipomatous Tumors of Skin and Soft Tissue

Hamartomas
Nevus lipomatosus cutaneous superficialis
Folded skin with lipomatous nevus
Congenital lipomatosis:
  Proteus syndrome
Benign neoplasms of white fat
  Homogeneous:
    Mature lipoma
  With heterogeneous mesenchymal elements:
    Fibrolipoma
    Myxolipoma
    Ossifying lipoma
    Angiolipoma
    Myolipoma
    Angiomyolipoma
  With specific clinicopathogenic settings:
    Perineural lipoma
    Lipoma of tendon sheath and synovium
    Multiple lipoma syndromes
    Adiposis dolorosa (Dercum's disease)
    Benign symmetric lipomatosis
    Familial multiple lipomatosis
  Pseudosarcomatous benign adipose tumors:
    Spindle cell lipoma
    Pleomorphic lipoma
    Chondroid lipoma
    Lipoblastoma and lipoblastomatosis
    Inter- and intramuscular lipoma
    Cervical symmetrical lipomatosis
    Pelvic lipomatosis
    Diffuse lipomatosis
Benign neoplasm of brown fat:
  Hibernoma

Histopathology. Inapparent at the gross level, angiolipomas microscopically show sharp encapsulation, numerous small-caliber vascular channels containing characteristic microthrombi, and variable amounts of mature adipose tissue (Fig. 34-12). These thrombi are well demonstrated by phosphotungstic acid–hematoxylin staining and are likely artifacts of removal because they show no organization. The degree of vascularity is quite variable, ranging from only a few small angiomatous foci to lesions with a predominance of dense vascular and stromal tissue (57). The angiomatous foci are composed in part of well-formed, dilated capillaries engorged with erythrocytes. Other capillaries appear tortuous and have poorly formed lumina and prominent proliferation of pericytes. Perivascular fibrosis may be prominent. Fat cells are sparse, and small vessels predominate in the cellular variant (60). With myxoid stroma, the term *angiomyxolipoma* (61) can be used. Scattered mast cells are expected. A normal karyotype implies hamartomatous pathogenesis.

Differential Diagnosis. Lesions with prominent perithelial fibrocytes may bring to mind spindle cell lipoma, which, however, lacks the conspicuous capillary channels with fibrin thrombi. Nearly all angiolipomas contain fibrin thrombi within their capillaries, often to a considerable degree. Cellular angiolipomas composed almost entirely of vascular channels and prominent spindle cells are sometimes confused with Kaposi's sarcoma or angiosarcoma. Subcutaneous position, encapsulation, septation, small size, diminutive nonatypical endothelial cells, microthrombi, and clinical presentation in healthy individuals help to exclude a malignant diagnosis (62). The term *infiltrating angiolipoma*, as used by Dionne and Seemayer (63) and by Puig and associates (64), is synonymous with *intramuscular angioma* (65), a vascular tumor with copious mature fat that is not acknowledged in its name. Its vessels are larger, and this lesion has a significant recurrence rate.

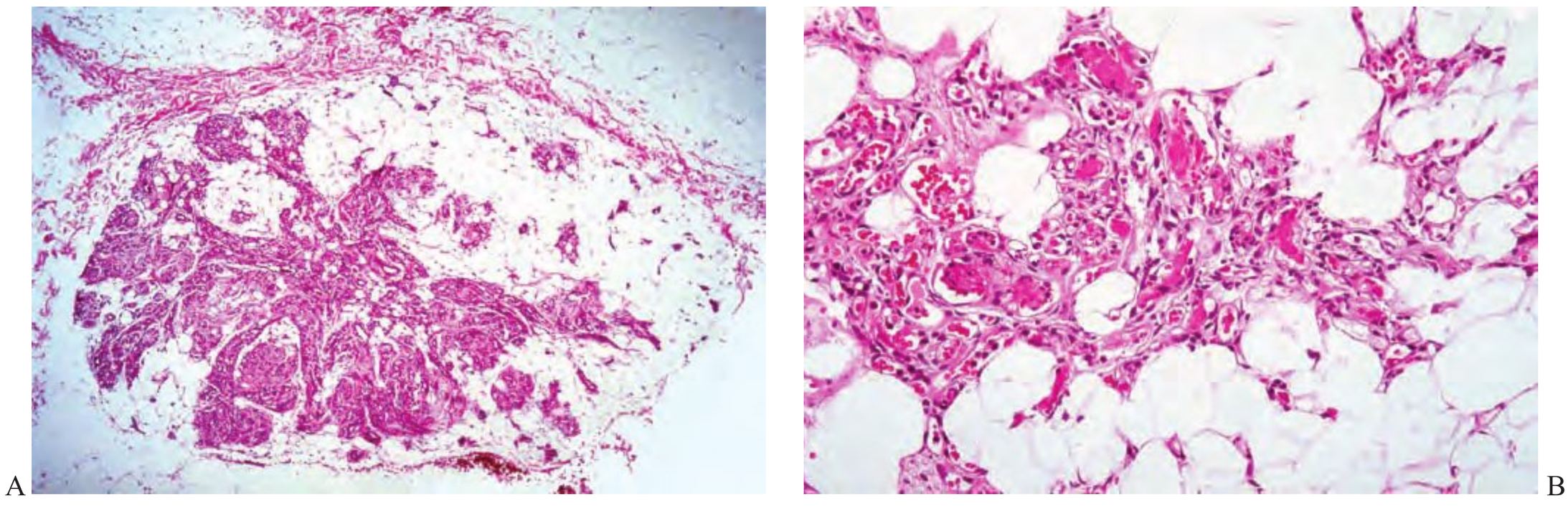


FIGURE 34-12. Angiolipoma. A: Prominent vessels radiate through a fibrous background into mature fat (incidental finding in a melanoma resection specimen). Prominent vascularity can impersonate a primary vascular neoplasm. B: At higher magnification, fibrin thrombi without organization occur in capillary lumina.

Nodular-cystic fat necrosis, also called *mobile encapsulated lipoma* (66), *encapsulated angiolipoma*, and *encapsulated necrosis*, can be shifted laterally, perhaps by several inches, and cause pain. They are most often in the subcutis of the elbow or hip. The pathogenesis seems to be ischemic changes secondary to trauma. They have no permanent attachment to a blood supply. Histologically, the fully developed lesions are thinly encapsulated, rounded nodules with well-preserved outlines of nonnucleated adipocytes devoid of inflammation or saponification but may calcify. Diffuse formation of pseudomembranes may make diagnosis difficult, leading to consideration of a wide range of potential diagnostic possibilities. This entity should be distinguished histologically from lipoma, angiolipoma, alpha 1-antitrypsin deficiency-associated panniculitis, membranous fat necrosis, and pancreatic fat necrosis (67).

SPINDLE CELL LIPOMA

A generally solitary, slowly growing subcutaneous tumor, spindle cell lipoma exhibits a predilection for the posterior neck and shoulder girdle region in men in their fifth to seventh decades. Clinically, the tumor is a slowly growing, painless nodule centered in the dermis or subcutis and measuring from 1 to 13 cm and potentially "massive" (68). This tumor does not recur or metastasize. Cytogenetics finds monosomy 16 or partial loss of 16q, a difference from liposarcoma (69). Abnormalities of chromosome 13 are reported (70).

Histopathology. Although the lesion is well circumscribed, it is seldom encapsulated. It is comprised of mature fat cells and uniform, slender spindle cells within a mucinous matrix (71). Spindle cell lipoma is polymorphous as a result of variations in cellularity, collagen content, and the ratio of spindle cells to mature adipocytes. In some areas, the neoplasm consists of a pure spindle cell population, often arranged in thick bundles, without fat cells. In other areas, the spindle cells are intermingled with scattered groups of mature fat cells (Fig. 34-13). The spindle cells, functioning as fibroblasts, produce varying amounts of collagen. If abundant, the diagnosis is fibrous spindle cell lipoma (72). Numerous mast cells are scattered throughout the tumor. Some tumors also show a prominent admixture of blood vessels ranging from capillaries to thick-walled vessels containing smooth muscle bundles to prominent sinusoidal channels that divide the tumor into irregular lobules. Irregular branching spaces between villiform, vascularized tumor projections constitute the *pseudoangiomatous* variant (73). Osseous or cartilaginous metaplasia is rare. The spindle cells are positive for CD34 and vimentin but not S-100. Some factor XIIIa–positive stromal cells are present. Ultrastructurally, they have abundant rough endoplasmic reticulum similar to fibroblasts and nonmembrane-bound lipid vacuoles (74). The cytogenetics parallels pleomorphic lipoma with loss of 16q material and less frequently 13q (75). A number of variants have been reported, including spindle cell lipoma with pseudoangiomatous change, composite spindle cell lipoma-hibernoma, and composite spindle cell lipoma/pleomorphic lipoma.

About 10% are the "low-fat" and "fat-free" spindle cell lipoma variants easily confused with nerve sheath tumors (76).

Differential Diagnosis. Nuclear palisading may be reminiscent of a neural tumor. Myxoid change and hypocellularity may bring myxoma to mind. A prominent hemangiopericytoma-like vascular pattern may be seen or a plexiform vascular pattern that may resemble myxoid liposarcoma. The diagnosis of liposarcoma or fibrosarcoma can usually be excluded without difficulty because of the uniformity of the proliferated spindle cells and the absence of multivacuolated lipoblasts, nuclear atypia, or atypical mitotic figures in spindle cell lipoma (71). Larger unvacuolated cells with some atypia, with or without floret giant cells, constitute transitional features to pleomorphic lipoma. Consider also mammary type and extramammary myofibroblastoma and solitary fibrous tumor (77).

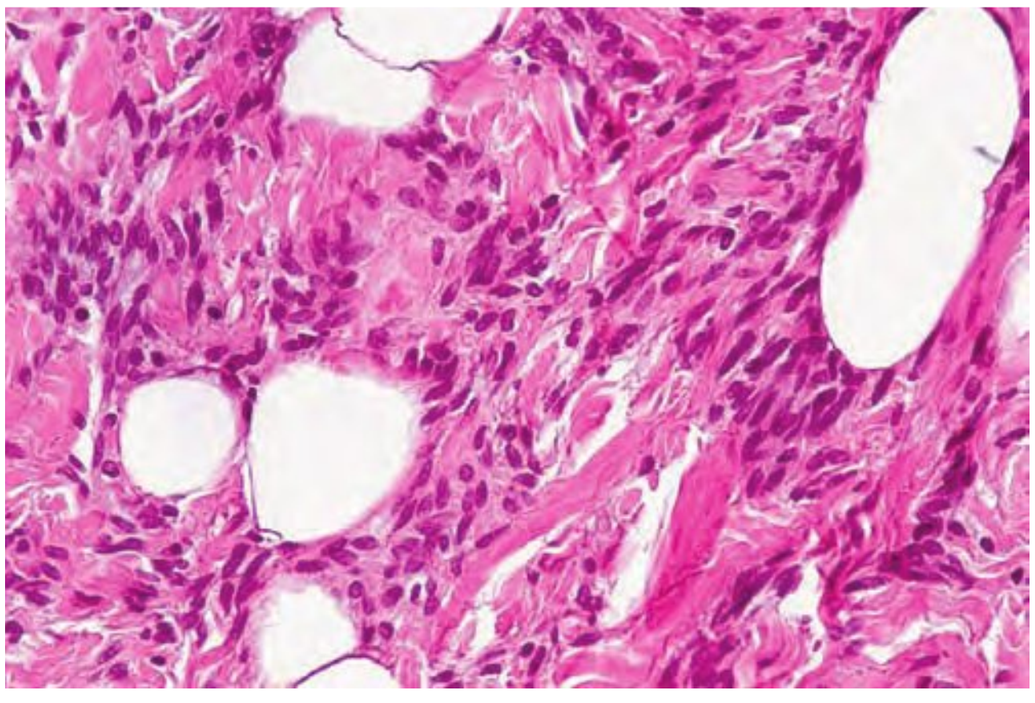


FIGURE 34-13. Spindle cell lipoma (62-year-old man; small back nodule). Uniform collagen-forming spindle cells expand the space between mature fat cells.

PLEOMORPHIC LIPOMA

Like spindle cell lipomas, the great majority of pleomorphic (giant cell) lipomas are solitary tumors of the shoulder girdle and neck in men in the fifth to seventh decade. The rare cutaneous spindle lipomas and pleomorphic lipomas, in contrast to subcutaneous forms, are more common in females and have a wider anatomic distribution (7). The lesion presents as a slowly growing, well-circumscribed dermal or subcutaneous mass averaging 5 cm, grossly resembling an ordinary lipoma (78) save for possible gelatinous gray areas on the cut surface. Like spindle cell lipoma, there is loss of chromosome 16q material (69).

Histopathology. The well-circumscribed tumor displays a wide morphologic spectrum. Although areas of mature fat cells are present, some of them show enlarged, hyperchromatic nuclei (79). In addition, most fat cells show marked variation in size. About half of the tumors contain occasional multivacuolated cells that have the appearance of lipoblasts (78). The mature and immature fat cells are situated singly and in groups in a

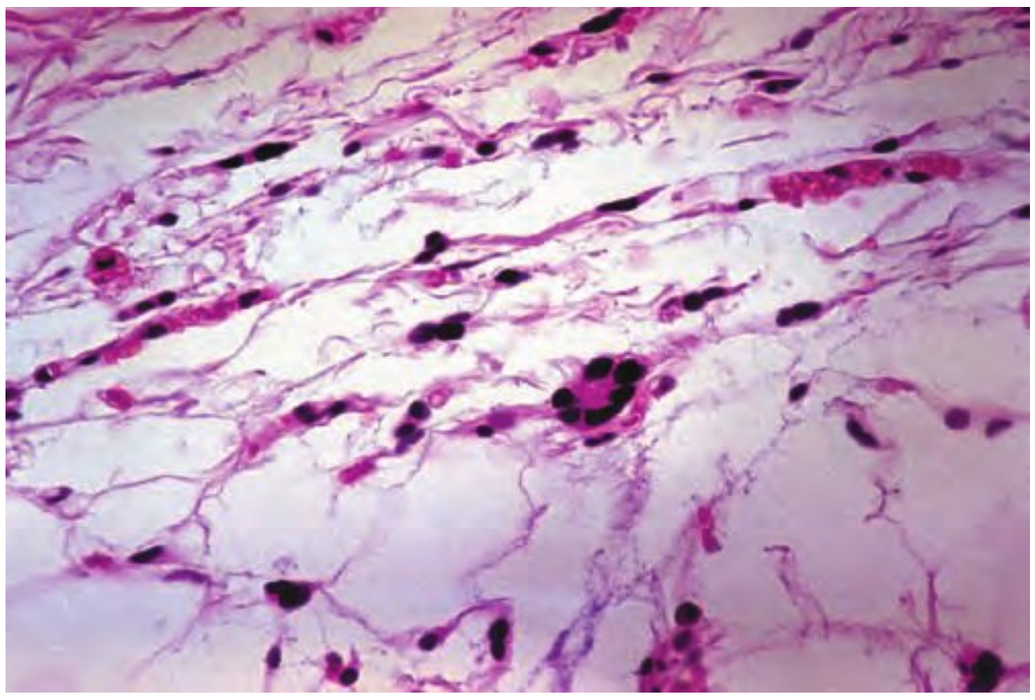


FIGURE 34-14. Pleomorphic lipoma with local regrowth (59-year-old man; interscapular local regrowth that had regained its original size of 9 cm 8 years after initial surgery). A characteristic floret-type giant cell with multiple peripherally placed nuclei and deeply eosinophilic cytoplasm is near center.

mucinous stroma traversed by dense collagen bundles. Pseudopapillary structures as in the pseudoangiomatous spindle cell lipoma may be seen (80). A very helpful feature in the diagnosis of pleomorphic lipoma is the presence of characteristic multinucleated giant cells, which are found in most but not all cases (79). These giant cells exhibit, within an eosinophilic cytoplasm, multiple, marginally placed, and often overlapping hyperchromatic nuclei. This peculiar arrangement is not unlike that of the petals of a small flower, and these giant cells are therefore referred to as *floret-type giant cells* (78) (Fig. 34-14). Rarely, pleomorphic lipoma histology comprises a sharply demarcated nodule within an otherwise ordinary lipoma. Also, small foci of spindle cell lipoma may be encountered in some pleomorphic lipomas (78). Some pleomorphic lipomas have inflammatory cells, including lymphocytes, plasma cells, mast cells, and occasional histiocytes in a perivascular or diffuse stromal distribution. Mitoses are rare.

Differential Diagnosis. Pleomorphic lipoma microscopically may resemble a liposarcoma (81). However, it is a slow-growing and well-circumscribed lesion with a benign behavior. Despite occasional lipoblast-like cells and atypical mitotic figures, local excision should be curative. No single feature confirms the diagnosis of pleomorphic lipoma and excludes liposarcoma. Only a multivariate analysis leads to the correct diagnosis, and such an analysis should consider the age and sex of the patient, anatomic location, size, epicenter of growth (deep or superficial), degree of local invasion, and histologic appearance. Liposarcomas differ from pleomorphic lipomas by their infiltrative growth, greater cellularity, more nuclear atypicality including atypical mitoses, more numerous multivacuolated lipoblasts, prominent necrosis, and absence of thick collagen bundles. Floret-type giant cells are rarely seen in liposarcomas and then only in small numbers (78).

CHONDROID LIPOMA

Chondroid lipoma is an uncommon firm, yellow tumor, averaging 3 to 5 cm, generally encountered in adults, comprised of vacuolated fat cells similar to brown fat in a chondromucinous stroma. Based on 20 cases (82), the age range is 14 to 70 years, with a 4:1 female predominance and predilection for the limbs and limb girdles. These nonpainful masses of weeks' or years' duration range from 1.5 to 11.0 cm in diameter, with a median of 4.0 cm. Perhaps half of these well-demarcated, encapsulated, yellow-to-white or gray-tan masses are in the subcutis or involve the superficial fascia of the skeletal muscle (Fig. 34-15A, B). The remainder are more deeply situated, possibly within muscles. The lower extremity is the most common location. This lesion, almost invariably mistaken for a sarcoma, especially myxoid liposarcoma or myxoid chondrosarcoma, is nonaggressive and has a benign clinical course without local regrowth or metastases in the original 12 cases with follow-up (82). A three-way translocation between chromosomes 1, 2, and 5 together with an 11;16 translocation with a breakpoint in 11q13 is reported (83).

Histopathology. In chondroid lipoma, a variable background of mature adipose tissue is associated with a predominant, partially fibrinous to hyalinized myxoid matrix (Fig. 34-15C). Within this matrix are nests, strands, and sheets of eosinophilic and vacuolated cells, which contain glycogen and fat droplets, resembling brown fat cells, lipoblasts, and chondroblasts. The eosinophilic cells frequently contain one or several clear lipid vacuoles and an appearance similar or indistinguishable from lipoblasts. Vacuolated cell forms (hibernoma-like cells) simulate lipoblasts or chondroblasts. These cells lack pleomorphism and mitoses and adopt a lacunar appearance when surrounded by the prominent myxoid or hyalin matrix (Fig. 34-15D). The characteristic reaction panel is positivity for S-100 protein, CD68, and KP1. Chondroid lipoma can be diagnosed by fine-needle aspiration biopsy (84), but more confidently in cell block sections where immunochemistry and special stains can be brought to bear (85). The sulfated stroma is strongly metachromatic with toluidine blue at pH 4.0, Alcian blue positive, hyaluronidase resistant, and aldehyde fuchsin positive at pH 1.7.

Differential Diagnosis. The differential diagnosis includes primarily extraskeletal myxoid chondrosarcoma (where myxoid matrix obscures the mature fatty component), soft tissue chondroma (mainly hands and feet), myxoid liposarcoma, hyaline variant of chondroid syringoma, and occasionally myoepithelial tumors. The plexiform, capillary-like vasculature and myxoid matrix allow recognition of myxoid liposarcoma (82).

Pathogenesis. Electron microscopy reveals that the tumor cells have abundant intracytoplasmic lipid and glycogen as well as numerous pinocytotic vesicles characteristic of adipocytes rather than chondroblasts. This favors the view that chondroid lipoma is a tumor of pure white adipocytes with a hyalinized extracellular matrix that resembles cartilage under light microscopy (86).

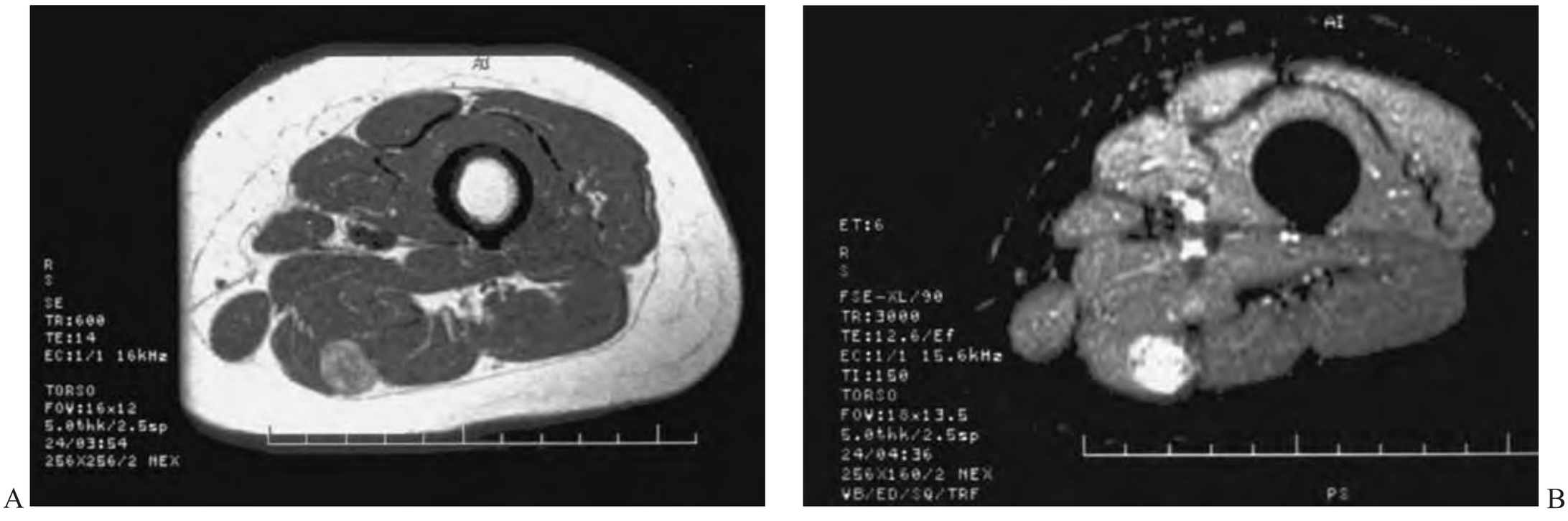
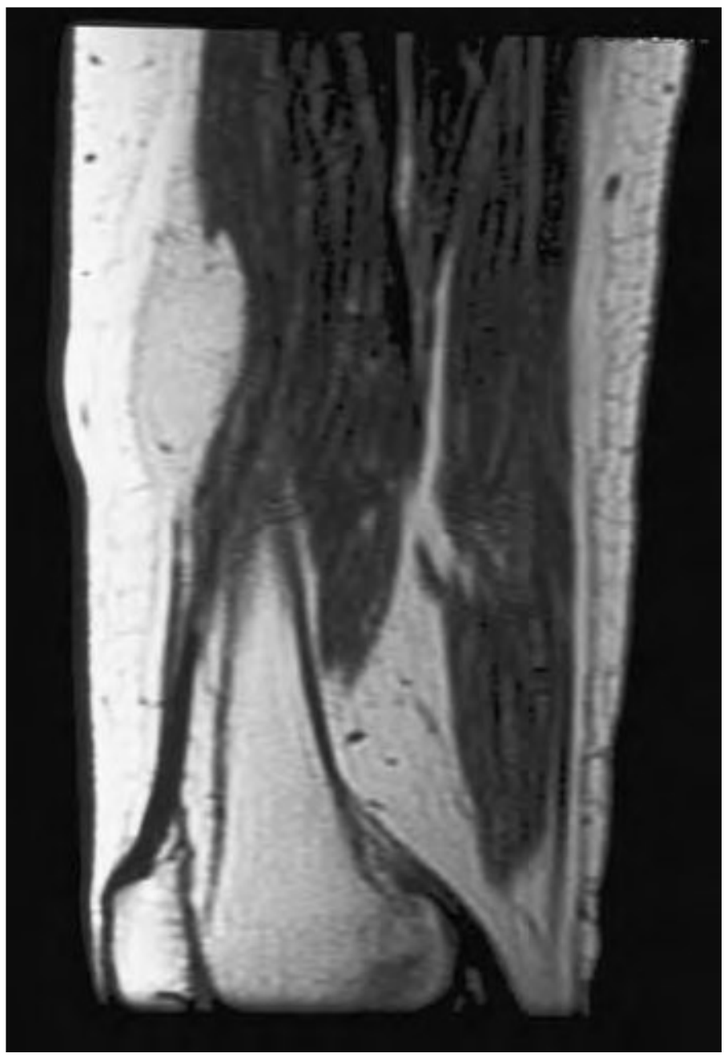


FIGURE 34-15. Chondroid lipoma (60-year-old woman; 6-month history of posterior leg nodule). A: A T1-weighted MRI of proximal thigh reveals a well-demarcated intramuscular mass with areas of high and low to intermediate signal consistent with fat. B: In a short tau inversion recovery (STIR) image, the foci of high T1 signal suppress, indicating fat. The bulk has high signal consistent with increased water content (myxoid) and cartilage. C: Chondroid lipoma is a lobular, well-circumscribed tumor comprised of strands and nests of rounded or polygonal eosinophilic cells in a stroma of mature fat, myxoid and chondroid material, and partly hyalinized fibrous tissue. D: The eosinophilic tumor cells have lipid vacuoles and grossly simulate lipoblasts. They contain neutral fat and glycogen and stain positively with oil red O and PAS stains. They are positive for vimentin and S-100 protein.

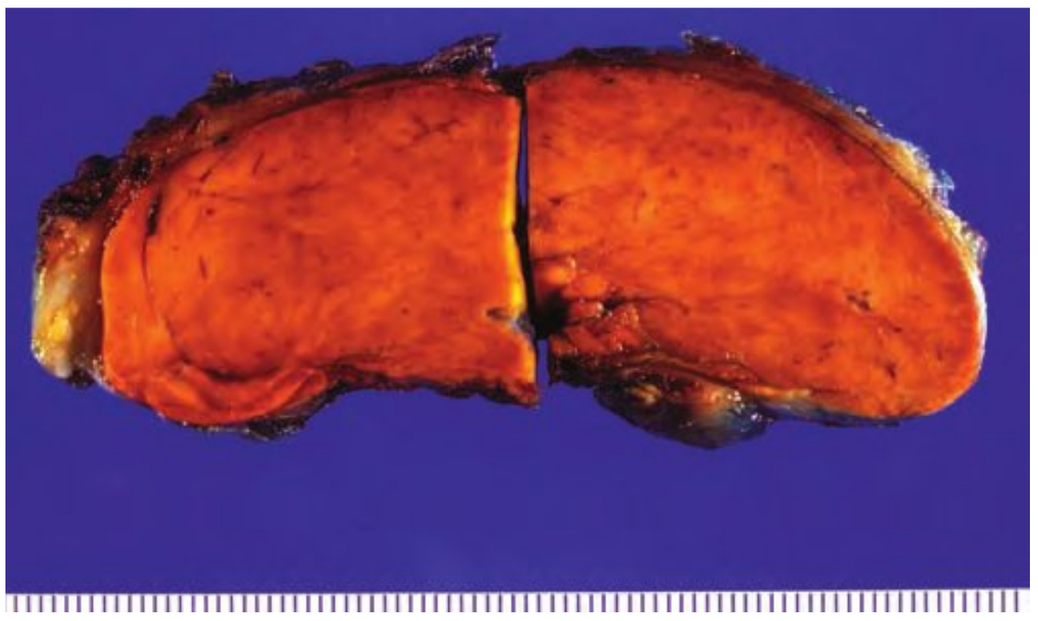
Another view is that the cells have features of embryonal fat and embryonal cartilage (87). Female predominance raises the possibility of hormonal factors in pathogenesis (82).

HIBERNOMA

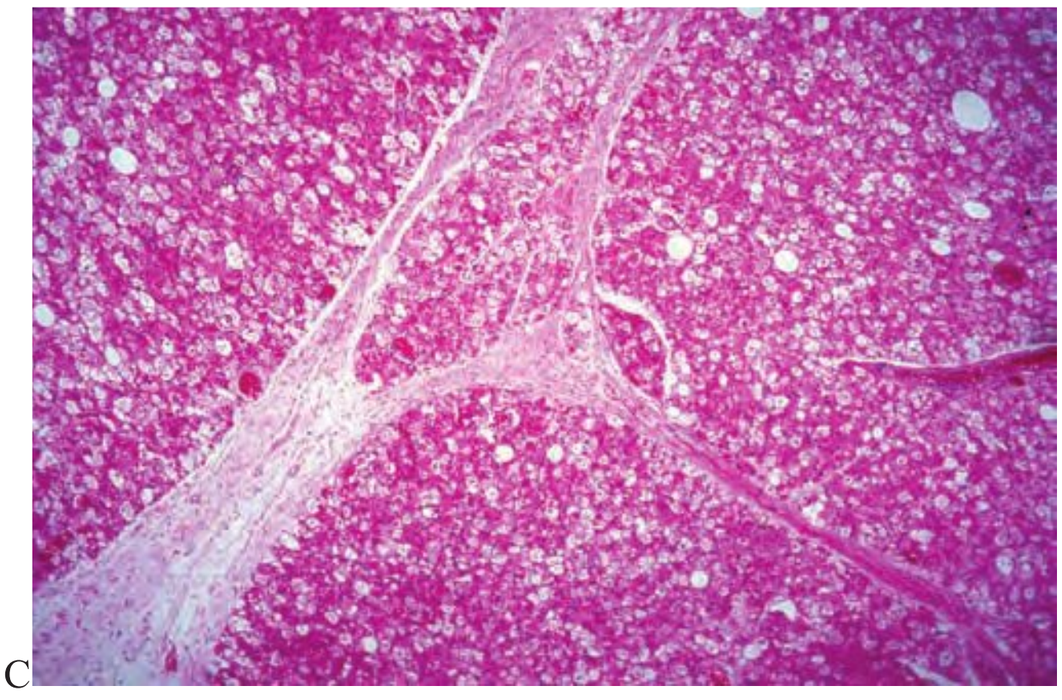
Hibernomas may appear in childhood and slowly increase in size but occur chiefly in adults, with a peak incidence during the third decade of life—on average, considerably younger than those with ordinary (mature) lipoma. This rare tumor arises most frequently at the few sites in which brown fat is encountered in adults—for example, in the subcutis of the shoulder girdle, posterior neck, axilla (88), and mediastinum (89). Vestigial remnants of brown adipose tissue are impugned (90). However, some hibernomas occur at rarer sites such as abdomen, retroperitoneum, thigh, popliteal fossa, neck, chest wall, inguinal area, larynx, parotid region, mammary, and intradural–extramedullary spinal. The tumor is rarely described in the dermatology literature because locations where a dermatologist would likely be consulted, such as pertaining to the scalp (91) or forehead (92), are virtually unique. Clinically, hibernomas are indistinguishable from common lipomas. They are slowly growing and painless, typically occurring in the subcutis or rarely in muscle, and often noted several years before excision. Although usually asymptomatic, they are occasionally tender. Overlying skin may have increased warmth (93). This benign, moderately firm, solitary, subcutaneous, tan or red-brown tumor is generally from 5 to 10 cm in diameter, although examples up to 20 cm have been reported. The MRI finding of a lesion that is diffusely slightly hypointense to surrounding subcutaneous fat should prompt consideration of hibernoma in the differential diagnosis (94) (Fig. 34-16A).



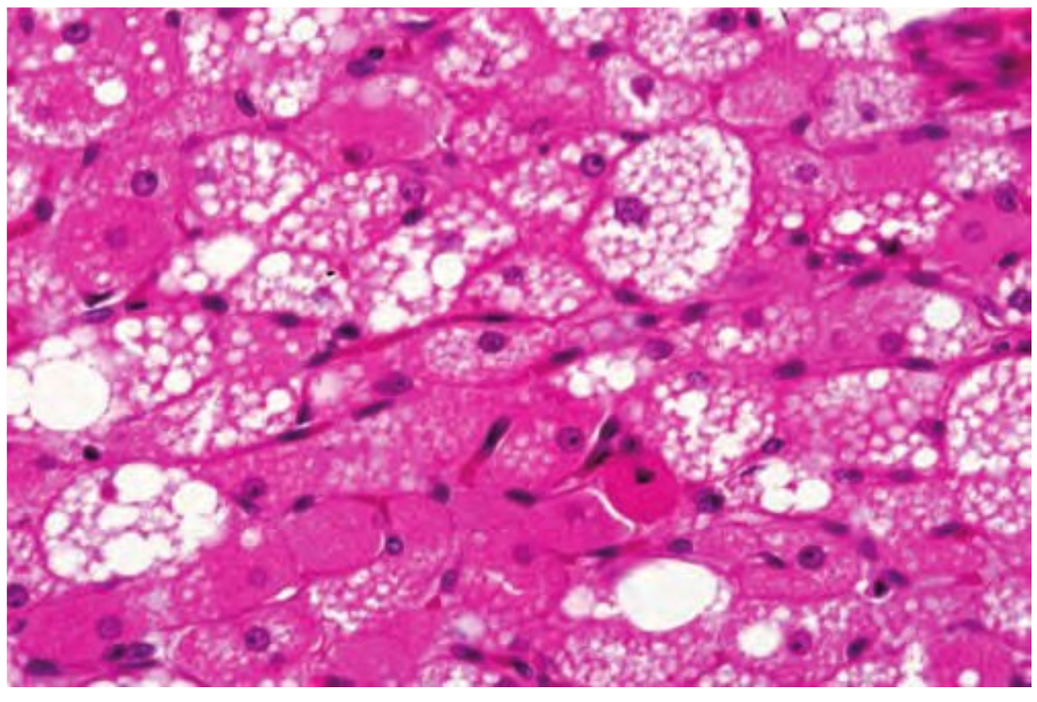
A



B



C



D

FIGURE 34-16. Hibernoma (69-year-old woman; 2- to 3-year history of slowly growing thigh mass). A: A longitudinal MRI of the thigh discloses a fusiform tumor between subcutaneous fat and muscle with less T1 signal than mature fat. B: The characteristic brown color of this hibernoma contrasts with the pale yellow color of attached pericapsular white fat on each end of it. It results from the prominent vascularity and many mitochondria in tumor cells. C: A low-magnification view displays the distinct lobular pattern characteristic of hibernoma. D: At higher magnification, hibernoma cells show varying degrees of complete modulation to signet-ring fat cells. These cells range from uniform round to oval granular eosinophilic cells to multivacuolated cells with multiple small oil red O–positive lipid droplets and centrally placed nuclei to intermixed univacuolar cells with one or more large lipid droplets and peripherally placed nuclei (lipocytes).

On gross cross-section, the well-circumscribed, somewhat lobulated mass varies from tan to a deep red-brown. The distinct brown color of the gross cut surface (Fig. 34-16B) is due to prominent vascularity and a profusion of mitochondria in the granular tumor cells. Adequate treatment consists of complete excision (91,95) sparing vital structures. Like lipomas, hibernomas have little tendency to recur locally after excision, although continued enlargement has been reported after 70% removal of an 11-cm infraclavicular tumor (96). A malignant counterpart of hibernoma (97) remains speculative. An intensely FDG-avid lesion on positron emission tomography/computed tomography (CT) examination can mimic a metastasis (e.g., melanoma) (98).

Histopathology. Histologic examination reveals that the tumor is divided into numerous lobules by well-vascularized connective tissue (Fig. 34-16C). In contrast to ordinary lipoma of white fat, the highly vascular nature of the tumor is readily

apparent in most sections. Hibernoma's constituent cells resemble those of brown fat tissue, which is present in the human fetus and newborn infants but gradually diminishes in quantity throughout adult life. The tumor cells are round or polygonal and are closely apposed to one another within the lobules (Fig. 34-16D). Three principal types of cells in varying proportions can be recognized (90): (a) a small cell (average, 37 μ) with granular, eosinophilic cytoplasm and with or without rare, multiple small oil red O–positive lipid droplets and centrally placed nuclei and distinct cellular membranes; (b) a larger, multivacuolated fat cell (average, 54 μ) with scanty granular, eosinophilic cytoplasm, referred to as a *mulberry cell*; and (c) a still larger, univacuolated fat cell (average, 64 μ) with peripherally placed nucleus, variably present and perhaps predominating, making distinction from ordinary lipoma difficult. The nuclei of the granular and multivacuolated cells are usually centrally located, and the nuclei of the univacuolated fat cells are peripheral. Cells of the three principal types, with transitional forms, usually are dispersed randomly throughout the lobules. In most tumors, multivacuolated mulberry cells predominate. Some tumors, however, contain a few lobules, particularly at their peripheries, that are composed entirely of univacuolated cells (90). The vacuoles in both the multivacuolated and univacuolated cells stain positively with Sudan black or oil red O. Nuclear pleomorphism or hyperchromatism and lobate nuclei are rarely seen (97), and mitoses are absent. Based on the nature of the stroma and the appearance of the multivacuolated cells, four categories of hibernomas are described: typical, lipoma-like, myxoid, and spindle cell. The myxoid variant is very rare (99).

Ultrastructure. Each tumor cell is invested by a basal lamina. There is an inverse relationship between lipid droplet size and the number of mitochondria per unit of cytoplasm that conspicuously lacks membrane systems. Pleomorphic mitochondria have dense matrices and transverse lamellar cristae, micropinocytotic vesicles, and periodic short plasmalemmal densities.

Pathogenesis. The term *hibernoma* reflects the fact that these tumors are composed of cells that resemble the brown fat of hibernating animals. The incomplete modulation of the mulberry cells may be attributable to underdevelopment of enzyme systems. Like many other benign lipomatous tumors, hibernoma has a characteristic cytogenetic abnormality, specifically, abnormalities of the long arm of chromosome 11 (11q13-21) (100) and 10q22 (101).

Differential Diagnosis. Rhabdomyoma and granular cell tumor should be thought of before diagnosing hibernoma. Immunohistochemically, rhabdomyomas are strongly positive for myogenic markers (desmin, actin, and myoglobin) but negative for S-100, while hibernoma and granular cell tumor strongly express S-100. Hibernomas are to be distinguished from granular cell tumors that have no lipid vacuoles and from myxoid and round cell liposarcoma, which usually contain diagnostic multivacuolar lipoblasts. The larger, univacuolated fat cell may predominate, making distinction from ordinary lipoma difficult.

LIPOFIBROMATOSIS

Lipofibromatosis is a rare pediatric neoplasm that has been variously interpreted as a type of infantile or juvenile fibromatosis, a variant of fibrous hamartoma of infancy, and a fibrosing lipoblastoma. Although it is likely that this tumor comprises part of the spectrum of what has been referred to in the literature as *infantile/juvenile fibromatosis*, its clinicopathologic features and, in particular, its distinctive tendency to contain fat as an integral component, warrant separate classification as a *lipofibromatosis*. Males predominate in a ratio of 2:1. The patients present with a soft tissue mass from 1 to 7 cm involving the hand, arm, leg, foot, trunk, or head that may be evident at birth. Histologically, the adipose tissue has a spindled fibroblastic element with focal fascicular growth, typically has limited mitotic activity, and chiefly involves the septa of fat and skeletal muscle, generally without extensive architectural effacement of fat as is common with conventional fibromatoses. The primitive nodular fibromyxoid component of fibrous hamartoma of infancy is absent. The fibroblastic element exhibits cytologic atypia and occasional mitoses. Small collections of univacuolated cells are often present at the interface between some of the fibroblastic fascicles and the mature adipocytes. The tumors entrap vessels, nerves, skin adnexa, and skeletal muscle. Focal immunoreactivity is present in some tumors for CD99, CD34, alpha-smooth muscle actin, and BCL-2 and, less frequently, S-100 protein, muscle actin (HUC 1-1), and EMA. However, no reactivity is detected for desmin (D33 and D-ER-1 clones), keratins, or CD57. Follow-up data for 25 individuals (median follow-up period, 6 years and 7 months) found regrowth of the tumor or persistent disease documented in 17 (72%), correlating with congenital onset, male sex, hand and foot location, incomplete excision, and mitotic activity in the fibroblastic element (102).

BENIGN LIPOBLASTOMA

Lipoblastoma and lipoblastomatosis (103) are rare benign neoplasms of fetal white fat that occur almost exclusively in infants and children (104) and typically as a stable or slowly to rapidly enlarging, asymptomatic soft lobular mass in the superficial or deep layers of soft tissue on the trunk or extremities, especially lower. Other sites of occurrence include the head, neck, retroperitoneum, trunk, back, extremities, heel (105), buttock, inguinal canal, scrotum, retroperitoneum, peritoneal cavity, and lung (106). In a child younger than 3 months of age, images showing a predominantly fatty but inhomogeneous soft tissue mass are suggestive of lipoblastoma (107). Two basic forms of benign lipoblastoma occur. The variant called *lipoblastomatosis* is deeply situated and poorly circumscribed, presenting as a superficial mass that extends from the subcutis

to the underlying muscle (108), mostly, but not entirely, of fat on MRI (109). Lipoblastoma is relatively superficial and encapsulated. Each form commonly presents as a painless nodule or mass, affecting boys twice as frequently as girls. Circumscribed lipoblastoma is more common than diffuse infiltrative lipoblastomatosis. Sizes range from 1 to >20 cm in greatest dimension. They may cause dysfunction of other organ systems due to mass effect. Lipoblastomas occurring on the back can have intraspinal extension (110). Complete resection is the only definitive treatment and should not be delayed when impingement on surrounding structures is imminent. These neoplasms have no malignant potential but have a tendency to recur despite presumed complete excision up to 25% of the time (111). Patients with diffuse lipoblastoma (lipoblastomatosis) are likely to have recurrent disease (usually within 2 years) and should undergo close follow-up (112) for a minimum of 5 years. Cellular maturation has been reported in serial biopsies over time. A "wait and see" approach may be justified, at least in infants with huge invasive lesions requiring a mutilating excision, since complete spontaneous resolution of a diffuse lipoblastoma in the thigh has been shown in a 2-day-old male at 1 year by MRI (113).

Histopathology. Peripheral immature lipoblasts with fat vacuoles of various sizes and central mature fat cells containing single, large fat vacuoles are characteristic (Fig. 34-17) whether the tumor is deeply or superficially situated. The lipoblasts vary in size. Most of them contain single vacuoles that are variable in size but smaller than those found in mature fat cells. These vacuoles displace the nuclei against the cytoplasmic membrane. A few small lipoblasts contain two, three, or occasionally more vacuoles. Some benign lipoblastomas also show lipoblasts with finely vacuolar cytoplasm and centrally placed nuclei resembling hibernoma cells. Nonvacuolated cells that are spindle shaped or stellate are observed in the mucinous stroma with a fine vascular network that is strikingly similar to myxoid liposarcoma and from which it may be indistinguishable. Fibrous septa partition lobules in the circumscribed form.

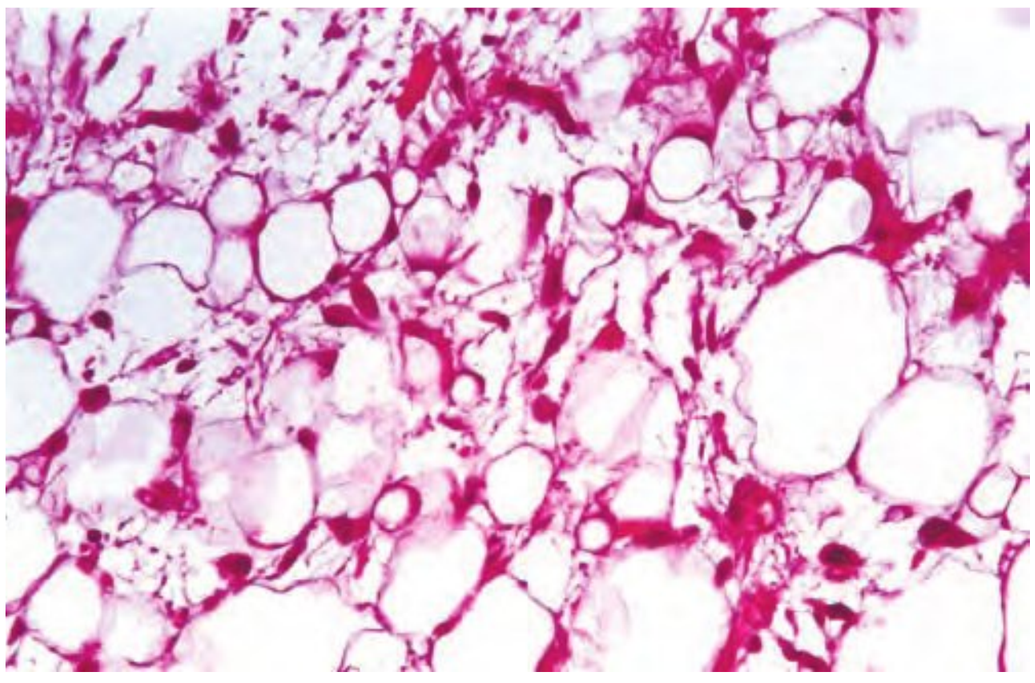


FIGURE 34-17. Lipoblastomatosis. The tumor is comprised of partly differentiated lipoblasts and has a prominent capillary vascular pattern with areas of mucoid matrix. Cells with large hyperchromatic nuclei are absent.

Differential Diagnosis. Only the age of the patient, the abundance of lipoblasts, the absence of atypical mitoses, and a sometimes subtle lobularity distinguish it from liposarcoma—especially the myxoid type (103). Although liposarcomas occur very rarely in infants and young children, the distinction may be impossible by light microscopy alone. Therefore, when performing a biopsy of a childhood adipose tumor with unusual features, such as progressive or invasive growth, fresh tissue should be submitted for cell culture. The tumor karyotype will in most cases aid in differentiating lipoblastoma from myxoid liposarcoma (114). Rearrangements of chromosome 8 q11-q13 region leading to rearrangement of the PLAG1 gene are a discriminative marker that distinguishes lipoblastoma and lipoblastomatosis from myxoid liposarcoma (104). Fluorescent *in situ* hybridization can serve as a decisive tool in the differential diagnosis of lipoblastoma and lipoma-like liposarcoma apart from its role in the distinction between lipoblastomas and myxoid/round cell liposarcoma (115). Confusion with typical lipoma may occur. In fact, lipoblastoma's early occurrence, its ability to mature into a simple lipoma, its cellular composition of mainly mature adipocytes, and its benign course suggest that it may more accurately be termed an *infantile lipoma* (116).

LIPOSARCOMA

Liposarcomas, constituting 15% to 20% of all soft tissue sarcomas, are generally deep-seated tumors most likely in the retroperitoneum or the deep soft tissues in or below buttocks (117). Most commonly, they originate in the intermuscular fascial planes, with a special predilection for the thighs (118). From a fascial plane, they can extend to subcutaneous tissue. Liposarcomas are slightly more prevalent in males and tend to occur on the right side of the body more commonly than on the left. Infrequently, liposarcomas may be multicentric. Liposarcoma can occur in subcutaneous location and rarely in dermis. As with most other dermal sarcomas, local recurrence is a more frequent problem than distant metastases (119).

Liposarcomas arise as such and for practical purposes do not develop from lipomas. The average age of onset is 50 years. Occasionally, liposarcomas arise in children from 10 to 15 years of age, comprising 4% of childhood soft tissue sarcomas (120) but are exceedingly rare, if not nonexistent, in children younger than 10 years (121).

The morphologic classification of liposarcoma is into three main groups: (a) well-differentiated liposarcoma (including adipocytic or "lipoma-like," sclerosing, inflammatory, spindle cell, and their dedifferentiated variants), characterized by ring or long marker chromosomes derived from the long arm of chromosome 12; (b) myxoid and round cell (poorly differentiated myxoid) liposarcoma, characterized in most cases by a reciprocal translocation t(12;16)(q13;p11); and (c) pleo-

morphic liposarcoma, characterized by complex karyotypes (liposarcoma) (122). In some tumors, more than one type can be recognized. The well-differentiated and myxoid types have better prognoses than the round cell and pleomorphic types. Myxoid variants are more common in the young, whereas well-differentiated and pleomorphic subtypes are more often encountered in older patients.

Well-differentiated liposarcomas are low grade and may regrow locally but do not metastasize. The clinical outcome of well-differentiated lipoma-like liposarcoma is best predicted by anatomic location (123). In the subcutis, they are usually cured by local excision, rarely regrow, and do not metastasize. Therefore, the term *atypical lipoma* was been introduced for the subcutaneous form of well-differentiated liposarcoma (79). Great debate has been generated by the introduction of that term, with most now agreeing that well-differentiated liposarcoma and atypical lipoma should be considered synonyms that describe lesions identical both morphologically and karyotypically (122). This is the form of liposarcoma most likely to be biopsied by the dermatologist. Because of this benign course, Evans (124) later suggested an even less committal designation for this neoplasm, *atypical lipomatous tumor*. It has been recommended that this term be restricted to subcutaneous tumors, especially those of small size with minimal atypical changes, and the term *well-differentiated liposarcoma* for the same histology at other sites (125).

For the more aggressive liposarcomas, circumscription of the lesion may offer false hope of eradication by simply shelling out the tumor. In reality, liposarcomas extend microscopic pseudopod-like extensions that commonly insinuate between fascial planes. Occasionally, small satellite nodules become separated from the lobulated sarcomatous mass, leading to an erroneous impression of multicentricity. Biopsy and resection should be carefully planned, guided by MRI and radiographic findings in a manner that eliminates prior biopsy tracts and any plane potentially contaminated by surgical exposure or spreading hematoma. The depth of atypical and malignant neoplasms showing lipomatous differentiation correlates with the tendency for local recurrence that is especially uncommon in subcutaneous location (123). Metastases are common, especially in round cell and pleomorphic liposarcomas where increased numbers of mitoses, in either in the primary tumor or a local recurrence, predict metastases (123). The lungs and liver are the most common sites. Myxoid and round cell liposarcoma sarcoma have marked propensity to involve intra-abdominal sites, other soft tissue areas (especially the neck), and bone. Therefore, abdominal CT and bone scan are recommended in the initial evaluation as well as follow-up of high-risk patients with larger, locally recurrent or high-grade tumors of any size (117). Myxoid liposarcoma metastasizes preferentially to serosal surfaces (e.g., pleura, pericardium, pelvic sidewall). If found in a trunk biopsy, an occult primary tumor in an extremity should be sought (126).

Histopathology. Liposarcoma is diagnosed only when there is convincing evidence of synthesis and storage of fat by the tumor cells (117), the hallmark of which is the lipoblast. For a cell to be designated as a lipoblast, it must show the ability to synthesize and accumulate nonmembrane-bound lipid in the cytoplasmic matrix. Acceptable malignant lipoblasts are quite variable, because they may recapitulate any stage in the normal maturation sequence. Their common morphologic denominator is well-demarcated cytoplasmic lipid that displaces or indents one or more irregular hyperchromatic nuclei. The nucleus conforms to the contours of the lipid droplet, creating an apparent delicate scalloping of the nuclear membrane. Hyperchromaticity and variability from lipoblast to lipoblast support a malignant diagnosis. Despite these criteria, the distinction between malignant lipoblast and "atypical lipocyte" is at times subjective, especially in the more well-differentiated lipoma-like variants of liposarcoma. A "true" lipoblast is defined not only by a multivacuolated or univacuolated fat cell with indented or scalloped nucleus but also by its histologic context (82). Benign fat necrosis, myxoid changes in structural fat, lipogranulomas, lymphomas with signet-ring changes, and carcinomas can contain vacuolated cells that mimic lipoblasts. Lesions such as pleomorphic lipomas and lipoblastomas illustrate that even unequivocal lipoblasts do not always signal malignancy.

The cells of liposarcoma bear a close resemblance to different stages in the development of fat and are found in variable proportions as a function of histologic subtype but show a much greater individual variability.

In *well-differentiated lipoma-like liposarcoma*, the tumor is composed predominantly of univacuolated fat cells of various sizes. The nuclei of the fat cells are slightly pleomorphic, and some of them are hyperchromatic.

Well-differentiated liposarcoma (*atypical lipoma*) histologically features distended fat cells that vary slightly in size and shape, with occasional interspersed lipoblasts. Broad, fibrous septa containing cells with enlarged hyperchromatic atypical nuclei are a characteristic feature (Fig. 34-18). Foci of well-differentiated smooth muscle may be found but do not influence the behavior (127). The emergence of a high-grade sarcoma pattern within a well-differentiated liposarcoma or in recurrence is known by the biologically imprecise term *dedifferentiation* and is limited for practical purposes to these tumors when they are located in body spaces, especially the retroperitoneum (128).

Spindle cell liposarcoma represents an uncommon variant of well-differentiated liposarcoma that tends to recur locally and may "dedifferentiate". Morphologically, it is composed of a fairly bland neural-like spindle cell proliferation set in a fibrous and/or myxoid background and is associated with an atypical lipomatous component (122).

Myxoid liposarcoma (Fig. 34-19) is the most common type of liposarcoma and displays various quantities of four elements: (a) proliferating lipoblasts, (b) delicate plexiform capillaries, (c) myxoid matrix, and (d) acid mucopolysaccharide lakes (Fig. 35-19A). Mitotic figures are conspicuously absent. These tumors have been subdivided into a well-differentiated type with little tendency to metastasize and a poorly differentiated type that commonly metastasizes (118). A well-differentiated myxoid liposarcoma contains, in addition to lipoblasts with spindle-shaped nuclei and several lipid vacuoles, more highly differenti-

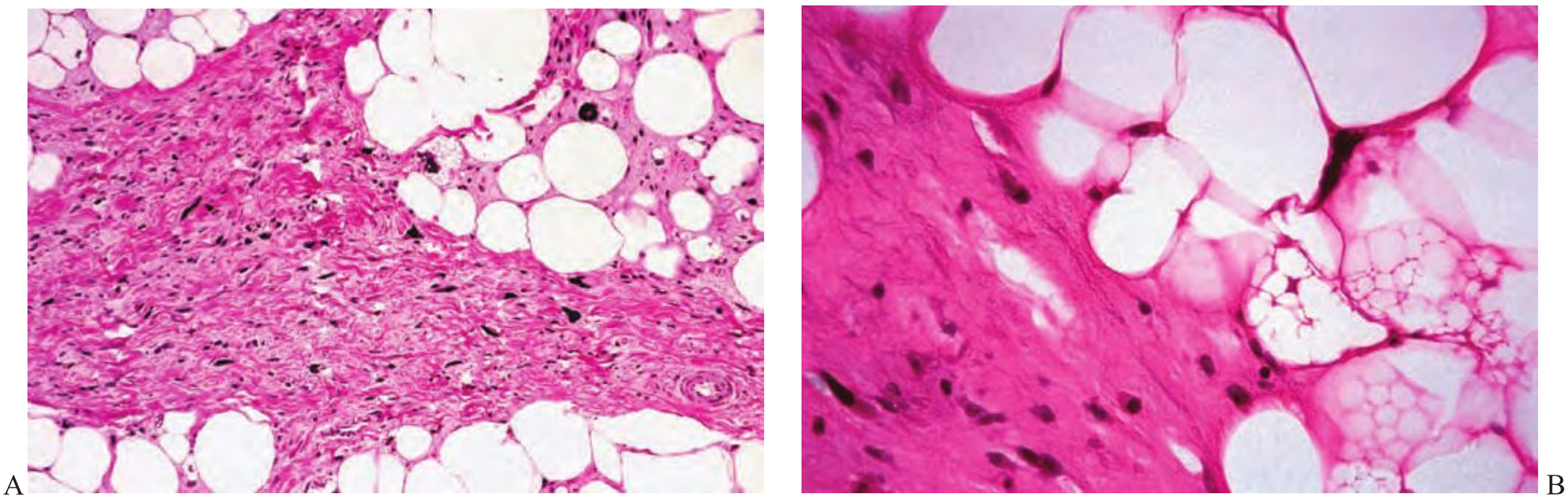


FIGURE 34-18. Well-differentiated lipoma-like liposarcoma (atypical lipoma). A: A broad, fibrous septum containing cells with atypical hyperchromatic nuclei partitions a tumor of fat-filled rounded cells, some of which are lipoblasts. (Courtesy of Andrew E. Rosenberg.) B: A higher magnification shows hyperchromatic nuclei in the fibrous septum and a dark-staining triangular lipoblast nucleus in adjacent fat (compare with Fig. 34-4). Prolonged searching may be required to find enlarged, irregular, hyperchromatic nuclei (some indented by clear lipid vacuoles) in atypical lipoma.

ated fat cells, such as so-called *signet-ring* cells (Fig. 35-19B), which have single large vacuoles occupying a major portion of the cytoplasm, and even mature fat cells. The tumor cells are arranged loosely in a myxoid stroma. In a poorly differentiated myxoid liposarcoma, the spindle-shaped lipoblasts have large, atypical nuclei and usually only small numbers of lipid droplets. Depending on the amount of myxoid stroma, there is considerable resemblance to either a myxosarcoma or an undifferentiated fibrosarcoma, because the latter may also have a certain amount of myxoid stroma.

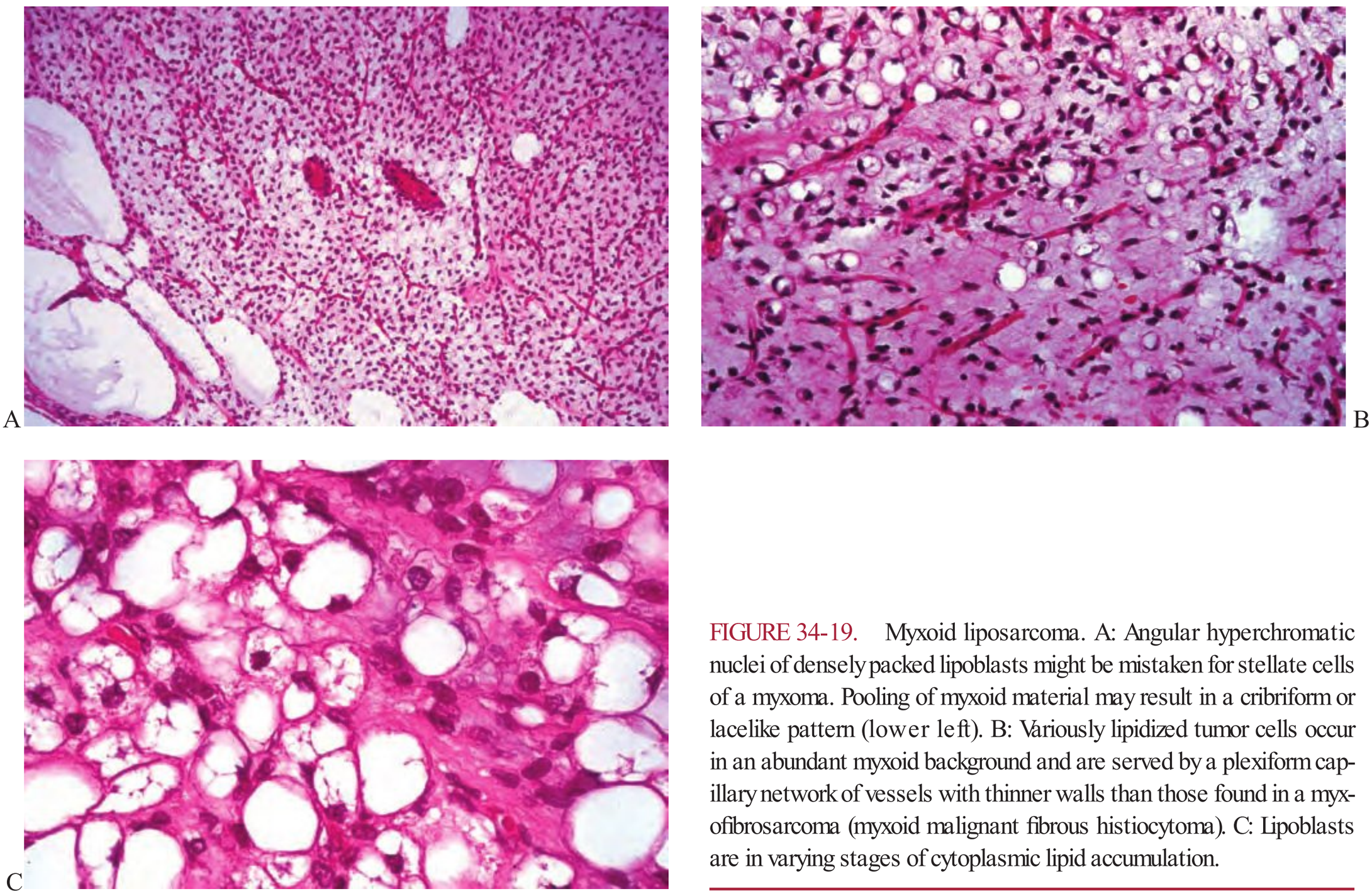


FIGURE 34-19. Myxoid liposarcoma. A: Angular hyperchromatic nuclei of densely packed lipoblasts might be mistaken for stellate cells of a myxoma. Pooling of myxoid material may result in a cribriform or lacelike pattern (lower left). B: Variously lipidized tumor cells occur in an abundant myxoid background and are served by a plexiform capillary network of vessels with thinner walls than those found in a myxofibrosarcoma (myxoid malignant fibrous histiocytoma). C: Lipoblasts are in varying stages of cytoplasmic lipid accumulation.

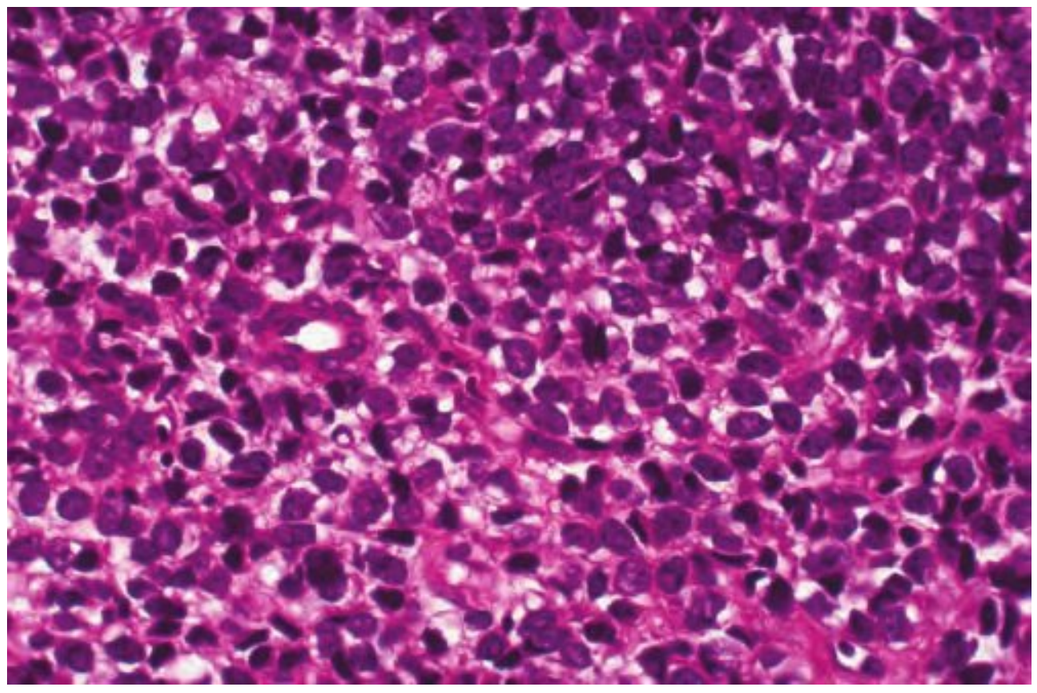


FIGURE 34-20. Round cell liposarcoma. Small, dark-staining tumor cells have little or no lipid accumulation. Because glycogen is involved in lipogenesis, these cells are PAS positive, and this should not be taken as evidence for Ewing's sarcoma.

Because of the more aggressive behavior of *round cell liposarcoma*, accurate diagnosis is important. As indicated by its name, round cell liposarcoma is characterized by an excessive proliferation of uniform, closely packed, rounded or oval cells, some of which contain no lipid. Others contain only small cytoplasmic vacuoles or a thin rim of clear cytoplasm (Fig. 34-20). These cells are vaguely reminiscent of Ewing's sarcoma (and, similarly, may contain glycogen), malignant lymphoma, or small cell anaplastic carcinoma. Their association with other patterns of liposarcoma points to their liposarcomatous nature. Multivacuolated lipoblasts are few in number. Most tumor cells have hyperchromatic and atypical nuclei, with frequent mitoses. This tumor can be thought of as a less-differentiated modification of liposarcoma in which the cells are largely incapable of lipid accumulation. At least focal transition toward the myxoid variant, or, less frequently, a well-differentiated or pleomorphic subtype, is always present. As indicated previously, these transitions are central to the correct diagnosis of round cell liposarcoma.

Myxoid and round cell liposarcoma account for about 30% to 35% of all liposarcomas and, even if still classified by the World Health Organization as two distinct subtypes, share both clinical and morphologic features. Lesions combining both patterns are frequent, and wide agreement exists in considering round cell liposarcoma as the high-grade counterpart of myxoid liposarcoma (122). Furthermore, myxoid and round cell liposarcoma share the same characteristic chromosome change represented most frequently by a reciprocal translocation t(12;16)(q13;p11) that fuses the CHOP gene with the TLS gene (129).

Clinically, myxoid and round cell liposarcoma tend to occur in the limbs, with a peak incidence ranging between the third and the fifth decade. In general, when more than 25% of the cellular elements are round cells, the diagnosis of round cell liposarcoma should be made. However, any more than 5% round cell component in a myxoid liposarcoma portends a higher risk of metastasis or death from disease (130). A peculiar tendency to metastasize to the soft tissue is observed that should not be interpreted as multicentricity (129).

Pleomorphic liposarcoma, an unlikely prebiopsy diagnosis (131), is characterized by a disorderly growth pattern, an extreme degree of cellular pleomorphism, and bizarre giant cells. Pleomorphic liposarcoma is a high-grade pleomorphic sarcoma, containing multivacuolated lipoblasts, which usually develops during late adult life. It usually occurs in the deep soft tissues and uncommonly arises in the subcutis, the dermis representing an exceedingly rare site of occurrence (132). Despite high-grade morphology, the intradermal tumor shows a relatively favorable prognosis (7). Diagnostic considerations include pleomorphic lipoma, clear cell atypical fibroxanthoma, balloon cell melanoma, and metastatic clear cell carcinoma of renal origin.

Two histologic variants of pleomorphic liposarcoma have been described. The majority of pleomorphic liposarcomas display limited numbers of lipoblasts admixed with smaller, polygonal, round or spindle-shaped cells with eosinophilic cytoplasm. Mitotic figures are usually rare. In any given microscopic field lacking a lipoblast, the separation of this entity from the pleomorphic storiform variant of malignant fibrous histiocytoma is difficult if not impossible. A less common variant contains giant lipoblasts. These extremely large cells have numerous cytoplasmic lipid droplets of variable size (Fig. 34-21). Multinucleation and amphophilia of the cytoplasm causes these cells to have the appearance of atypical mulberry cells; thus, the tumor is suggestive of a "malignant" hibernoma. No myogenic (skeletal or smooth) ultrastructural features as well as positivity for vimentin but not for desmin or alpha-smooth muscle actin are expected (133).

Whereas it is accepted that liposarcoma rarely occurs in the subcutaneous soft tissue, the dermis seems to represent an

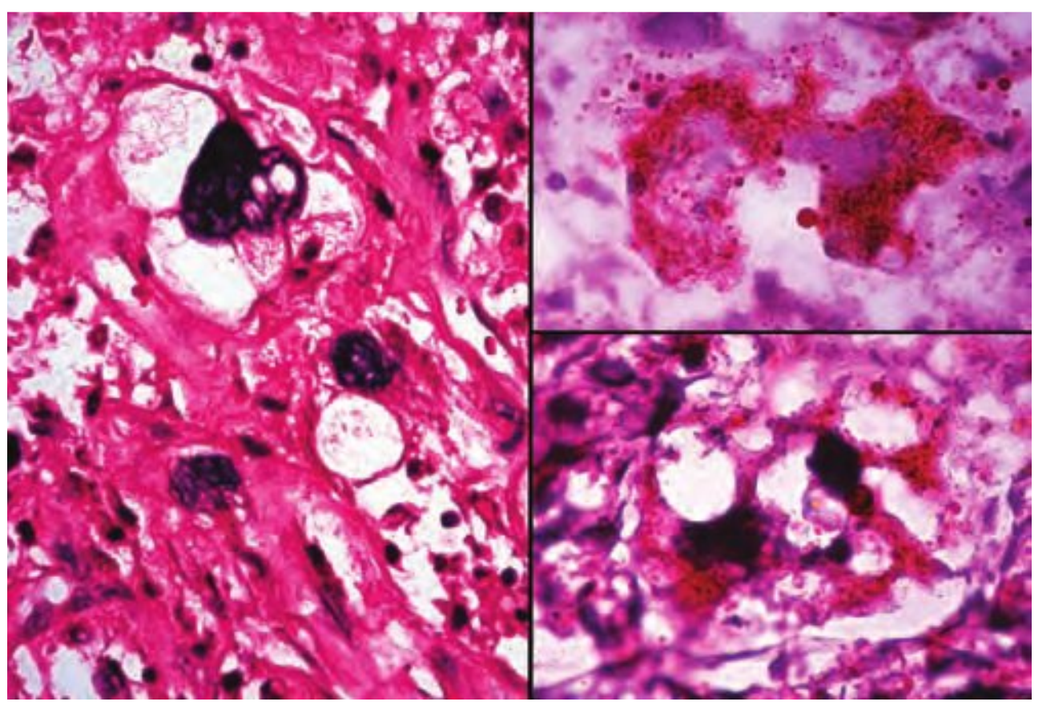


FIGURE 34-21. Pleomorphic liposarcoma. Multivacuolar lipoblasts have large, irregular hyperchromatic nuclei (left panel). The cytoplasmic lipid content of lipoblasts (lost in routine processing) can be demonstrated by frozen sections on fresh (top right panel) or formalin-fixed (bottom right panel) tissues stained with oil red O.

exceedingly rare site of occurrence (119). Exceptionally, liposarcoma occurs primarily in the skin, presenting clinically as a dome-shaped or polypoid lesion that despite an apparent tendency to show high-grade morphologic features seems to exhibit relatively indolent clinical behavior in this location (132).

A subtype of pleomorphic liposarcoma in which transition from low-grade to high-grade nonlipogenic morphology within a well-differentiated liposarcoma is observed (122) is known by the pathobiologically imprecise designation *dedifferentiated liposarcoma*. The interface between the two zones is usually abrupt. A peculiar biology is displayed, which at least in most cases shows neither "anaplasia" nor "dedifferentiation" but most likely "transdifferentiation" of part of the neoplastic cells to a cellular phenotype of a different mesenchymal differentiation lineage (134). A well-differentiated (lipoma-like) or myxoid liposarcoma (135) component has superimposed nonlipogenic areas resembling high-grade fibrosarcoma or malignant fibrous histiocytoma with the full range of potential patterns from storiform pleomorphic and myxoid to the less common giant cell and inflammatory forms. Less common are undifferentiated large round cells resembling carcinoma or melanoma, meningothelial-like whorls, (136,137) or myofibroblastic, rhabdomyosarcomatous, leiomyosarcomatous, even osteoblastic, differentiation. Dedifferentiated liposarcoma rarely exhibits heterologous (most often myoid) differentiation. A peculiar "neural-like whorling pattern" of dedifferentiation also has been described. Recently, it also has been proposed that dedifferentiated liposarcoma should be further classified into low and high grade. Surprisingly, the clinical outcome of dedifferentiated liposarcoma is less aggressive than in other high-grade pleomorphic sarcomas, but genetic as well as molecular data exist that may partially justify such a discrepancy (122).

The histologic subgroups of pleomorphic liposarcoma have not been shown to have prognostic value, perhaps because of the limited number of cases available for study. Its karyotype is complex (138). DNA flow analysis shows benign and low-grade liposarcomas to be diploid and high-grade tumors to be generally aneuploid, regardless of histogenetic type (139).

Differential Diagnosis. A poorly differentiated myxoid liposarcoma may contain very little lipid material. A lipid stain then often aids in the diagnosis. The demonstration of neutral lipid in cells with special stains (e.g., Sudan black, oil red O) on frozen sections of tumor tissue is insufficient for a diagnosis of liposarcoma unless lipoblasts are also found. Many other mesenchymal tumors and some carcinomas (e.g., of the kidney and adrenal) routinely contain fat, as do tumors injured by ischemia or radiation. The differential diagnosis of myxoid liposarcoma includes benign lesions, such as myxoid spindle cell lipoma, intramuscular myxoma, and lipoblastoma, and malignant ones, such as low-grade myxofibrosarcoma (a.k.a. myxoid malignant fibrous histiocytoma) and extraskeletal myxoid chondrosarcoma.

The main utility of immunohistochemistry in the diagnosis of liposarcoma is one of exclusion, because no specific or useful immunohistochemical marker has been found for malignant fatty tumors. Immunohistochemistry can be quite helpful in revealing the true identities of various sarcomas that may contain vacuolated bizarre cells, such as malignant schwannoma (S-100 protein), rhabdomyosarcoma (myoglobin), and leiomyosarcoma (desmin). But smooth muscle and even rhabdomyosarcomatous differentiation (140) can be found in primary liposarcoma. Alpha-1-antitrypsin and alpha-1-antichymotrypsin can be demonstrated in "malignant fibrous histiocytoma," regardless of subtype, and are constant and diagnostically useful characteristics. However, these markers may also be present in other spindle cell malignant tumors. By electron microscopy, cytoplasmic lipid is not membrane bound in liposarcoma, unlike in malignant fibrous histiocytoma (117). Late granulomatous reactions from silicone injection can cause an incorrect diagnosis of liposarcoma (141).

TUMORS OF SMOOTH MUSCLE

Smooth muscle in the skin serving as the substrate for tumors consists of arrector pili muscles, mural muscle of blood vessels, and specialized muscle in genital sites (i.e., scrotum [dartos], vulva, and nipple [areolar]).

SMOOTH MUSCLE HAMARTOMA

Smooth muscle hamartoma usually presents as a single patch that is several centimeters in diameter, on the extremities or trunk, most commonly in the lumbar region, and rarely scrotal (142). It may be present at birth or may arise in childhood or early adulthood (143). Usually, there are small, follicular papules throughout the patch, although the entire lesion may be slightly elevated and/or linear (144). Transient elevation (pseudo-Darier sign) can often be elicited on rubbing (145). Associated vermiform movements are rarely seen, suggesting that the lesion is acting as an innervated functional (although abnormal) unit (143). The patch shows hyperpigmentation and hypertrichosis in some patients (146) but not in others (147). If hyperpigmentation and hypertrichosis are present, an association with Becker's melanosis (see Chapter 28) exists (148). These two entities represent different poles of the same developmental spectrum of hamartomatous change (146). There is no known associated systemic involvement beyond being a potential component of the Michelin tire syndrome (see page 1060) or malignant transformation (143). Induration, hyperpigmentation, and localized hypertrichosis diminish with time (149).

Histopathology. Numerous thick, long, straight, well-defined bundles of smooth muscle fibers are scattered throughout the dermis and extend in various directions (Fig. 34-22) without the circumscription of a cutaneous leiomyoma. Smooth muscle bundles can be readily distinguished from collagen bundles by the trichrome stain, which stains smooth muscle red and collagen green or blue. The overlying basal layer is often pigmented,

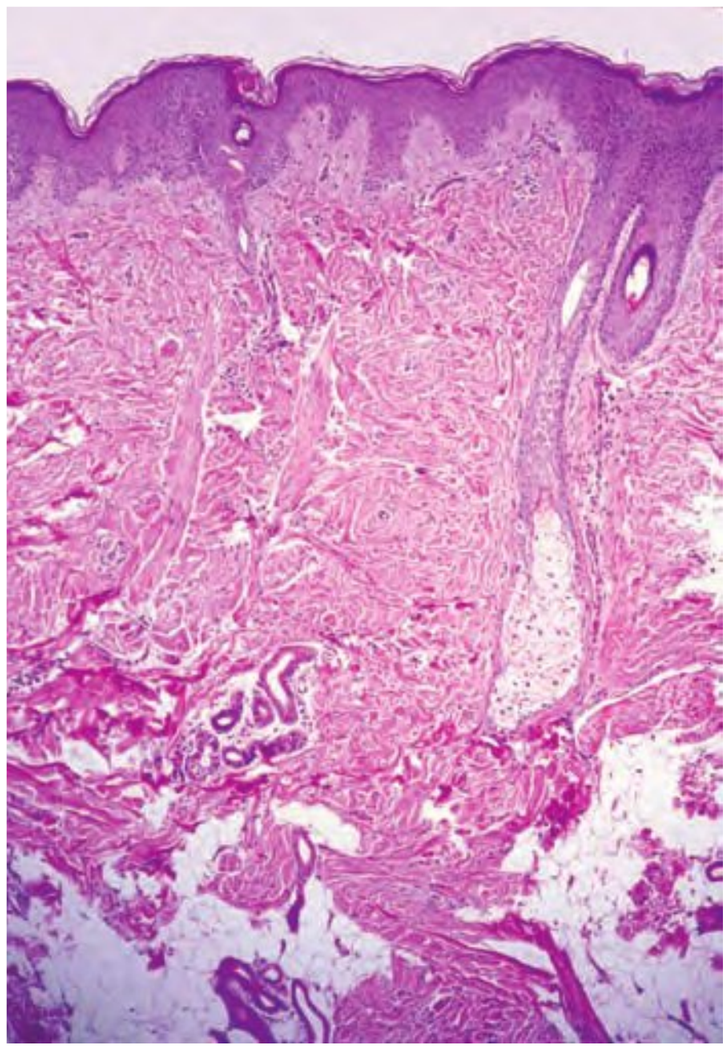


FIGURE 34-22. Smooth muscle hamartoma. Numerous thick, long, straight, well-defined bundles of smooth muscle fibers extend in various directions throughout the dermis.

and above that, hyperkeratosis and papillomatosis (143). Hypertrichosis, if present, is due to increased hair shaft diameter and length, not increased hair density (143). Some of the smooth muscle bundles show connections with large hair follicles (148).

Differential Diagnosis. The arrangement of the smooth muscle bundles in the dermis differs from that observed in piloleiomyoma, in which the smooth muscle bundles form a large aggregate.

Pathogenesis. In fetal life, hair muscles originate in a diffuse metachromatic zone of the mesoderm, near but not part of the fibroepithelial hair germ. Overproduction in these pilar fields may lead to stable hamartomatous overgrowths or progressive neoplasms (150). Intermediate lesions support the hypothesis that congenital smooth muscle hamartoma is one end of a spectrum of dermal smooth muscle proliferative disorders, with Becker's melanosis at the other end. However, the former is present at birth and the latter acquired beginning in the first or second decade, with hyperpigmentation preceding hypertrichosis (143).

LEIOMYOMA

The five types of leiomyomas of the skin are (a) multiple piloleiomyomas and (b) solitary piloleiomyomas, both arising from arrectores pilorum muscles; (c) solitary genital leiomyomas, arising from the dartoic, vulvar, or mammillary muscles; (d) solitary angioleiomyomas, arising from the muscles of veins; and (e) leiomyomas with additional mesenchymal elements.

Multiple piloleiomyomas, by far the most common type of leiomyoma, are small, firm, red or brown intradermal nodules arranged in a group or linear pattern, primarily affecting the trunk and extremities but may occur on the face and neck and rarely in the mouth (151). Lesions may run into the hundreds and cluster to form plaques, zosteriform groups, or, in symmetrical distribution (152,153), nevus leiomyomatosus systematicus (154). Often, two or more areas are affected. Usually, but not always, the lesions are tender and give rise to occasional painful paroxysms (150). Pain can be spontaneous or triggered by exposure to cold, pressure, trauma, or emotion (151). When multiple, excision of larger lesions and analgesics for pain, even oral nitroglycerin, phenoxybenzamine, nifedipine, and calcium channel-blocking drugs can be tried, either alone or in combination (151).

Uterine leiomyomas or erythropoietic activity are rare associations. Hereditary leiomyomatosis and renal cell carcinoma is an autosomal dominant familial syndrome characterized by the development of cutaneous and uterine leiomyomas as well as renal tumors, most often of the papillary type (155). The mutation of this condition has been identified in the fumarate hydratase (FH, 1q42.3-q43) gene. These renal tumors have a characteristic large nucleus with a very prominent inclusion-like orangophilic or eosinophilic nucleolus surrounded by a clear halo and are associated with poor prognosis (155), often with early metastasis despite small primary tumor size (156).

Solitary piloleiomyomas (157) are intradermal nodules that are usually larger than those of multiple piloleiomyomas, measuring up to 2 cm in diameter. Females predominate. Congenital occurrence is rare. Most of them are tender and also occasionally painful (158). Simple excision may suffice for one or a few lesions (151).

Genital leiomyomas originate from the dartoic, vulvar, or mammary smooth muscle (159). Solitary genital leiomyomas are located on the scrotum, labia majora (160,161), or, rarely, nipples (160). Supernumerary breasts (polymastia) and supernumerary nipples (polythelia areolaris) are not uncommon along the course of the embryologic milk line. This extends from the anterior axillary fold to the inner thigh on either side of the midline. Supernumerary breast tissue (160) or aberrant areolae (159) located outside the milk line are extraordinary. Genital leiomyomas are intradermal, and in contrast to the other leiomyomas, most are asymptomatic (158).

Solitary angioleiomyomas are usually subcutaneous and only rarely intracutaneous in location. As a rule, they do not exceed 4 cm in diameter. The lower extremities are the most common site. Pain and tenderness are evoked by most, but not all, angioleiomyomas (150).

The rare *cutaneous angiolipoleiomyoma* is an acquired asymptomatic tumor and always acral. The lesion has a strong male rather than female predilection (162). Unlike the renal counterpart, there is no association with tuberous sclerosis. Recurrence after surgery is not anticipated.

Histopathology. Piloleiomyomas, whether multiple or solitary, and genital leiomyomas are similar in histologic appear-

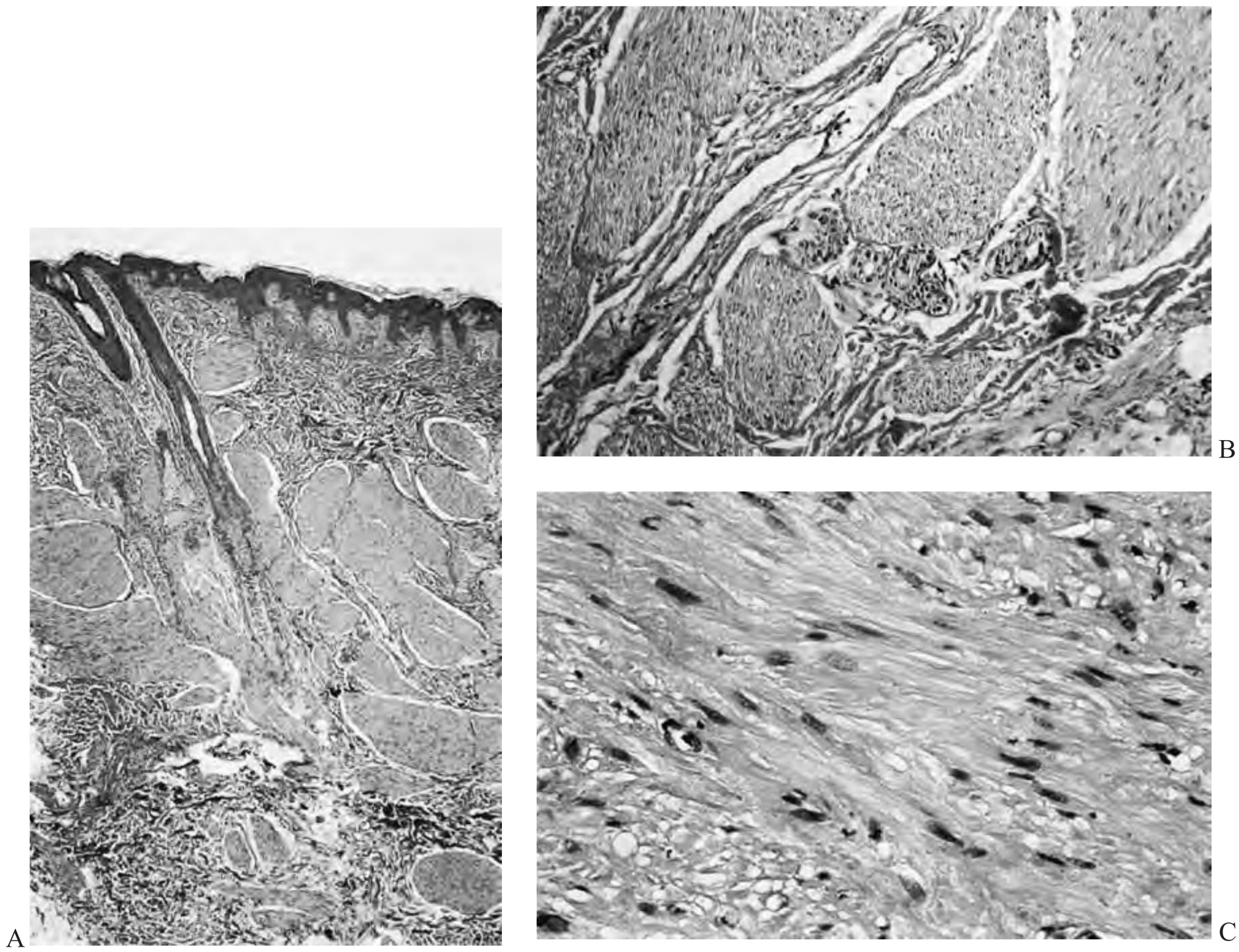
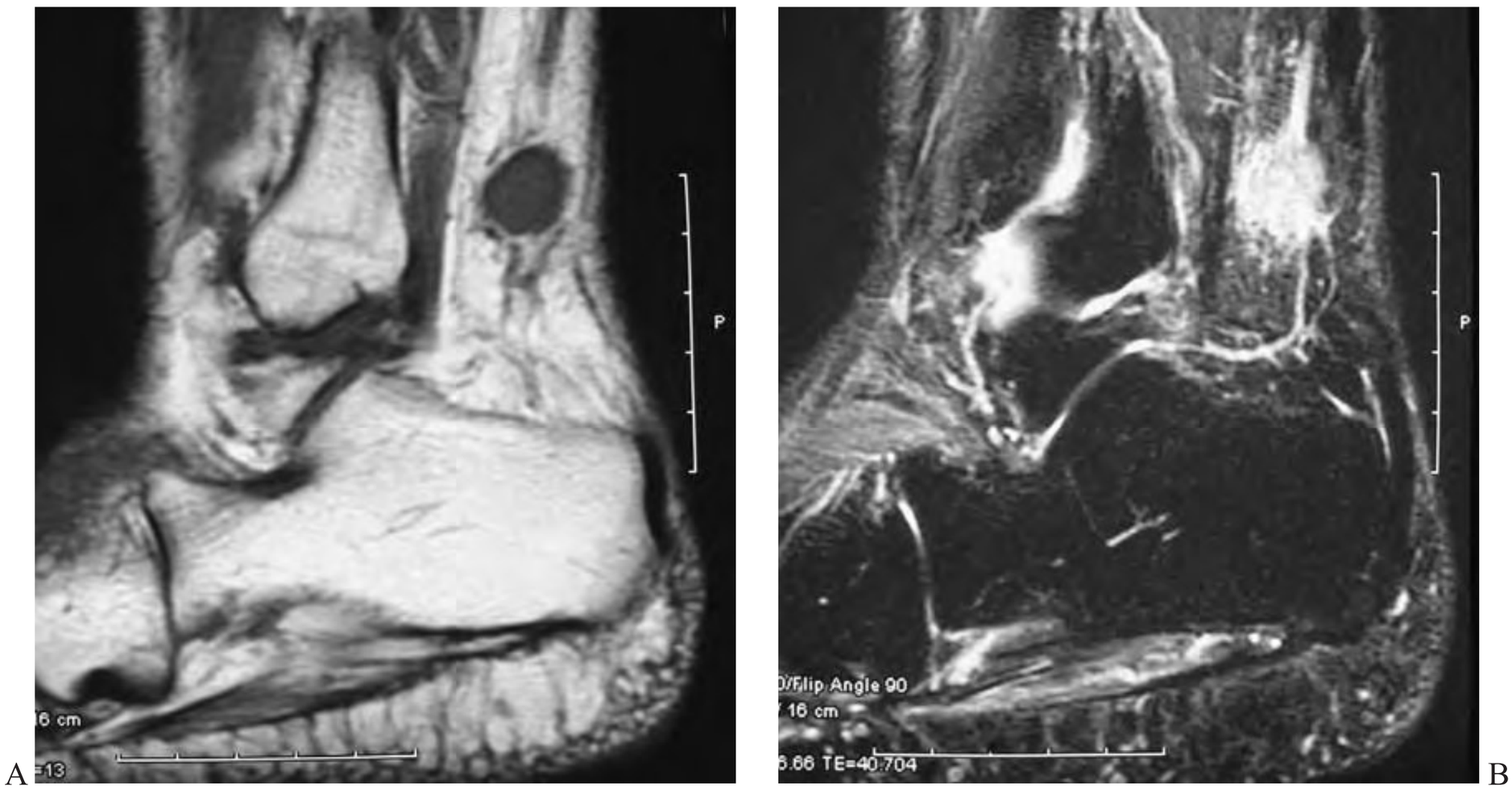


FIGURE 34-23. Piloleiomyoma. A: Bundles of smooth muscle interlace around follicular structures in the dermis. B: Well-defined smooth muscle bundles resembling pilar muscles surround sweat gland coils. C: Benign smooth muscle cells have some variation in nuclear size and chromaticity, blunt nuclear ends, and no conspicuous mitotic activity.

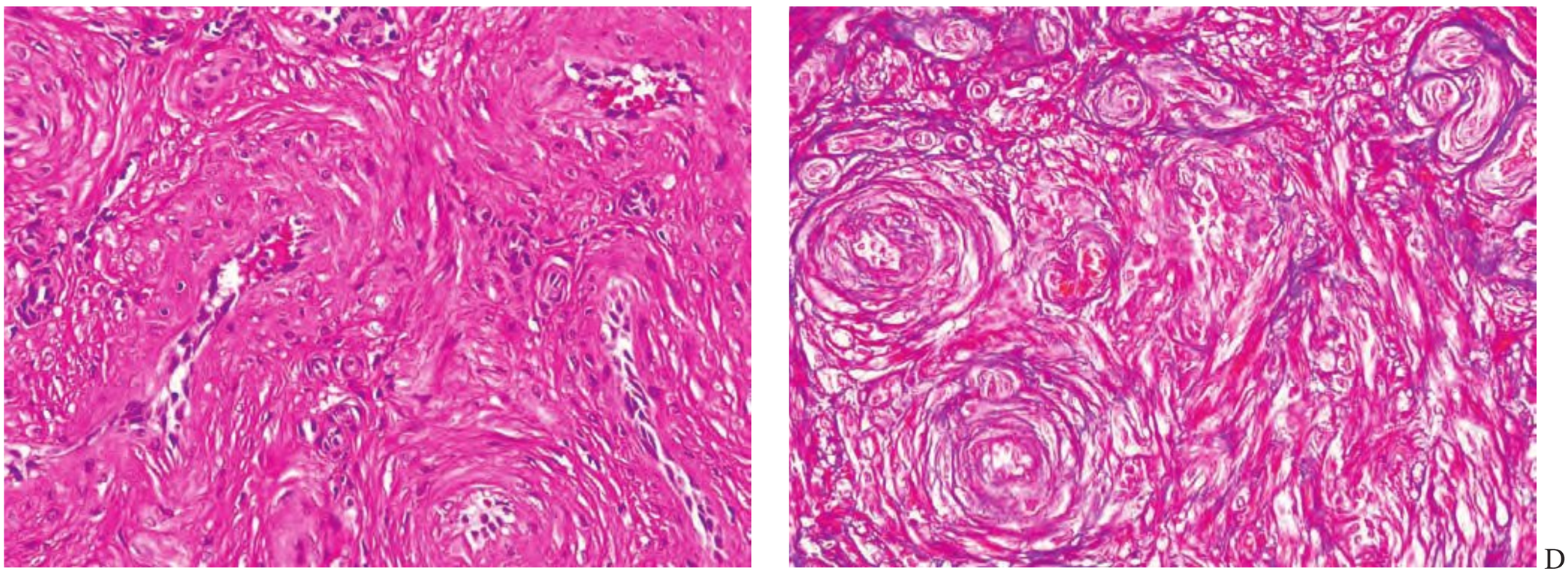
ance (158). They are poorly demarcated and are composed of interlacing bundles of smooth muscle fibers with which varying amounts of collagen bundles are intermingled (Fig. 34-23). The muscle fibers composing the smooth muscle bundles are generally straight, with little or no waviness; they contain centrally located, thin, very long, blunt-edged, "eel-like" nuclei. Overlying epidermal hyperplasia is seen in about half. Hair follicles may persist in the lesion (163). Rare variants show granular (164) or clear cell (165) change.

Leiomyomas of arrector pili origin may exhibit a low mitotic activity of <1 per 10 high-power field (HPF), and this does not adversely affect the prognosis for these patients (166). Pleomorphic multinucleated tumor giant cells can occur in cutaneous "symplastic" leiomyomas (167) and pleomorphic angioleiomyoma (168), but more commonly in the uterus. Vulval leiomyomas express estrogen and progesterone receptors, unlike pilar tumors (169).

Angioleiomyoma presents as a painful mass in approximately 60% of cases. One distinct clinical feature is the increase in size of the swelling with physical activity of the involved part, especially in the hand. It should be considered in the differential diagnosis of painful nodular lesions of the extremity (170). *Angioleiomyomas* differ from the other types of leiomyomas in that they are encapsulated and contain numerous vessels (Fig. 34-24). As a rule, they contain only small amounts of collagen (Fig. 34-24D). The numerous veins that are present vary in size and have muscular walls of varying thickness. On this basis, angioleiomyomas have been subdivided into a capillary or solid type, a cavernous type, and a venous type (171). In the capillary type, the vascular channels are numerous but small. Tumors of the cavernous type are composed of dilated vascular channels with small amounts of smooth muscle. Tumors of the venous type exhibit veins with thick muscular walls. In venous tumors, smooth muscle cells extend tangentially from the peripheries of the veins and merge with the intervascular tumor substance (Fig. 34-24C). The veins usually have a rounded or slitlike lumen, but some, because of contraction of their muscular tissue, have a stellate lumen. The veins have no elastic lamina. Areas of mucinous alteration are often present, especially in large angioleiomyomas. The smooth muscle may exhibit pleomorphism (171). An intravascular variant is rare (172).



A B



C D

FIGURE 34-24. Angioleiomyoma (posterior ankle mass in a 73-year-old man diagnosed by correlation of a needle biopsy specimen with MRI). A: A T1-weighted sagittal MRI highlights high signal tissue (fat) but not the nodule behind distal fibula, anterior to the Achilles tendon, excluding lipoma. B: A STIR-weighted image, fat suppression sequence highlights fluid content and therefore the blood in a vein that is interrupted by the high signal (i.e., well-vascularized) nodule. C: Smooth muscle of vessel walls merges without borders into intervening muscle. D: Myoplasm is bright red in a Masson trichrome stain, while modest blue-staining collagen outlines vessel walls.

Lipoleiomyomas comprise long, intersecting bundles of bland, smooth muscle mixed with the additional mesenchymal element of nests of mature fat cells (173). *Cutaneous angiolipoleiomyoma* could arguably be considered an angioleiomyoma with fat cell modulation (Fig. 34-25). However, elastic laminae completely or partially rim the vascular channels and are absent in angioleiomyomas. These subcutaneous, well-circumscribed tumors are composed of benign smooth muscle, vascular spaces, connective tissue, and mature fat, which may predominate. Masson trichrome will separate the muscular from fibrous components that are invariably present. The smooth muscle cells have a more mature fascicular arrangement than in the renal analog. Blood vessels in these subcutaneous well-circumscribed tumors intermittently have an elastic lamina (Fig. 34-25C) (162). Cutaneous angiolipoleiomyomas are unreactive for HMB-45, in contrast to renal and extrarenal angiomyolipoma (162,164,174), yet have been reported under the term *angiomyolipoma* (174,175).

The muscle bundles of various leiomyoma variants stain pink with H&E, just as collagen does, but can be distinguished from collagen bundles by the following differences in appearance. The nuclei of the fibroblasts located in the collagen are

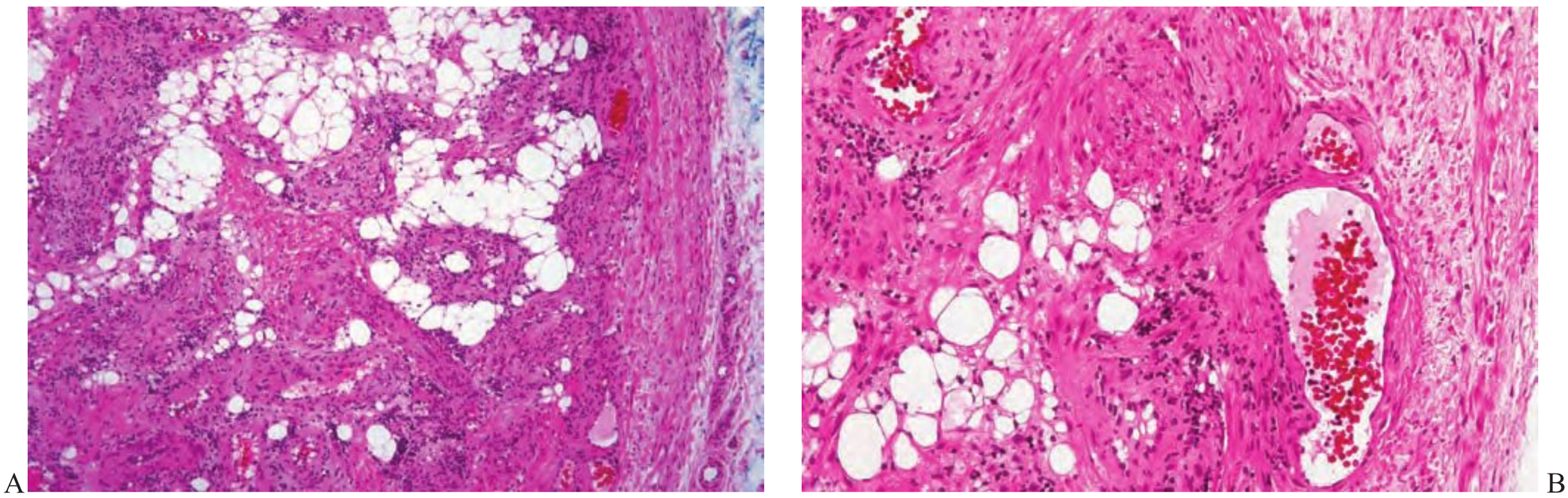


FIGURE 34-25. Angioleiomyoma with fat (51-year-old man; nonpainful 1.5-cm knee "cyst" present 10 years but enlarging). A: A well-circumscribed nodule has prominent vascular spaces, redundant smooth muscle, and much mature fat. B: The smooth muscle cells have a fascicular arrangement. C: Elastic lamina partly rim a representative vascular channel (elastic tissue stain).

shorter than the nuclei located in the smooth muscle fibers and show tapering at their ends, whereas smooth muscle nuclei tend to have blunt ends; the cytoplasm of the smooth muscle cell is more conspicuous than in quiescent fibroblasts. In contrast to collagen bundles, smooth muscle bundles usually show slight vacuolization, especially in cross-sections, as a result of a perinuclear clear zone. Reliable differentiation between muscle and collagen bundles is possible with the aid of one of the collagen stains, such as the aniline blue stain or the trichrome stain. With the aniline blue stain, muscle stains red and collagen blue; with the trichrome stain, muscle stains dark red and collagen green or blue. The Masson technique is superior to that of Gamori. Longitudinal intracytoplasmic myofibrils often can be visualized as striations in H&E sections and can be more easily resolved if stained with phosphotungstic acid–hematoxylin, where they appear as purple threads.

Differential Diagnosis. The discrete bundles set in dermal collagen of smooth muscle hamartoma are unlike the circumscription of most cutaneous leiomyomas and the scant intralesional collagen common in the multiple papular variant of pilar leiomyoma (176). The differential diagnosis of angiolipoleiomyoma includes angiolipoma with fibrosis (lacks muscle on Masson trichrome), angioleiomyoma (usually lacks elastic laminae and has female predominance), arteriovenous hemangioma (but it is uncircumscribed and without a fibrous pseudocapsule, fascicles of smooth muscle and intermixed lipocytes), and even cavernous hemangioma (but with larger vascular spaces having thinner walls and no surrounding fascicles of smooth muscle or fibrous pseudocapsule) (162). The histologic differential diagnosis of lesions with an intravascular growth pattern includes intravascular angioleiomyoma, intravascular pyogenic granuloma, papillary endothelial hyperplasia, reactive angioendotheliomatosis, intravascular nodular fasciitis, hemangiopericytoma, and intravascular glomus tumor (172). *Palisaded angioleiomyoma*, a histopathologic variant of angioleiomyoma with prominent Verocay body formation, should be added to the ever-expanding list of tumors that demonstrate nuclear palisades, along with neurilemoma, but immunohistochemistry gives positive reactions for actin and desmin and is negative for S-100 (177).

Pathogenesis. Arrectores pilorum gives rise to smooth muscle tumors. Electron microscopic examination has shown that piloleiomyomas are composed of normal-appearing smooth muscle cells. Each of these cells has a central nucleus surrounded by an area containing endoplasmic reticulum and mitochondria and, peripheral to this area, numerous myofilaments arranged in bundles. Both cytoplasmic and marginal dense bodies are present. The cause of the frequent pain or tenderness has not been satisfactorily determined. Some authors have observed, by electron microscopy, ultrastructural damage to nerve fibers through distortion and disruption of the myelin sheath (178), and only scanty unmyelinated nerve fibers (179) are postulated factors. It

is probable, therefore, that the pain is a result of muscular contractions. Familial cases of multiple piloleiomyomas have been reported in autosomal dominant–incomplete penetrance mode (151). Since cutaneous leiomyomas show no positive staining for ER-1D5 or PGR-1A6 antibodies, the tumorigenesis of cutaneous leiomyomas does not appear to be related to estrogen or progesterone receptor-mediated effects (169).

LEIOMYOSARCOMA

Among 26,758 soft tissue sarcomas, leiomyosarcomas have accounted for 23.9%, malignant fibrous histiocytomas 17.1%, liposarcomas 11.5%, dermatofibrosarcomas 10.5%, rhabdomyosarcomas 4.6%, and angiosarcomas 4.1%. Almost half (47.9%) of the sarcomas arose in the soft tissues, *14.0% in the skin* and 7.0% in the uterus (180). Cutaneous leiomyosarcoma is a rare soft tissue sarcoma with negligible metastatic potential, but local recurrence rates after surgical excision have ranged from 14% to 42% (181). Unlike other sarcomas, guidelines for the optimal surgical excision margin of cutaneous leiomyosarcoma are not clearly defined in the existing literature (181).

Leiomyosarcomas, malignant nonepithelial tumors with smooth muscle differentiation, are generally deemed to be derived from mural smooth muscle cells of vessels or in viscera such as the uterus or stomach, the urogenital system, or in the retroperitoneal space. Leiomyosarcomas of the dermis and subcutaneous tissues are rare, accounting for $<$5% of all soft tissue sarcomas in adults. Superficial leiomyosarcomas are most common in the fifth and sixth decades of life, and reports differ as to whether there is (182) or is not (183) a male predominance.

Cutaneous leiomyosarcomas (Fig. 34-26) exhibit a predilection for proximal extremity extensor surface location (184), which coincides with the areas of greatest hair distribution. They are believed to derive from the arrector pili muscles, from smooth muscle that surrounds sweat glands in the nearby adipose tissue, or from vessel walls (183). Clinically, a solitary red-pink nodule may be painful or tender (150) but only rarely ulcerates. In some cases, several nodules are present, but this should arouse suspicion of metastases, for example, from a retroperitoneal, uterine, or alimentary tract primary (185), which favor the scalp and back. Leiomyosarcoma has been reported in an ectopic areola (186). Radiation dermatitis (187), trauma, lupus vulgaris, and origin in an angioleiomyoma (188) are other associations for leiomyosarcoma.

Subcutaneous leiomyosarcomas (189) are deemed to be vascular in origin and analogous to angioleiomyomas. Radiation dermatitis may be a substrate here as well (187). They are subcutaneous nodules or diffuse swellings over which the nondiscolored skin usually is freely movable. They cause pain of a local or radiating nature in only a few patients. Wide surgical excision of leiomyosarcoma with close follow-up is recommended (183), as local recurrence is common (40%–60%), with inadequate excision as the presumed risk factor (181). They are relatively radioresistant, according to a small number of treated cases (182,190).

The division of superficial leiomyosarcoma into two distinctly different histogenetic and prognostic categories (cutaneous and subcutaneous) (191) is more significant in predicting metastatic potential than is mitotic activity (182). Cutaneous leiomyosarcomas have a good prognosis. When confined to the dermis, the sarcoma may recur in up to half of all cases. Metastases to regional lymph nodes may occur, but they are not usually fatal (181). In at least one reported instance, however, distant metastases ultimately led to the death of the patient (185). Subcutaneous leiomyosarcomas are more aggressive, exhibiting a higher growth rate, greater recurrence (40%–60%), metastatic potential (30%–60%), and ultimately fatal outcome (30%–40%) than their cutaneous counterparts (181). Subcutaneous leiomyosarcoma may cause hematogenous metastases, usually to the lungs (182) but only rarely to lymph nodes, and lead to death in about one third of patients (182). Aneuploid tumors are more prone to metastasize than diploid (192).

Purely subcutaneous leiomyosarcomas must be differentiated from leiomyosarcomas involving skeletal muscle or fascia, which can present as a skin or subcutaneous tumor (Fig. 34-27) and are often fatal (193). In assessing depth, remember that subcutaneous leiomyosarcoma may invade the dermis and that cutaneous leiomyosarcoma generally is contained within the dermis, although larger lesions may extend into the adjacent subcutis and epidermis (181). MRI may be helpful in the distinction (Fig. 34-27A).

Vulvar and *scrotal leiomyosarcomas* tend to be larger and better circumscribed than those in skin or subcutaneous locations. Their traditional inclusion under the general heading of cutaneous leiomyosarcoma has been challenged (191,193). Vulvar smooth muscle tumors that manifest three or all of the four following features should be considered sarcomas: (a) $\geq$5 cm in greatest dimension, (b) infiltrative margins, (c) $\geq$5 mitotic figures per 10 HPF, and (d) moderate to severe cytologic atypia. Those that have only one of these characteristics should be diagnosed as leiomyoma, and those that exhibit only two of these features should be considered benign but atypical leiomyomas (194). The sarcomas should be excised with wide negative margins; the leiomyomas and the atypical leiomyomas should be excised conservatively, with long-term, careful follow-up.

Histopathology. Cutaneous leiomyosarcomas (Fig. 34-26) vary from moderately well to poorly delimited, nodular or diffuse (195) intradermal tumors that may extend into the subcutaneous tissue. In the center, the tumor shows nodular aggregates and densely packed, interlacing bundles of smooth muscle cells. At the margin of the tumor, strands of smooth muscle cells extend between collagen bundles. Cutaneous leiomyosarcomas, with their fascicular, infiltrative, peripheral growth pattern, presumably are derived from arrectores pilorum muscles (182). Minimal criteria for malignancy in a well-differentiated lesion include crowded cellularity, some plump and hyperchromatic nuclei constituting cellular atypia, irregular extension into dermis, and a few mitoses (Fig. 34-26C). Areas of lesser differentiation are present in all tumors, although to varying degrees. They show numerous irregularly shaped, anaplastic nuclei and usually also atypical giant cells with bizarre nuclei (182) (Fig. 34-27).

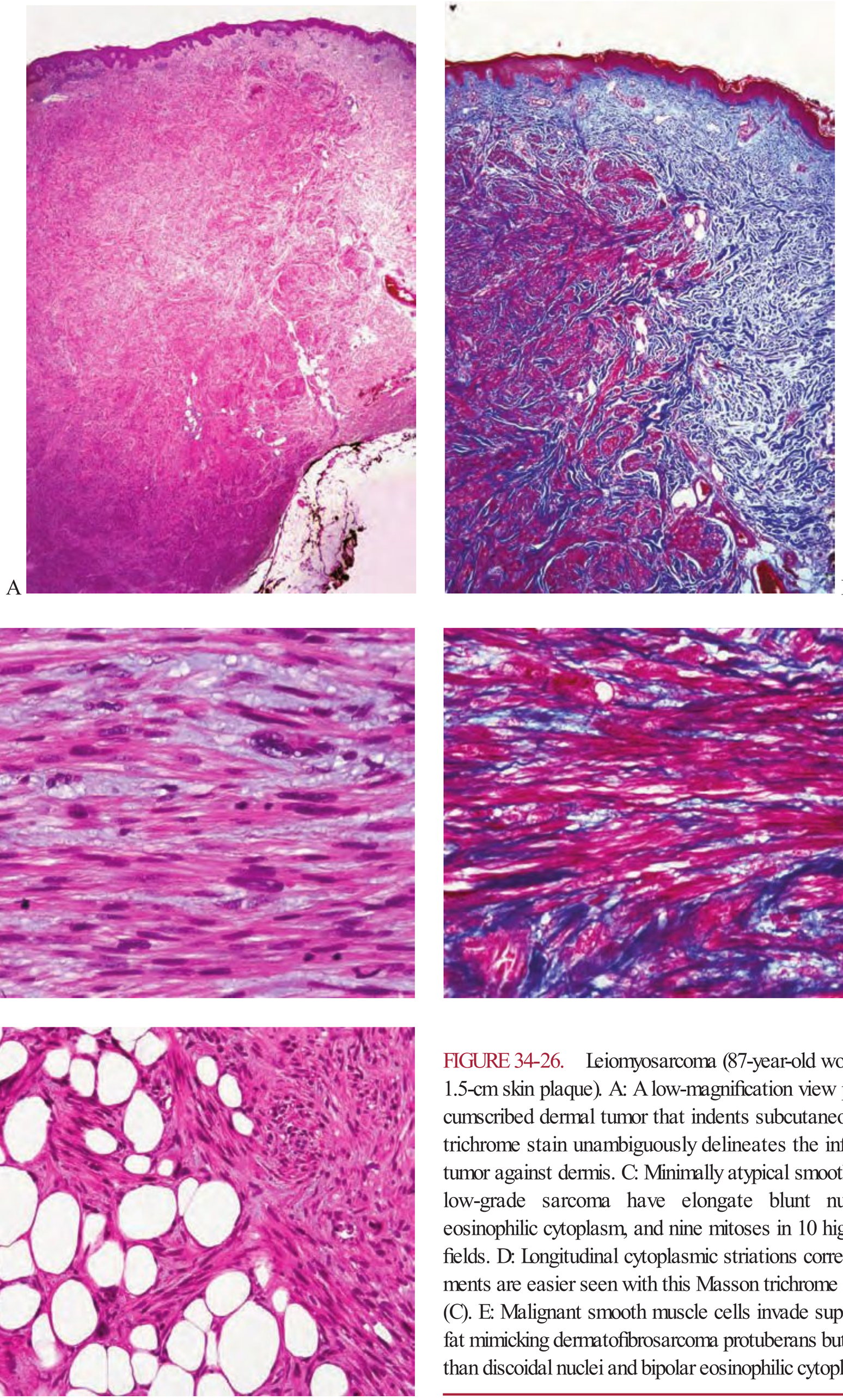
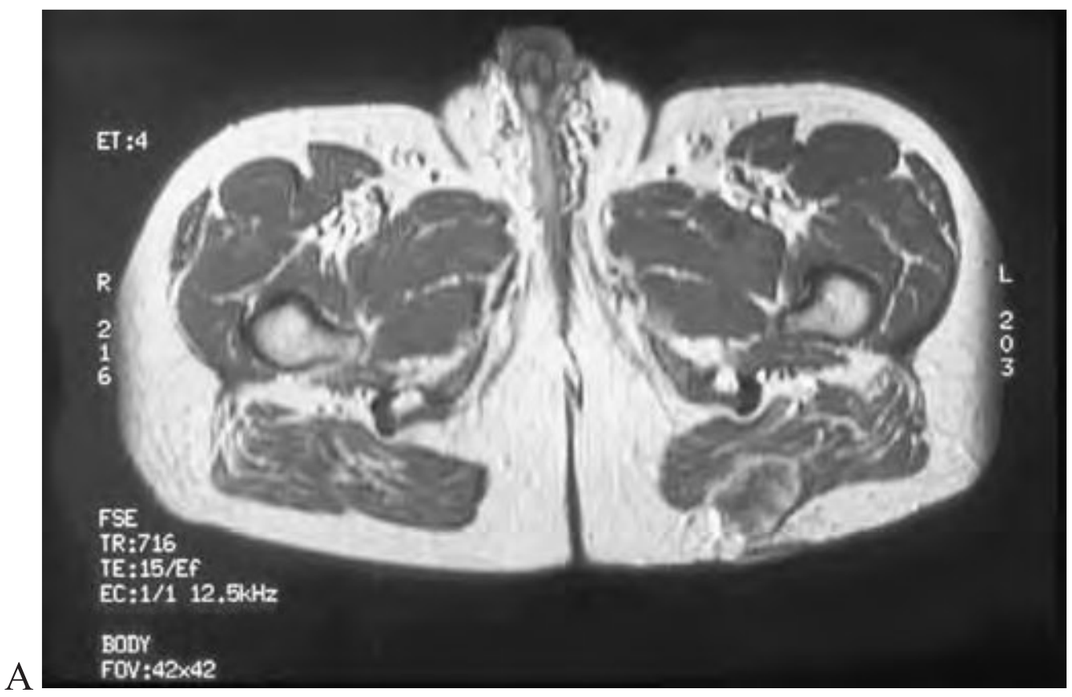
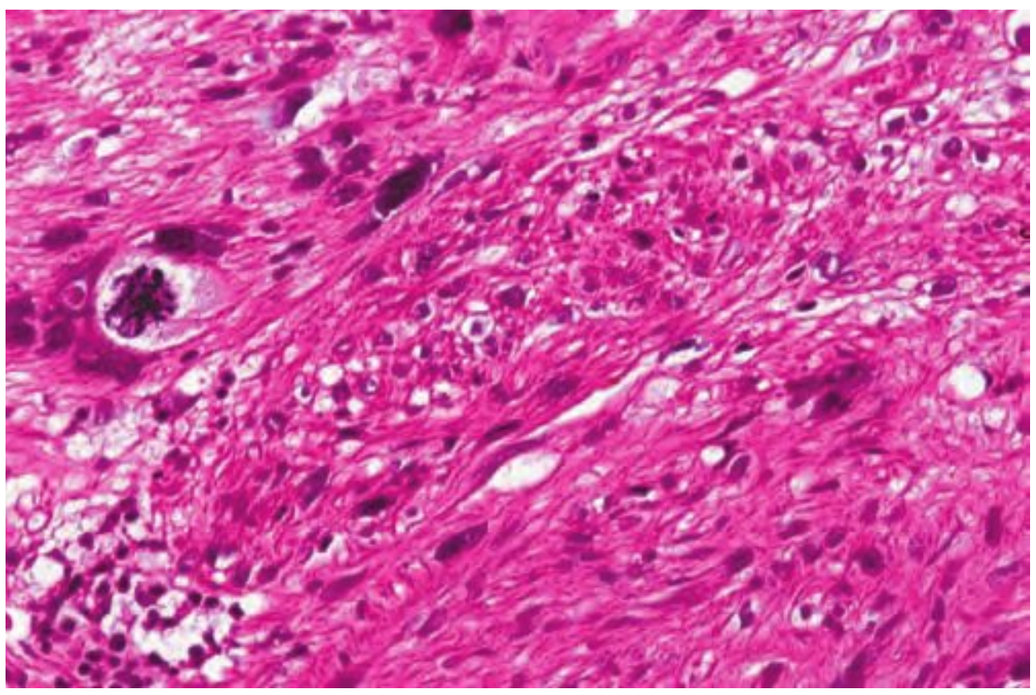


FIGURE 34-26. Leiomyosarcoma (87-year-old woman; rapidly growing 1.5-cm skin plaque). A: A low-magnification view presents a poorly circumscribed dermal tumor that indents subcutaneous fat. B: A Masson trichrome stain unambiguously delineates the infiltrative front of this tumor against dermis. C: Minimally atypical smooth muscle cells of this low-grade sarcoma have elongate blunt nuclei, conspicuously eosinophilic cytoplasm, and nine mitoses in 10 high-power microscopic fields. D: Longitudinal cytoplasmic striations correlating with actin filaments are easier seen with this Masson trichrome stain than in the H&E (C). E: Malignant smooth muscle cells invade superficial subcutaneous fat mimicking dermatofibrosarcoma protuberans but have elliptical rather than discoidal nuclei and bipolar eosinophilic cytoplasmic extensions.

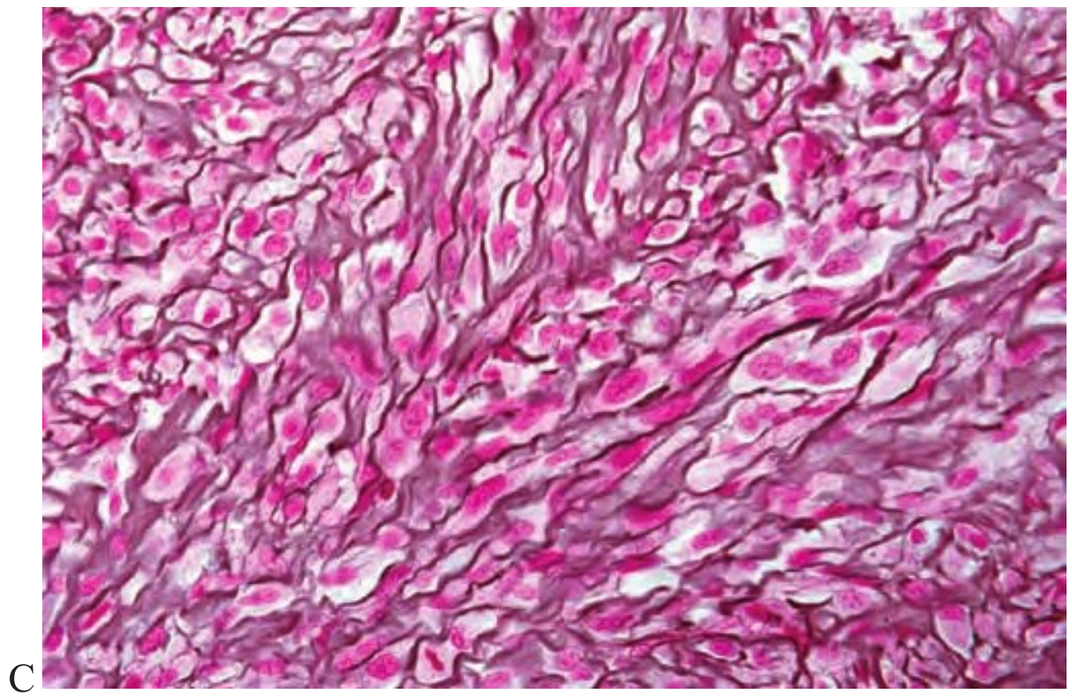
Still, the nature of the sarcoma usually can be established even in rather anaplastic tumors, because in some areas, there are bundles of fairly well-differentiated smooth muscle cells in which delicate myofibrils can be revealed by staining with phosphotungstic acid–hematoxylin (80) or trichrome. Epithelioid leiomyosarcoma, mainly occurring in the uterus, can rarely occur in the extremity soft tissue, skin, superficial veins and venules of the skin, and subcutis (196). Granular cell (197), inflammatory (198), and desmoplastic (199) leiomyosarcoma are other rare variants.



A



B



C

FIGURE 34-27. Intramuscular leiomyosarcoma (45-year-old male; nodule on buttocks noted on sitting; within 2 years of excision and local irritation, he had removal of 2 lung metastases and is alive with no evidence of disease now 5 years and 3 months after the original excision). A: Two thirds of an oval 4 × 5-cm buttock mass is within skeletal muscle, favoring its origin there, with secondary extension to subcutaneous fat where a biopsy might be mistaken for a superficial tumor. B: Substantial atypia and bizarre mitoses characterize this high-grade leiomyosarcoma that manifests brightly eosinophilic cytoplasm. C: A delicate reticulin network envelopes each tumor cell (reticulin stain).

The number of mitoses may be high in anaplastic areas even when there will be no metastases. A given leiomyosarcoma may have "mitotic hot spots" that might not be represented in single samples. Percentage of S-phase cells correlates with mitotic count but, like absence of desmin reactivity, is not predictive of patient survival (192). Although notable mitotic rate remains the main criterion for leiomyosarcoma (e.g., three or more per 10 HPF) (200), other histopathologic features of the tumor are important, as with uterine leiomyosarcoma (201), including atypical smooth muscle cells with peripheral extension into the surrounding tissue, pleomorphism, giant cells, and necrosis (182). Antidesmin positivity is found in 47% to 85% of superficial leiomyosarcomas and less common in higher-grade tumors. For those rare tumors in which routine histology and immunohistochemistry fail to provide a classification, electron microscopy offers another means for diagnosis (192).

Subcutaneous leiomyosarcomas may be well circumscribed and partially surrounded by a compressed rim of connective tissue. Irregular aggregates of more or less atypical smooth muscle cells can be seen intertwining haphazardly without the fascicular pattern characteristic of cutaneous leiomyosarcomas. Subcutaneous leiomyosarcomas show endothelium-lined, thin-walled blood vessels with variously shaped but often large lumina surrounded by smooth muscle cells (182). Vascular invasion is an adverse finding (202). Mitoses should be easily found. Osteoclast-like giant cells (203) or myxoid change (204) should not deter diagnosis. No correlation seems to exist between the degree of histologic malignancy of the tumor and metastases, which occur in up to 40% of cases (193). DNA content, as determined by flow cytometry, was a strong predictor of metastatic potential in one study (192). Involvement of underlying muscular fasciae or skeletal muscle is a likely harbinger of metastases (193).

Pathogenesis. Immunohistochemical staining of deparaffinized sections shows expression of desmin in all cutaneous leiomyosarcomas and of muscle-specific actin in the great majority (185). Only about half of the subcutaneous leiomyosarcomas show significant numbers of tumor cells that are positive for desmin and actin (193). These smooth muscle markers may be demonstrated in "myofibroblastic" lesions and therefore are not absolute diagnostic criteria. Some hold that ultrastructural study is a more reliable means for definite identification. Positivity for cytokeratin may be found and is attributed to "phenotypic shift" in terms of vimentin and cytokeratin expression for the supposed muscle of origin (205). Losses in the 13q4-21 region are the most frequent abnormality (206).

Electron microscopic examination has shown that the tumor cells have the characteristics of smooth muscle cells even when there is marked nuclear atypicality. Thus, the tumor cells show skeins of intermediate filaments punctuated by dense bodies, subplasmalemmal plaques, pinocytotic vesicles, and

external pericellular lamina (184,194). However, in some instances, the basal lamina is discontinuous (185).

Differential Diagnosis. The presence of bizarre giant cells in cutaneous leiomyosarcomas may cause a resemblance to malignant fibrous histiocytoma and atypical fibroxanthoma. However, at least in some areas, there are greatly elongated, thin, blunt-ended nuclei characteristic of smooth muscle cells. Also, demonstration of the enhancement of longitudinal striation due to myofibrils by staining with trichrome or phosphotungstic acid–hematoxylin will aid in the differentiation. The same holds true for subcutaneous leiomyosarcomas, in which the presence of endothelial-lined vessels may suggest a hemangiopericytoma. The more extended histologic differential diagnosis includes fibrosarcoma, rhabdomyosarcoma, dermatofibroma, dermatofibrosarcoma protuberans, malignant schwannoma, nodular fasciitis, and synovial sarcoma.

RHABDOMYOMATOUS MESENCHYMAL HAMARTOMA OF SKIN (STRIATED MUSCLE HAMARTOMA)

Rhabdomyomatous mesenchymal hamartoma of the skin, or striated muscle hamartoma, is a rare lesion that principally occurs in the face and neck of newborns but can present in adults as well (207). The typical presentation is as a small, solitary, dome-shaped papule or a polypoid pedunculated lesion, from a few millimeters to 1 to 2 cm. There is a strong male predominance. Hamartomas containing skeletal muscle have rarely been reported outside of the head and neck region (208).

Histopathology. Single or small groups of mature-appearing skeletal muscle fibers lie in the dermis and subcutaneous tissue below the normal epidermis. Mature fat, nerves, and adnexal structures may be admixed, and central calcification or ossification may be noted (209).

Differential Diagnosis. Fibrous hamartoma of infancy will have fat but not skeletal muscle fibers. Benign Triton tumor (neuromuscular choristoma), a rare subcutaneous, peripheral nerve-associated lesion, is composed of mature skeletal muscle and neural tissue. Juvenile rhabdomyoma has round and polygonal cells. A cutaneous embryonal rhabdomyosarcoma will show much less differentiation.

RHABDOMYOMA

Rhabdomyomas are extremely rare benign tumors of striated muscle (210) that are divided into cardiac and extracardiac types, which are then further subtyped on the basis of clinical and morphologic differences. *Adult-type rhabdomyomas* are slowly growing lesions that nearly always occur in the head and neck areas of older persons (Fig. 34-28). *Fetal-type rhabdomyomas*

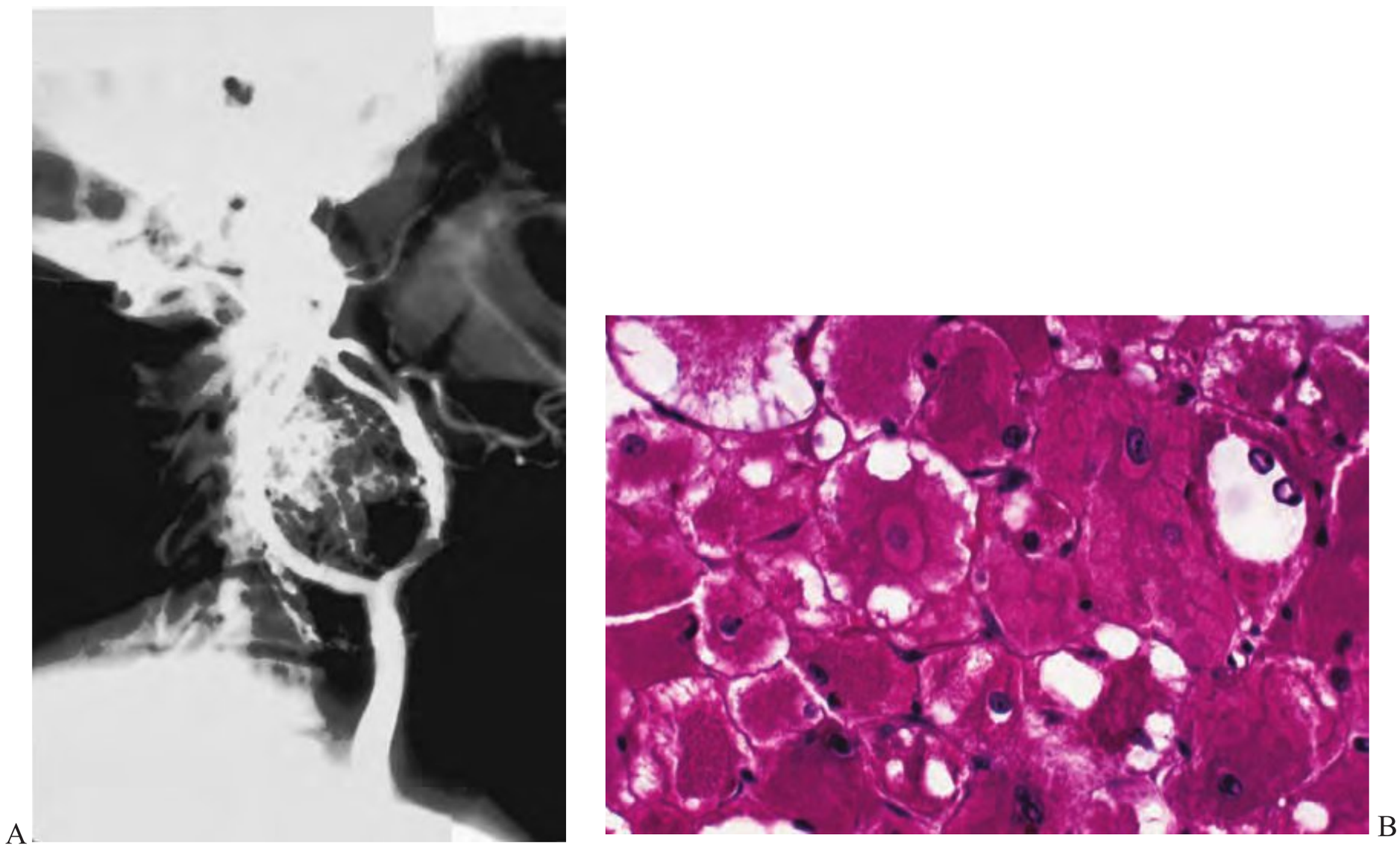


FIGURE 34-28. Adult-type rhabdomyoma (55-year-old man; 4-cm lateral neck mass). A: A hypervascular mass splays the carotid bifurcation in this carotid angiogram. B: Variably sized, deeply eosinophilic polygonal cells comprising this tumor have peripherally situated nuclei. Cytoplasmic cross-striations may be seen. Tissue processing removes intracellular glycogen and results in the pronounced vacuolated appearance of many of the cells. This lesion should not be mistaken for a granular cell tumor.

occur in the head and neck areas of children and adults. *Genital-type rhabdomyomas* are polypoidal tumor masses in the vagina and vulva of middle-aged women.

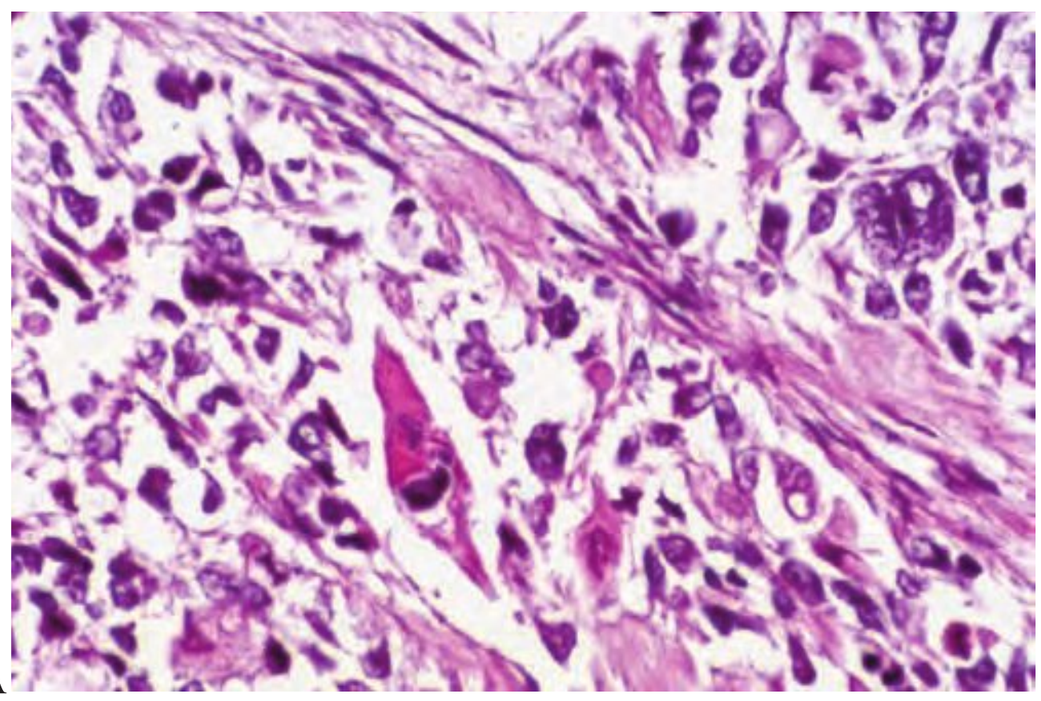
Histopathology. *Adult rhabdomyomas* contain cells with cytoplasmic vacuoles due to glycogen content but without easily observable cross-striations on H&E staining (Fig. 34-28B). Residual strands of cytoplasm between the vacuoles define "spider web cells" (211). The *fetal type* consists of immature skeletal muscle fibers. *Genital rhabdomyomas* contain interlacing fascicles or bundles of polymorphous cells, many with cross-striations, bland nuclei, and no mitoses. Immunohistochemical reactions identify positivity for desmin, myoglobin, actin, and myosin (212) and possibly weak S-100 staining (213). The tumor cells are surrounded by basement membrane laminin and type IV collagen (214).

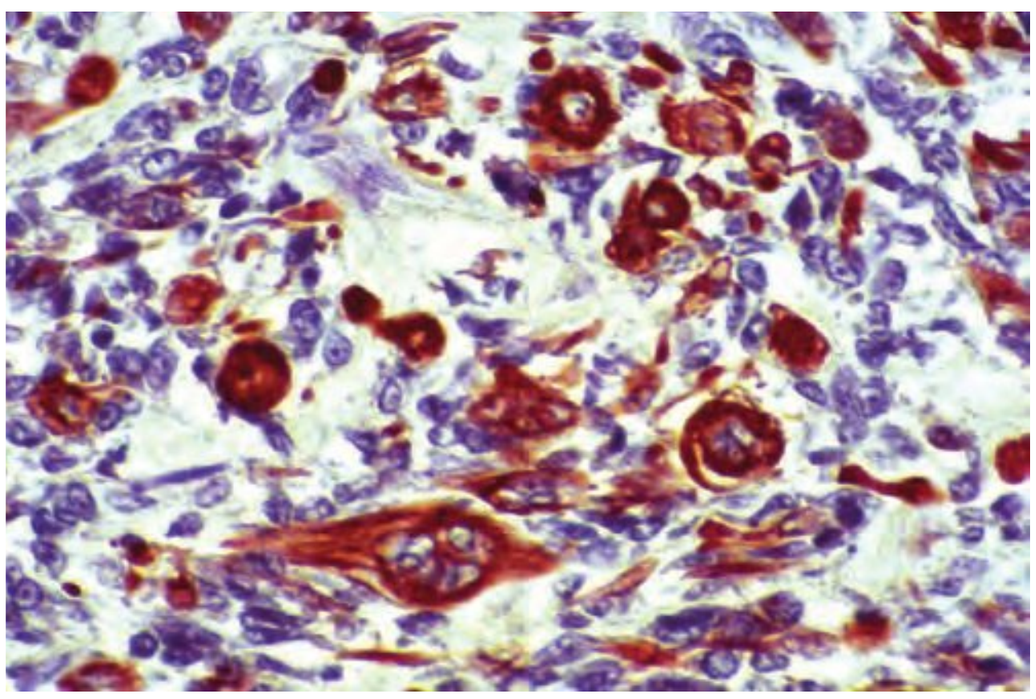
Differential Diagnosis. Both adult rhabdomyoma and fetal rhabdomyoma show polygonal eosinophilic cells with peripherally or centrally localized nuclei and cross-striations, while in hibernoma, multivacuolated cells with centrally localized nuclei are detected. In granular cell tumor, polygonal eosinophilic cells with granular periodic acid-Schiff–positive cytoplasm are found (215). Immunohistochemically, rhabdomyomas are strongly positive for myogenic markers (desmin, actin, and myoglobin) but negative for S-100, while hibernoma and granular cell tumor strongly express S-100. Also exclude a supernumerary (216), accessory, or hypertrophic (217) muscle presenting as a tumor-like mass.

RHABDOMYOSARCOMA

Although rare in adults, rhabdomyosarcomas are the most common soft tissue sarcomas in children. Most of these tumors are located in intramuscular locations or the genitourinary tract, usually deep to the introitus, most often in the vagina and less so in the vulva and perineum (218). Involvement of the skin is rare (219). Five primary and two metastatic rhabdomyosarcomas with primary presentation in the skin accounted for only 0.7% of the 682 cases of rhabdomyosarcoma collected at two large institutions with a main interest in soft tissue tumors (220). Only a few rhabdomyosarcomas have presented as dermal nodules (221). Subcutaneous indurations, congenital rashes (222), or multiple cutaneous metastases are other presentations. Rarely, rhabdomyosarcoma has arisen within congenital melanocytic nevi (223). The finding of both rhabdomyoblastic and melanocytic differentiation within the same lesion lends support to the hypothesis of their derivation from common pluripotential stem cells or neural crest cells.

Histopathology. Rhabdomyosarcomas often exhibit a low degree of differentiation, so their identification requires immunohistochemical studies (Fig. 34-29). Only some of these


A


B

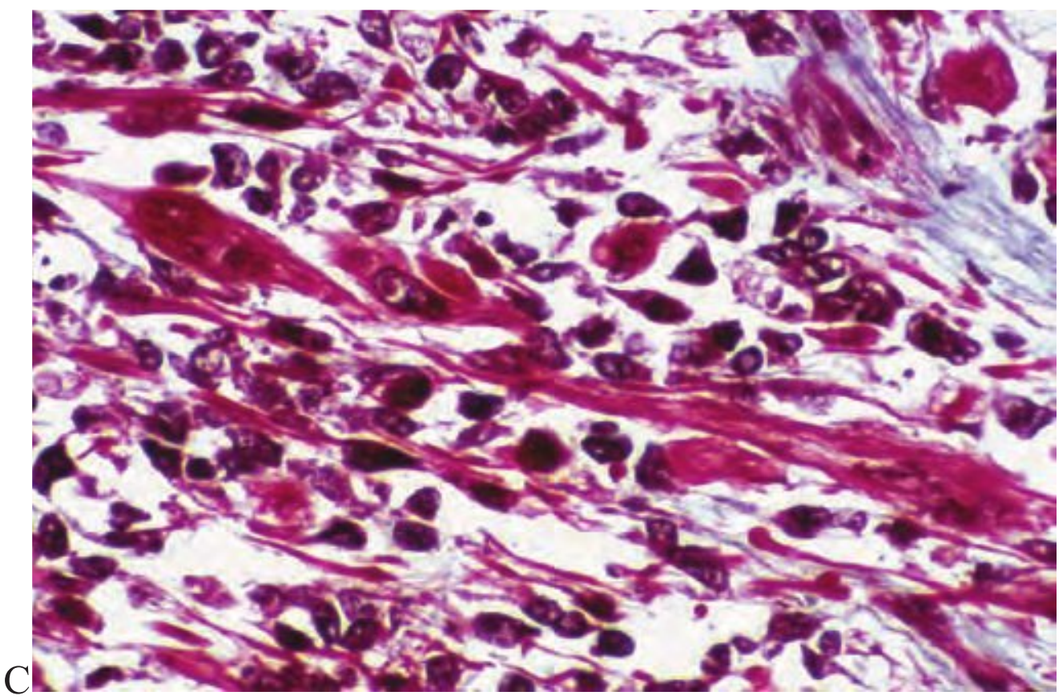

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FIGURE 34-29. Embryonal rhabdomyosarcoma pattern (14-year-old boy; 3-month history of a mass, ultimately 11 × 7 cm, partly cystic and hemorrhagic, along the spermatic cord with additional unfavorable histology including both alveolar and anaplastic features; patient is disease-free 8 years after removal of the tumor and ipsilateral iliac nodal metastases, plus radiation and chemotherapy.) A: Cytologically malignant round and elongate tumor cells occur together. B: The tumor cells are reactive for actin (but were negative for desmin) by immunoperoxidase technique. C: Myoplasm stains bright red in this Masson trichrome preparation.

tumors contain cells recognizable as rhabdomyoblasts by virtue of their cytoplasm exhibiting cross-striation that is best revealed by phosphotungstic acid–hematoxylin staining. Round cells of the *embryonal variant*, unlike those of lymphoma, neuroblastoma, cutaneous neuroendocrine (trabecular or Merkel cell) carcinoma, and Ewing's sarcoma, tend to have cytoplasmic rims that are stained red by trichrome (Fig. 34-29C). The *botryoid type*, a gross, morphologic descriptor meaning "grapelike," is a variant of the embryonal type found mainly in mucosa-lined hollow organs, but a few may be encountered in skin-covered surfaces such as the eyelid or anal region (219). Some tumors show alveolar spaces lined with small, round, dyshesive neoplastic cells, with tumor giant cells floating within these spaces (*alveolar rhabdomyosarcoma*) (224) (Fig. 34-30A). A *mixed form*, such as embryonal rhabdomyosarcoma with focal alveolar features, is not uncommon and for staging and prognostic purposes are classified as the alveolar type (219) that has a more aggressive clinical course. Pleomorphic cytologic features may be encountered in pediatric tumors still properly classified as embryonal or alveolar. Cells with elongated eosinophilic cytoplasm, so-called "strap cells," are suggestive but not diagnostic of rhabdomyosarcoma (224) (Fig. 34-30B) and may be found in the *pleomorphic type* (Fig. 34-30C). A sclerosing variant has cords of small, round malignant cells embedded in a densely hyalinized matrix having both a chondroid and osteoid-like appearance (225).

Histogenesis. Immunohistochemical studies of deparaffinized tissue may show undifferentiated cells to be positive only for vimentin, indicating a mesenchymal origin. More differentiated cells may be positive for desmin and myoglobin, which is indicative of muscular differentiation (224).

Differential Diagnosis. In younger patients, poorly differentiated round and spindle cell sarcomas should be excluded. Immunostains for muscle markers lack complete specificity. Rhabdomyosarcomatous differentiation can be seen in other sarcomas (e.g., "dedifferentiated" chondrosarcoma and malignant peripheral nerve sheath [malignant Triton] tumor) and in less expected settings such as cutaneous neuroendocrine (Merkel cell) carcinoma (226). Benign reactive lesions such as proliferative myositis and skeletal muscle regenerative giant cells in scars are to be excluded.

MALIGNANT EXTRARENAL RHABDOID TUMOR

Rhabdoid sarcoma (malignant rhabdoid sarcoma), comprising 2% of renal tumors, has a phenotype-characterized histopathology by the presence of eosinophilic cytoplasmic inclusions corresponding to masses of intermediate filaments on electron

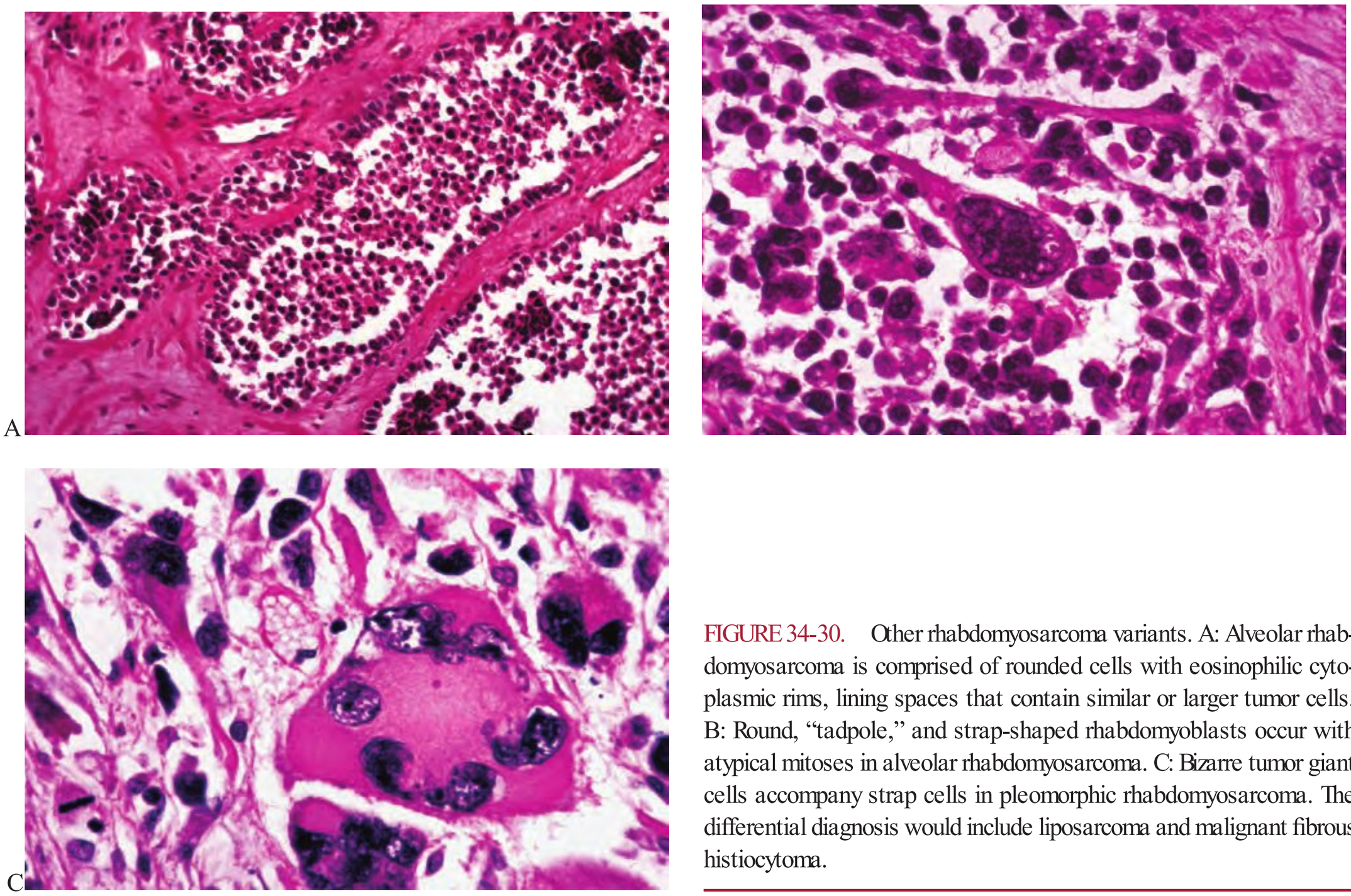


FIGURE 34-30. Other rhabdomyosarcoma variants. A: Alveolar rhabdomyosarcoma is comprised of rounded cells with eosinophilic cytoplasmic rims, lining spaces that contain similar or larger tumor cells. B: Round, "tadpole," and strap-shaped rhabdomyoblasts occur with atypical mitoses in alveolar rhabdomyosarcoma. C: Bizarre tumor giant cells accompany strap cells in pleomorphic rhabdomyosarcoma. The differential diagnosis would include liposarcoma and malignant fibrous histiocytoma.

microscopy that can arise in subcutaneous sites (227), congenitally, or in adults (228). Metastatic skin disease has been reported only in infants (229). The PAS-D- and vimentin-positive eosinophilic round cytoplasmic inclusions are negative for muscle-specific antigens. Prognosis is poor (230).

Differential Diagnosis. Carcinomas of various types including Merkel cell carcinoma (231), melanoma (232), and lymphoma (233) may have rhabdoid features.

Pathogenesis. It is arguable whether the rhabdoid phenotype may represent a "final common pathway" that many tumors take in escalating grade and aggressivity (234) or a clinicopathologic entity in its own right. Previously reported cases of rhabdoid tumors in adults support the contention that such tumors, although of distinctive morphologic phenotype, are of heterogenous lineage differentiation and do not represent a distinct clinicopathologic entity. A variety of lineage differentiation was shown by immunohistochemistry and electron microscopy, the lesions representing leiomyosarcoma, gastric carcinoma, epithelioid sarcoma, Merkel cell carcinoma, and desmoplastic small round cell tumor (235). Deletions and/or translocations of chromosomes 11p15 and 22q11 are found (236).

CUTANEOUS CHONDRO-OSSEOUS LESIONS

Extraskeletal osseous and cartilaginous tumors and tumor-like conditions of the extremities can often be differentiated radiologically; for those that cannot, knowledge of the spectrum of lesions will allow a suitably ordered differential diagnosis. Of the osseous lesions (myositis ossificans, fibro-osseous pseudotumor, fibrodysplasia (myositis) ossificans progressiva [FOP], soft tissue osteoma, and extraskeletal osteosarcoma), all but myositis ossificans are relatively rare. The differential diagnosis for these extraskeletal osseous and cartilaginous lesions includes soft tissue sarcoma, calcified tophi in gout, melorheostosis, pilomatricoma, and tumoral calcinosis (237).

CUTANEOUS OSSIFICATION

Cutaneous bone formation may be primary or secondary. If it is primary, there is no preceding cutaneous lesion; if it is secondary, bone forms through metaplasia within a preexisting lesion. Primary cutaneous ossification can occur in Albright's hereditary osteodystrophy (AHO) and as osteoma cutis. Aggressive, systemic forms of heterotopic ossification exist, generating lesions that often resist surgical treatment and producing a high rate of recurrence. These entities typically manifest during infancy as genetic syndromes such as fibrodysplasia ossificans progressiva or progressive osseous heteroplasia (POH) (238).

Albright's Hereditary Osteodystrophy

In AHO, first described in 1952 (239), multiple areas of subcutaneous or intracutaneous ossification are often encountered



FIGURE 34-31. Heterotopic ossification in pseudohypoparathyroidism. A plain film of a juvenile's thigh features irregular branching spicules and cords of bone in dermis and subcutaneous tissue medial to the femur.

(Fig. 34-31) in infancy and childhood, and its significance should not be overlooked, even in the normocalcemic patient (240). Early recognition of the skin manifestations of this syndrome and careful follow-up are important to prevent the deleterious effects of hypocalcemia. No definite area of predilection seems to exist; areas of ossification have been described on the trunk (241), extremities, and scalp. The areas of ossification may be so small as to be hardly perceptible or as large as 5 cm in diameter. Those located in the skin may cause ulceration, and bony spicules may be extruded through the ulcer. In addition to cutaneous and subcutaneous osteomas, bone formation may be observed in some cases along fascial planes.

AHO includes the syndromes of pseudohypoparathyroidism (PHP) and pseudopseudohypoparathryoidism. Patients with the former condition have hypocalcemia with a failure to respond to parathyroid hormone, whereas patients with the latter syndrome fail to respond to parathyroid hormone but have normal serum calcium values. PHP is described as AHO when a specific phenotype is present: short stature, round facies, and multiple skeletal abnormalities, such as curvature of the radius and shortening of some of the metacarpal bones (242). As a result of this shortening, some knuckles are absent when the fists are clenched, and depressions or dimples are apparent there instead (the Albright dimpling sign). Additional manifestations include basal ganglia calcification and mental retardation.

Pathogenesis. An autosomal dominant condition, AHO results from heterozygous inactivation of G(s)alpha, encoded by the

GNAS1 locus on the distal long arm of chromosome 20. Small insertions and deletions or point mutations of GNAS1 are found in approximately 80% of patients with AHO. The remainder may be accounted for by larger genomic rearrangements (243).

Histopathology. Spicules of bone of various sizes may be found within the dermis (244) or in the subcutaneous tissue. The bone contains fairly numerous osteocytes as well as cement lines that are best revealed with a strong (e.g., Harris) hematoxylin or in polarized light. In addition, osteoblasts with elongated nuclei can usually be seen along the edges where new bone is being laid down. The osteoblasts that form bone in all forms of primary cutaneous ossification originate in preexisting fibrous connective tissue, and thus their product is termed *intramembranous* rather than *enchondral* bone. Osteoclasts, if present, are cells with multiple large nuclei resembling multinucleated foreign body giant cells but are distinguished by their attachment to a bone surface. They excavate surface pits called *Howship's lacunae* into the bone substance as the initial step in remodeling. Osteons with haversian canals containing blood vessels and connective tissue are produced through internal remodeling and indicate the passage of significant time. The spicules of bone may enclose, either partially or completely, areas of mature fat cells, which represent the maturation of the lesion with establishment of a medullary cavity. Hematopoietic elements, however, are observed only rarely among the fat cells.

The incidence of cutaneous ossification in AHO is fairly high, estimated at 42% of patients with PHP and in 27% of those with pseudopseudohypoparathyroidism (244). However, the reason for the bone formation is not clear. Because the association of AHO with cutaneous ossification was not recognized until 1965 (245), the question arises as to how many cases of primary cutaneous ossification reported before then occurred in association with AHO. In a review examining this question (242), several cases originally reported as primary osteoma of the skin were recognized as showing evidence of AHO. Although the conclusion that most cases of primary osteoma cutis are associated with AHO seems somewhat exaggerated, it is nevertheless apparent that patients with extensive foci of ossification usually have AHO.

Differential Diagnosis. POH is a rare autosomal dominant condition of mesenchymal differentiation in females characterized by dermal ossification during infancy and progressive heterotopic ossification of cutaneous, subcutaneous, and deep connective tissues during childhood (246). Recently, paternally inherited inactivating mutations in the GNAS1 gene on chromosome 20q13 have been implicated in the pathogenesis, although sporadic cases have also been reported (247). It is clinically distinguishable from AHO and FOP, which can present as fibrous scalp nodules (248). The initial skin involvement tends to be a plaquelike or papulovesicular rash or reddened induration, with dermal ossification. The disorder can be distinguished from FOP by the presence of cutaneous ossification, the absence of congenital malformations of the skeleton, the absence of inflammatory tumor-like swellings, the asymmetric mosaic distribution of lesions, and the absence of predictable regional patterns of heterotopic ossification. Also, in FOP, cartilage production precedes ossification of deeper tissues (enchondral ossification), whereas the predominant pathway of bone formation in POH and AHO is intramembranous. POH can be distinguished from AHO by the progression of heterotopic ossification from skin and subcutaneous tissue into skeletal muscle, the presence of normal endocrine function, and the absence of a distinctive habitus associated with AHO. The genetic basis of POH is unknown; it may lie at one end of a clinical spectrum of ossification disorders mediated by abnormalities in GNAS1 expression and impaired activation of adenylyl cyclase (246).

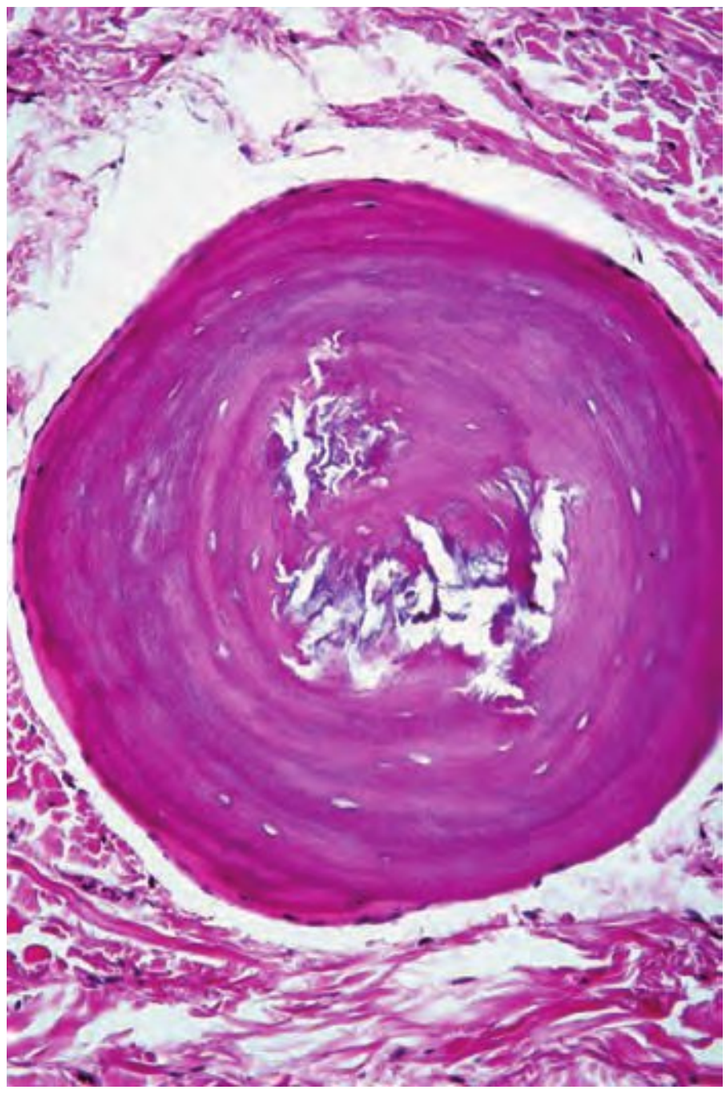
Osteoma Cutis

The term *osteoma cutis* is applied to cases of primary cutaneous ossification in which there is no evidence of AHO in either the patients or their families (249). Congenital osteomas occur in Gardner's syndrome and AHO or in patients presenting with numerous, spontaneous osteoma cutis lesions without systemic manifestations or disease (250). Multiple miliary osteoma cutis, a disfiguring disorder, can occur unassociated with AHO (251).

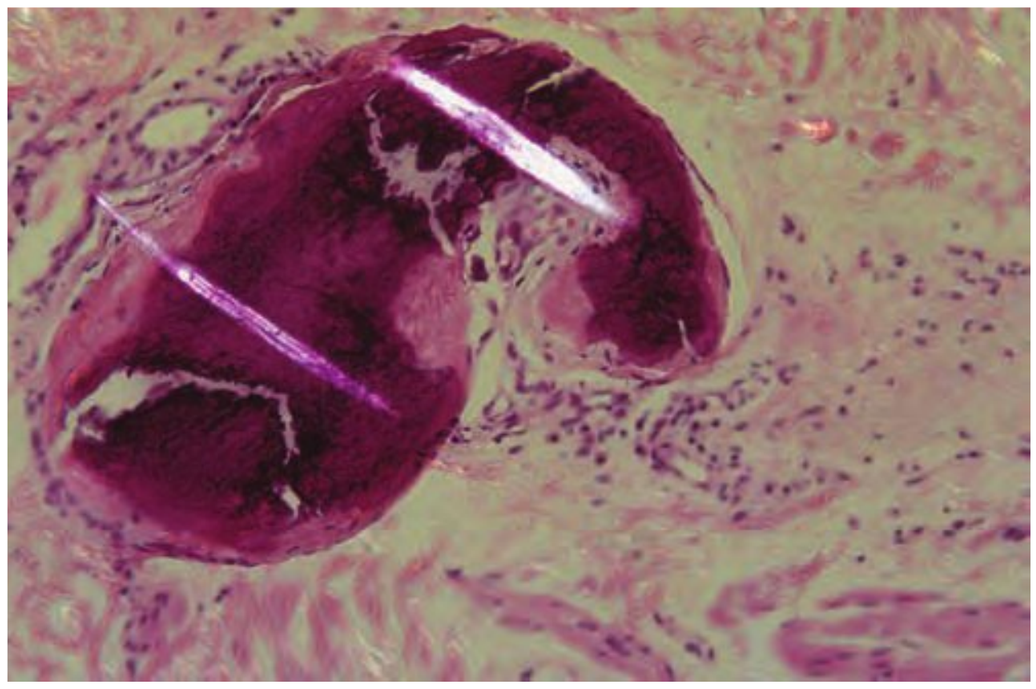
Less noticeable facial osteoma cutis is likely more common than reported, since in a series of randomly selected patients with histories of long-term acne vulgaris, three of seven patients had x-ray evidence of multiple cutaneous radiopaque deposits on the face (252).

The four groups of patients with osteoma cutis have osteomas limited in extent in all but the first group: (a) patients with *widespread osteomas* since birth or early life but without evidence of AHO; (b) patients with *single, large, plaquelike or platelike osteomas* present since birth either in the skin of the scalp (253) or in the skin or subcutaneous tissue of an extremity (254); (c) patients with *single, small osteomas* arising in later life in various locations (254); and (d) patients with *multiple miliary osteomas of the face.* In some instances of the latter, all of them women, the osteomas do not appear until late in life (255). In others, they are observed in young women in association with long-standing acne vulgaris; in these, the miliary osteomas have been interpreted as metaplastic ossification within acne scars (256). However, the absence of acne vulgaris among the patients in the older age group and the presence in one case of miliary osteomas also in the scalp, where acne does not occur (255), raise the possibility that the acne vulgaris is coincidental.

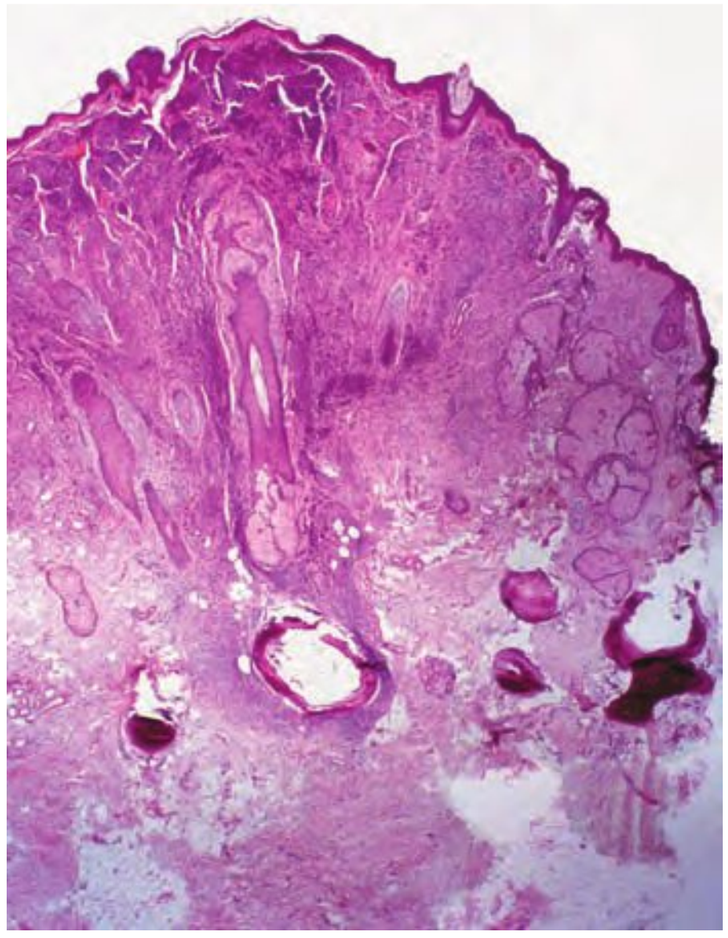
Histopathology. The histologic findings in osteoma cutis are the same as in primary cutaneous ossification occurring in conjunction with AHO. Small, generally spherical spots of ossification within the dermis often start initially against a speck of amorphous mineralization or demonstrably around extravasated keratin debris (Fig. 34-32A), hair shafts (Fig. 34-32B), or in the stroma of another lesion such as a melanocytic nevus (Fig. 34-32C, D). This bone is formed by the activities of flattened osteoblasts that appear to be derived through modulation from dermal fibroblasts (Fig. 34-32E). A



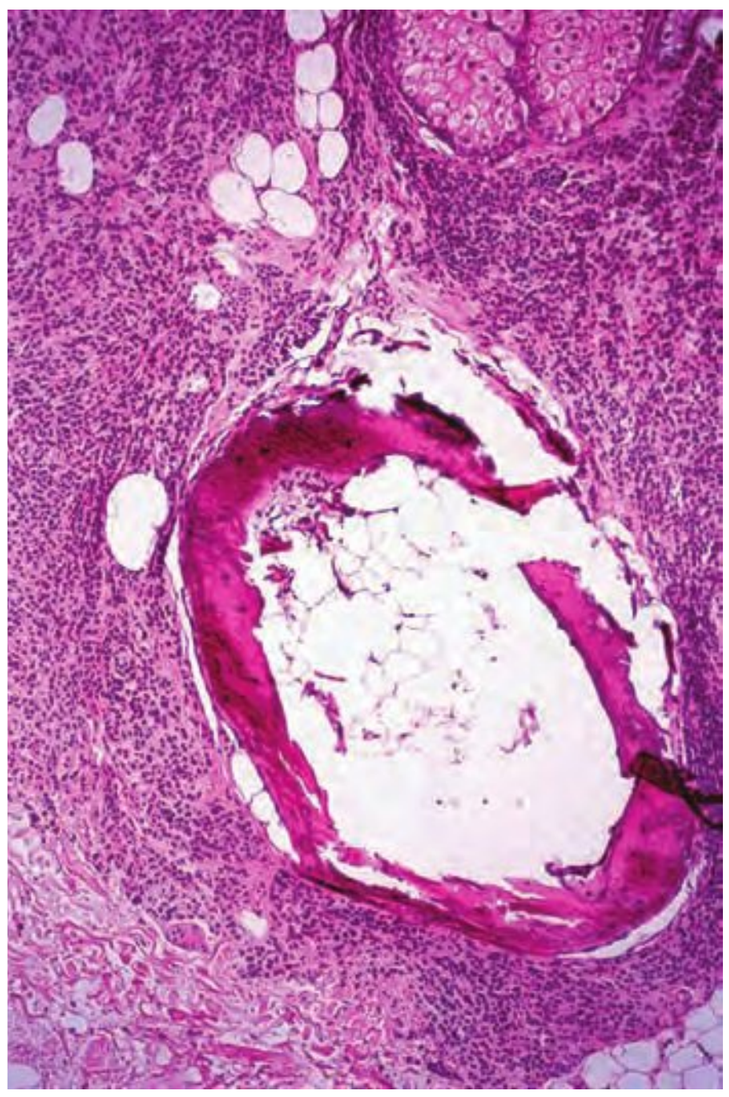
A



B



C



D

FIGURE 34-32. Osteoma cutis. A: A spherical osteoma cutis has resident osteocytes in oval lacunae of its laminations about a central nidus of mature squames (keratin flakes) that were likely extruded from a follicle or cyst (80-year-old woman; shoulder). B: A polarized light view highlights two hair shafts crossing an irregular osteoma cutis (70-year-old man; mid-back). C: Five rounded ossifications are in the base of this compound nevus (44-year-old woman; cheek). D: Fat is in the central chamber of one of the osteomas shown in (C). (continued)

minority of the formative cells persist in the osseous product as resident osteocytes. Osteomas undergo a high rate of remodeling (250), enlarging by continued bone application on outer surfaces with eventual central hollowing out by osteoclastic erosion (Fig. 34-32F). A circular outline is commonly achieved, with central space for fatty marrow and, rarely, trilineage hematopoietic marrow. They are at risk for all of the disorders of genuine skeletal members. In cases with transepidermal elimination, some patients show fragments of bone within channels lined by epidermis and leading to the surface (Figs. 34-32G, H), as with a foreign body, and others show such fragments within breaks in the epidermis. A sinus tract draining an underlying osteomyelitis or septic joint should enter the differential.

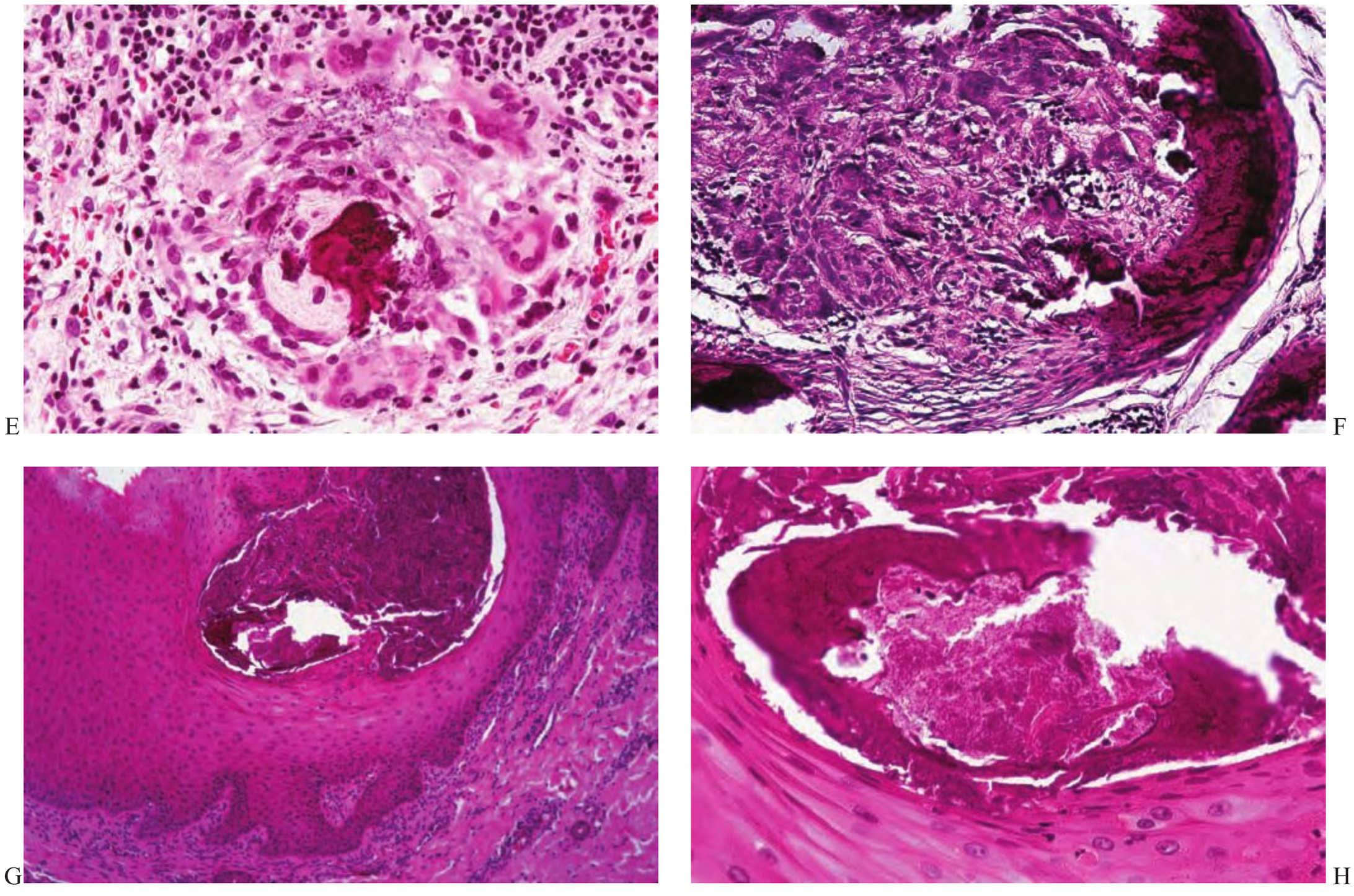


FIGURE 34-32. Continued. E: A very early stage in osteogenesis is depicted as it occurred near ruptured folliculitis (43-year-old man; back). F: Exuberant osteoclasia is hollowing out this osteoma that occurred in a nevus (36-year-old woman; face). G: An epidermal-lined channel is evacuating a small osteoma, no longer in dermis (74-year-old man; toe). H: A high-power view of the osteoma from (G) depicts osteoclastic erosions (Howship's lacunae) and autolysis of associated inflammatory exudate.

Pathogenesis. Postulation of "embryonal cell nests" or "primitive mesenchymal cells" as the source for osteoblasts (257) is unnecessary, since in the genesis of osteoma cutis, dermal fibroblasts have the ability to differentiate into osteoblasts (258). Cultured cells from the adult human hair follicle dermis can be directed toward adipogenic and osteogenic differentiation (259). They actively deposit type I collagen, as in mature bone, but also 80% to 85% of collagen in the skin. *In situ* hybridization techniques further indicate that given appropriate stimulation, indigenous fibroblasts have the ability to modulate into osteoblastic cells (see discussion of myositis ossificans) that have the same properties as those of osteoblasts, such as high alkaline phosphatase activity and a high expression of osteonectin (249). Osteogenesis by dermal fibroblasts cultured *in vitro* has been verified in a rabbit model (260). Dermal "fibroblasts" can be viewed with new respect. No (stem) cell rides idly. In multiple miliary osteoma cutis, a dynamic bone study using a tetracycline double- labeling technique demonstrated a high rate of internal remodeling (261).

Metaplastic or Secondary Ossification

Metaplastic or secondary ossification occurs within a preexisting lesion. A simple prerequisite seems to be some antecedent relatively rigid substrate. Virtually any process that calcifies may secondarily ossify (262).

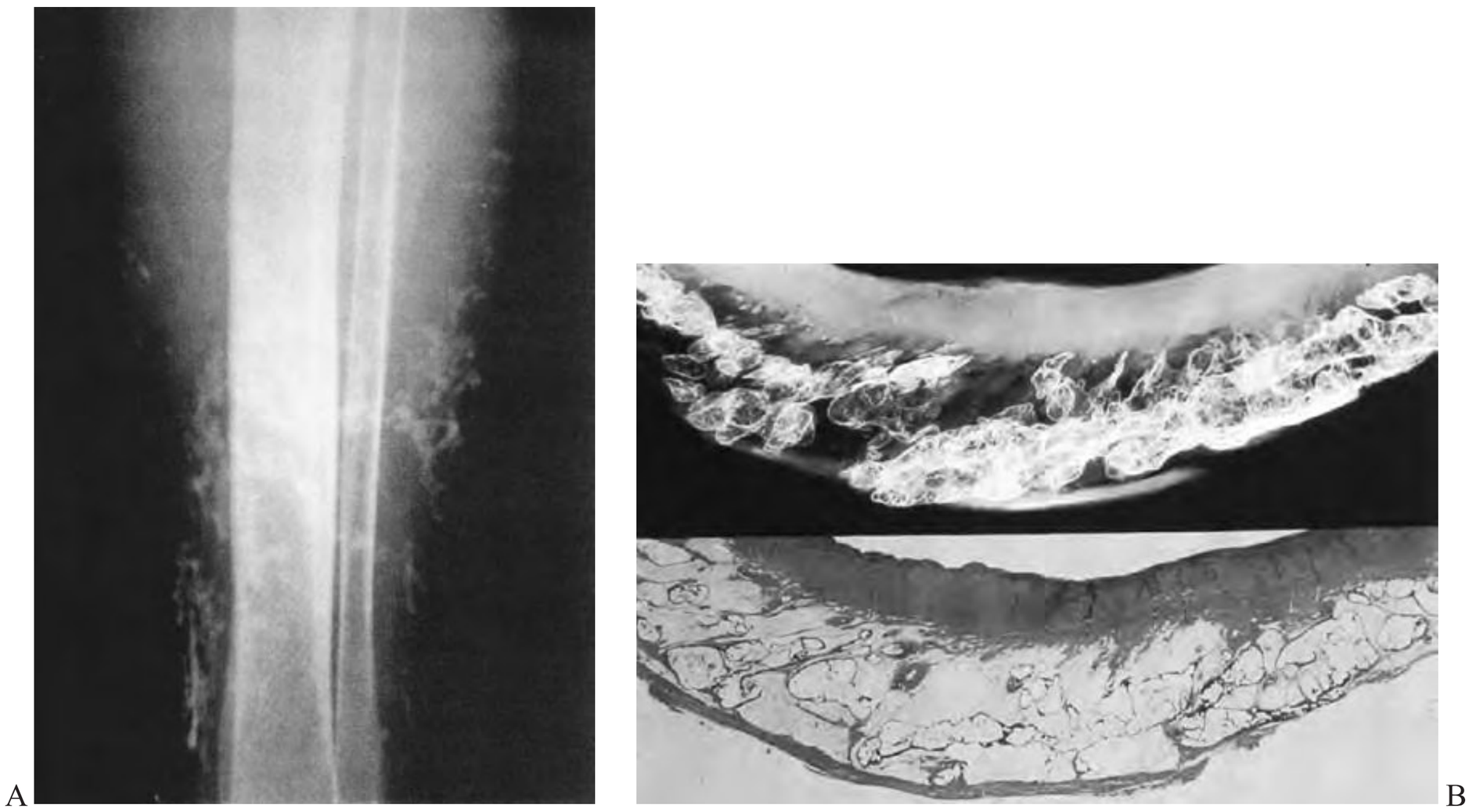
Histopathology. The tumor that most commonly shows metaplastic ossification is pilomatricoma (calcifying epithelioma of Malherbe) (see Chapter 30), in 14% to 20% of patients (263). Calcification of shadow cells attracts osteoclastic giant cells. Osteoclastic erosion of mineralized epithelium is followed by ("coupled to") osteoblastic deposition of osteoid against remnants of the shadow cell islands. The process is therefore similar to enchondral ossification, wherein mineralized cartilage is the inducing factor and can lead to a fat-filled

cancellous network with thin cortex resembling a normal rib cross-section. Ossification is also rarely found in basal cell carcinoma, where it takes place usually in the stroma but sometimes around mineralizing keratin microcysts. Basal cell carcinomas rarely have ossification (263), even including those in the nevoid basal cell carcinoma syndrome (264). In intradermal nevi, ossification usually follows folliculitis. In desmoplastic malignant melanoma, fibroplasia may be accompanied by cement production resulting in bone formation (265). Rare melanomas in which there is osteoid synthesis by S-100–positive tumor cells have been termed *osteogenic melanomas* (266). Metaplastic ossification is exceptional in scars, burns (267), venous stasis (Fig. 34-33), nephrogenic systemic fibrosis (268), cutis laxa–like pseudoxanthoma elasticum (269), and in inflammatory processes of the skin such as morphea, systemic scleroderma, dermatomyositis (270), and toxic epidermal necrolysis that resulted in multiple joint contractures (271).

Postinjury Ossification

Myositis ossificans (Fig. 34-34) results from a postinjury modulation of osteoblasts and can occur in a sufficiently superficial location to come to the attention of dermatology (272). The characteristic radiologic appearance is that of a mass with a peripheral rim of radiodensity correlating with the most advanced and mature bony parts of the lesion as well as a relatively lucent, maximally injured, and somewhat ischemic central area. Other nonneoplastic soft tissue processes with bone formation such as pseudomalignant osseous tumor of soft tissues (273) (Fig. 34-35), florid reactive periostitis (274), and bizarre parosteal osteochondromatous proliferation (275) occur more commonly in acral location than myositis ossificans. A differential diagnosis of these lesions includes periosteal and parosteal osteosarcoma, periosteal chondroma, and osteomyelitis.

Subungual exostosis (Fig. 34-36), first described by Dupuytren (276), is a fairly common benign bony projection that occurs on a distal phalanx beneath or beside the nail, often leading to nail deformity (277). It has also been reported as *subungual osteochondroma* (278), a term correctly applied only to the common anomalous tumor of epiphyseal cartilage generally seen in the growth years (279). The great toe is the most common site, but other toes and fingers can be affected. Although the nodule usually measures only a few millimeters in diameter, it can be larger and cause swelling of the entire distal phalanx, possibly with ulceration that is treated for a time as an ingrown nail with infection. There is frequently an association with trauma (280), and these anecdotes argue persuasively for traumatic induction. Radiographs reveal a bony projection from the edge of the terminal phalangeal tuft (Fig. 34-36A) and are indispensable in avoiding assigning an incorrect alternative diagnosis



A B

FIGURE 34-33. Heterotopic subcutaneous ossification associated with chronic venous stasis (60-year-old woman; chronic venous stasis of lower legs). A: In this plain film radiograph, irregular bony deposits unrelated to veins can be seen in the absence of fat necrosis or abnormal serum calcium or phosphorus. B: A specimen radiograph (top) correlates well with the large-format histologic section (bottom) showing the distribution of irregular lobulated ossific plates in and around subcutaneous fat. The ossification seems to have taken place in interlobular septa. In the histologic view, fibrosis markedly thickens dermis. Thick-walled veins are in subcutaneous fat (e.g., left of center).

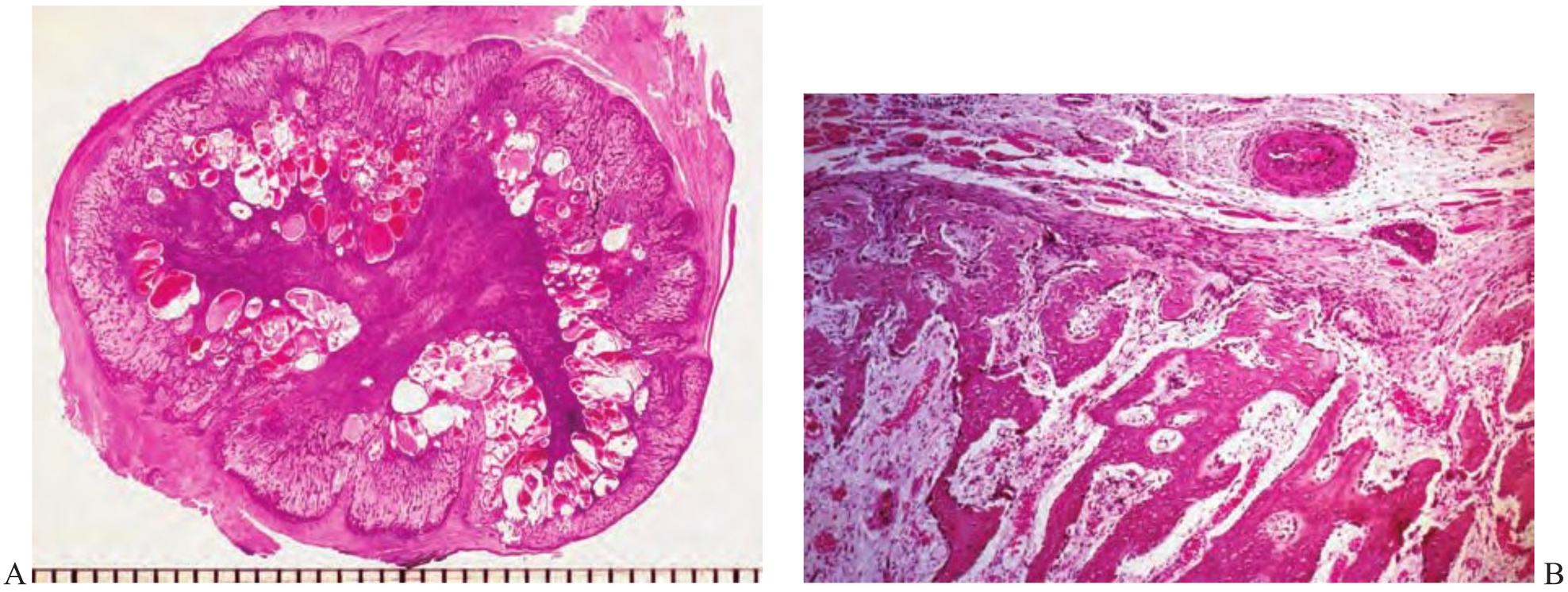


FIGURE 34-34. Myositis ossificans. A: A rounded 3-cm mass has central cellular bands without ossification and cancellous bone forming in the periphery. B: Involuting skeletal muscle fibers in what could be called a periosteum around the mass leave no doubt that interstitial connective tissue cells in injured muscle are the modulating osteogenic cells condensing to form the bone.

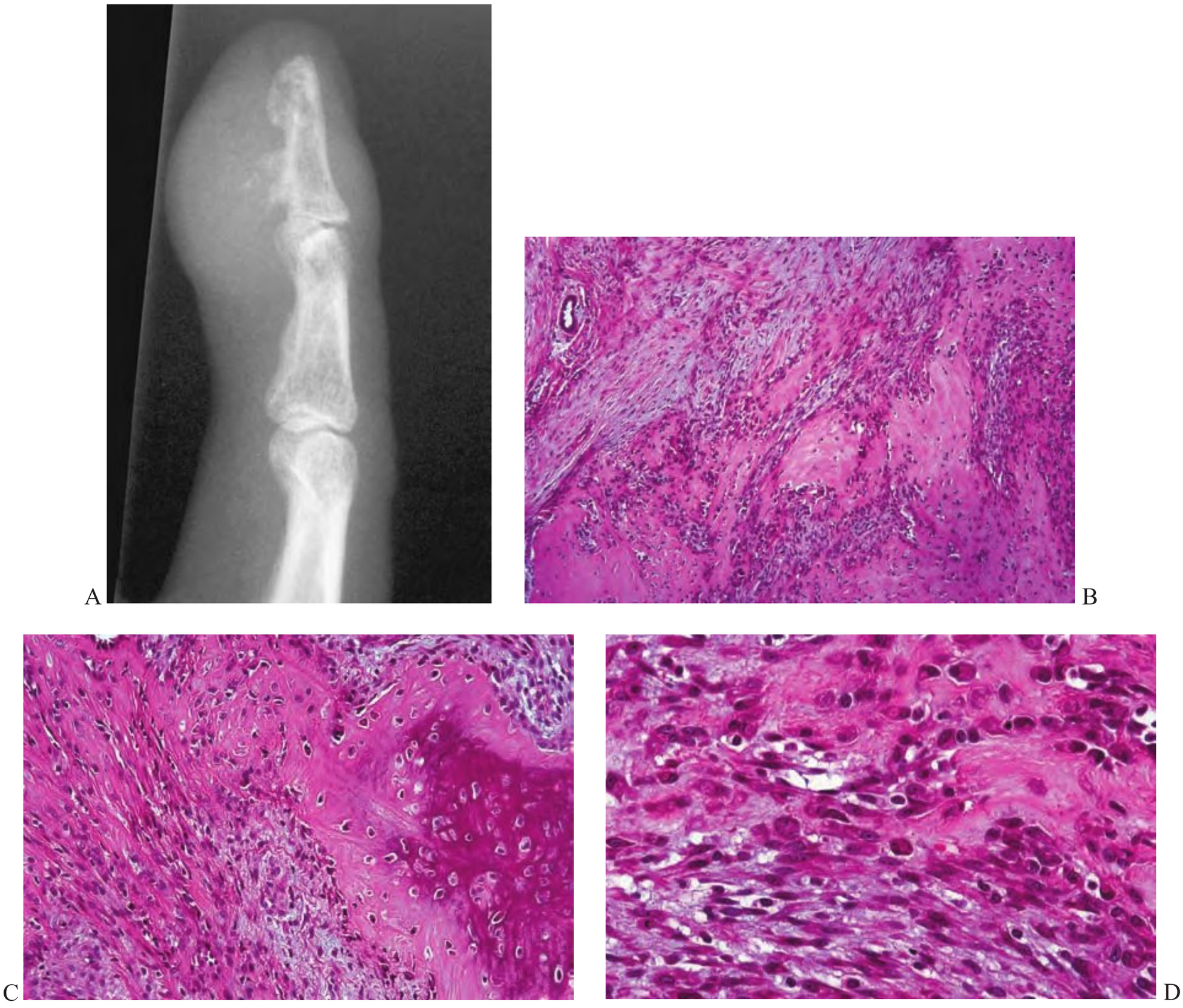
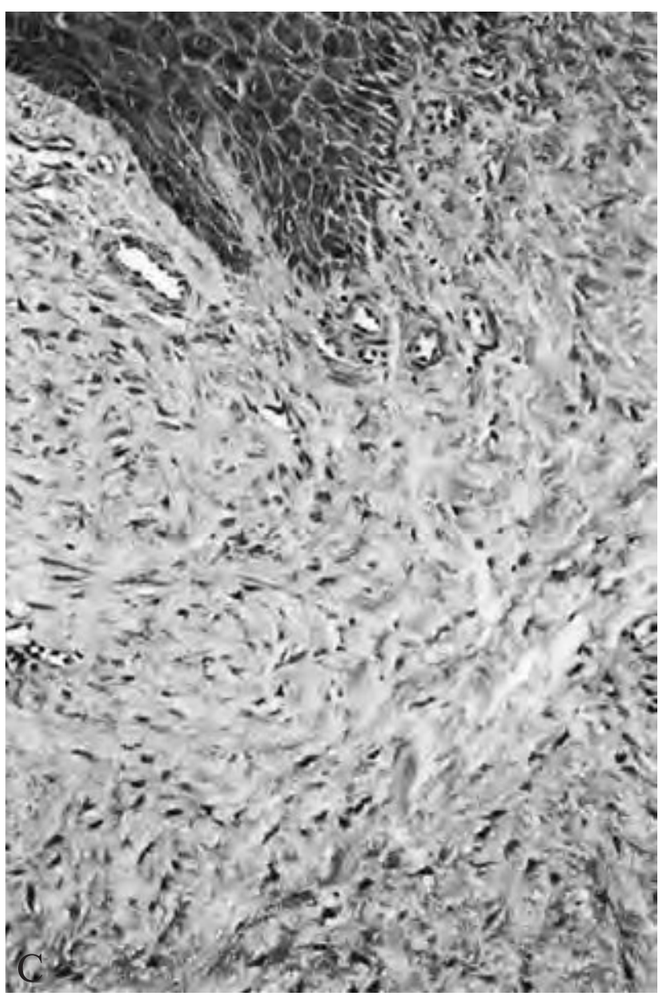
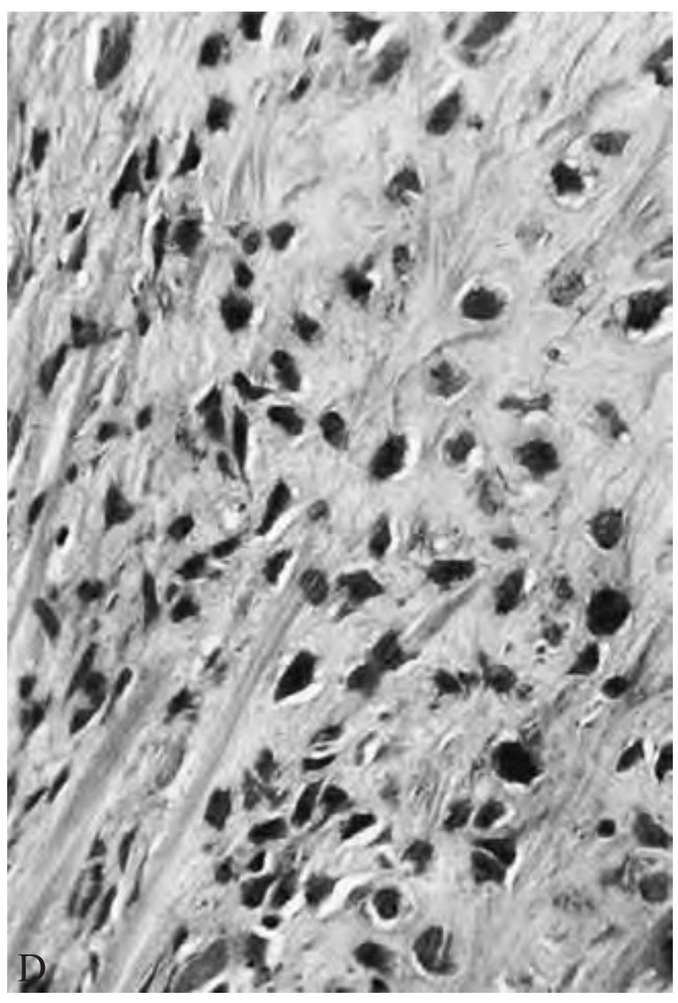


FIGURE 34-35. Fibro-osseous pseudotumor of digit (42-year-old man; rapidly enlarging fingertip with no recalled history of trauma). A: The terminal phalange of the fifth finger in this plain film radiograph has undergone bulbous enlargement and has some internal ossific density that may partly extend from the periosteal surface. B: A chaotic pattern of osteoid is emerging in an active spindle cell background. A sweat gland duct is at upper left. C: A medium-power view of this highly cellular reactive lesion shows basophilic mineralization of part of the osteoid product (right). D: The cellularity lacks the pleomorphism and abnormal mitoses of osteosarcoma.


A


B


C


D

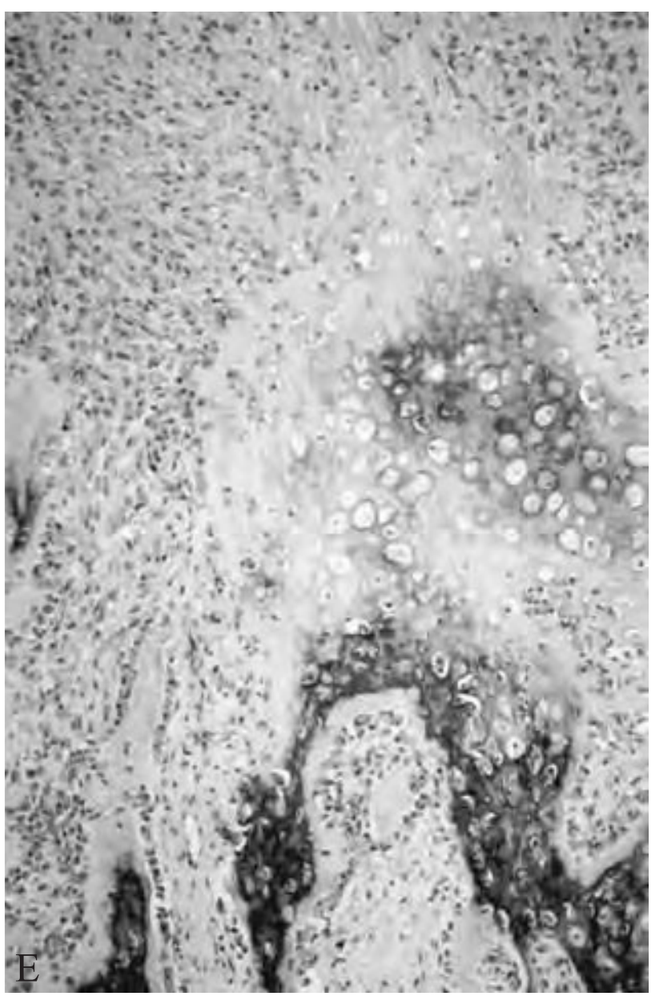

E

FIGURE 34-36. Subungual exostosis (14-year-old girl; 4 months previously, a horse stepped on her great toe). A: A polypoid bony projection extends from the tuft of terminal phalanx beneath the nail. An osteocartilaginous exostosis (osteochondroma) would be expected to be attached to the metaphyseal (more proximal) region of the phalanx, not to the tip. B: The excised exostosis consists of a cartilaginous cap (top) emerging from dermis beneath stretched epidermis and nail bed epithelium. This cartilage overlies a cancellous bony stalk built largely through the process of enchondral ossification. C: The earliest stage in the progressive enlargement of a subungual exostosis is the elaboration of myxoid material between dermal fibroblasts (bottom). D: With time, the myxoid material assumes the solidity of hyaline cartilage, and the intervening cells occupy lacunae within it. Deletion by osteoclastic erosion and substitution of bone tends to follow. E: Exuberant and reactive/reparative chondro-osseous tissue, as illustrated from another case, can be histologically disconcerting.

(281). The length and radiologic density are proportional to duration. The treatment is surgical.

Histopathology. *Myositis ossificans* and its subcutaneous counterpart, *panniculitis ossificans*, in early postinjury stages can mimic a cellular, mitotically active spindle cell sarcoma in its early posttrauma growth but lacks the abnormal mitoses and extreme pleomorphism of malignancy and manifests uniform nuclear chromaticity. Later, greater density and maturity of the bony product in the periphery around the still disturbingly cellular central zones is less of a diagnostic challenge since it is reverse of the architecture of soft tissue osteosarcoma and would not be seen in nodular fasciitis.

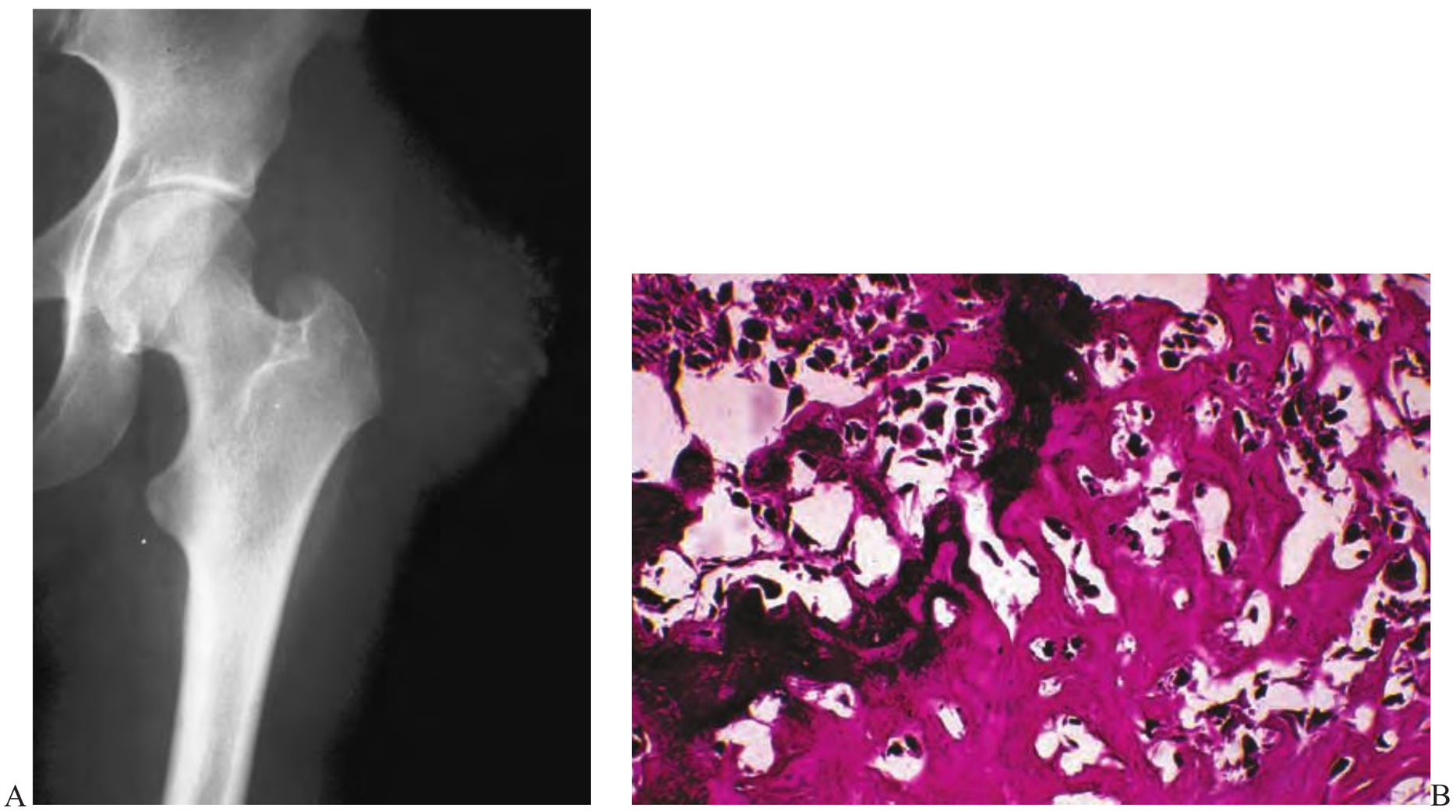
The earliest change in an *exostosis* (Fig. 34-36B) is mucopolysaccharide and osteoid elaboration by periosteum and modulated fibroblasts in the closely approximated contiguous dermis (Fig. 34-36C), eventuating in a gradational continuum of chondroid and osteoid that can be alarmingly cellular (Fig. 34-36E). As the cartilage achieves solid hyalin qualities, it becomes focally eroded along its deep surface by osteoclastic giant cells, followed immediately by enchondral bone deposition on any chondral remnant. In this way, a cancellous bony stalk is built out from original cortex at the expense of cartilage. The process continues, aggravated perhaps from ongoing irritation by footwear and as long as dermal fibroblasts continue to modulate into matrix-producing cells (281).

Bone formation in midline scars (282) is rare, and its etiology remains obscure. The lesion may not be discovered for a long period of time after it occurs, and the patient, except in rare circumstances, is asymptomatic (283). Clinically, it should be differentiated from scar recurrence following surgery for abdominal malignancy.

Button osteomas on the calvarium are usually approached surgically with a preoperative palpation diagnosis of cyst. They are common in modern (37.6%) and archaeologic (41.1%) populations and correlate with age (284). In one third of cases, there are two or more. The demographic characteristics of button osteoma, mainly its high frequency among ancient and modern populations, its independence of sex and race, its scarcity in other primates, and the fact that its macro- and microstructure with parallel lamella of compact bone, sometimes partly haversianized and best appreciated under polarized light, favor a hamartoma and not a neoplastic osteoma, although posttraumatic exostosis remains an attractive hypothesis.

Extraskeletal Osteosarcoma

This aggressive tumor, characterized by atypical mesenchymal cells synthesizing osteoid (Fig. 34-37), is extremely rare, especially in the skin (285). It can occur in the skin with no associated predisposing conditions (286), in an old burn scar (287), and under a previously electrodessicated actinic keratosis (288). There should be no connection to deeper structures and no demonstrable primary bone lesion (289). Other extraskeletal sites for primary osteosarcoma that may come to the attention of dermatologists include the penis (290) and tongue (291). Origin in antecedent myositis ossificans is possible (292). When osteosarcoma is concurrent with a distinct carcinoma pattern, such as that found in basal cell carcinoma, the term *carcinosarcoma* can be used. Alkaline phosphatase stain-



A B

FIGURE 34-37. Extraskeletal osteosarcoma. A: In this plain film, an oval mass lateral to the hip joint has irregular central bony density, unlike the peripheral ossification of myositis ossificans. B: Cytologically, malignant cells are forming osteoid. (Compare with Fig. 34-35D.)

ing compared with immunohistochemistry has proved to be superior in the differentiation from other pleomorphic sarcomas (291).

Differential Diagnosis. Metaplastic and reactive ossification may occur in and around various tumors with specific identity such as the ossifying fibromyxoid tumor of soft tissue (293), sarcomatoid (osteogenic) malignant melanoma (294), and "fibrohistiocytic" tumors such as dermatofibroma (295), atypical fibroxanthoma (296), so-called malignant fibrous histiocytoma, and peripheral nerve sheath tumors (e.g., malignant triton tumor). Merkel cell carcinoma may demonstrate "divergent" differentiation into bone, cartilage, or myogenous tissue (297). Follow-up data suggests an excellent prognosis for polypoid and exophytic sarcomatoid basal cell carcinoma after complete surgical resection (298). Electron microscopy can assist in detecting this deception of tumors with differing biologic behaviors. *Fibro-osseous pseudotumor* typically occurs in the digits of the hand and is characterized histopathologically by a fibroblastic proliferation with foci of osseous differentiation lacking the well-defined zonal pattern of myositis ossificans (299) (Fig. 34-35B). Because of its rapid growth and aggressive histopathologic appearance, this lesion can be mistaken for extraskeletal or parosteal osteosarcoma (294). A 2007 review of *cutaneous metastasis from osteosarcoma* found only eight cases and added one (300).

BENIGN CARTILAGENOUS TUMORS OF SKIN AND SOFT TISSUE

Soft Tissue Chondromas

The hallmark of all differentiated chondrogenic tumors is the presence of neoplastic chondrocytic cells responsible for the formation of the characteristic cartilaginous tumor matrix (134). Benign cartilage nodules and masses independent of bone, including cutaneous cartilage tumors, are variously regarded as neoplastic, metaplastic, or anomalous. Generically referred to as *soft part* or *extraskeletal chondromas* (Fig. 34-38), most of these nodules are located in the hands and feet, especially in the fingers of middle-aged adults, but other sites (e.g., the back) (301) and ages, and even infants (302), are not immune. Most are solitary and may attach to tendons, tendon sheaths, or joint capsules (303) (Fig. 34-38A). These slowly enlarging nodules are seldom painful or tender and rarely exceed 3 cm in diameter. Soft tissue chondroma may present as a painful finger (304), an acute inflammatory episode (305), trigger finger (306), and compression neuropathy (307). Few recur locally. True *cutaneous chondromas*, primarily located in the dermis, are rarely described in the dermatologic literature (308) but can be familial (309).

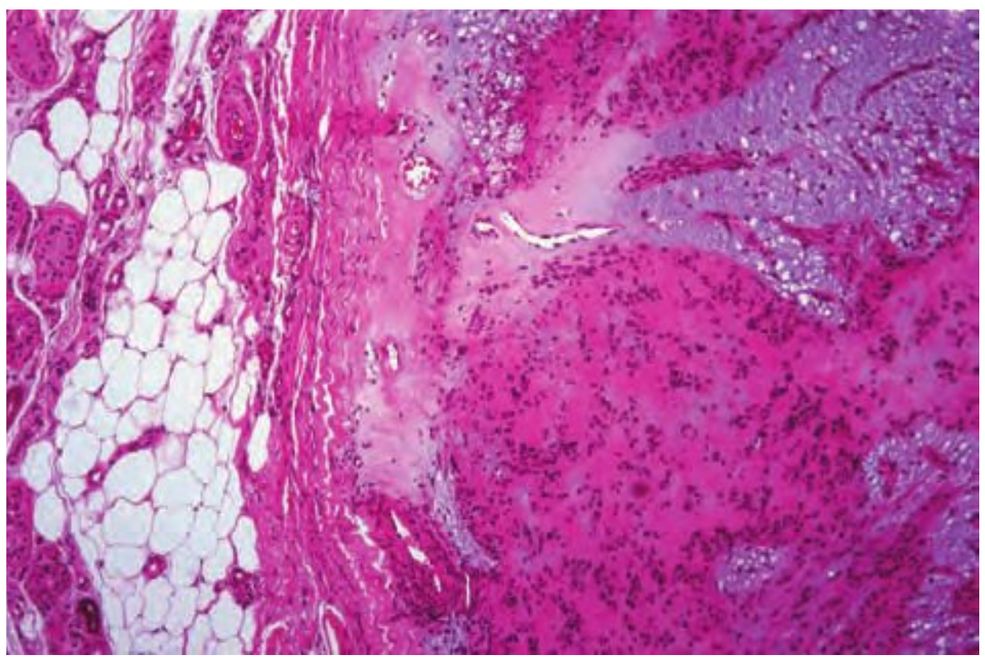
Synovial chondroma (intracapsular and periarticular) and multiple purely cartilaginous (chondromatosis) or chondro-osseous (osteochondromatosis) nodules in tenosynovium or joint synovium are metaplastic changes of subsynovial fibrous tissue that may create a mass around a joint or along a tendon. When near a joint, intracapsular and para-articular chondromas are to be differentiated from *synovial chondromatosis* (310) (Fig. 34-39). *Extraskeletal osteochondromas* are painless, slow-growing masses of mature hyaline cartilage, with extensive enchondral ossification (311). Tenosynovial osteochondroma independent of bone can cause carpal tunnel syndrome (312). Because of location, these tumors come to the attention of the dermatopathologist only rarely. Primary synovial chondrosarcoma is anecdotally rare (313).

Enchondromas are benign intraosseous hyaline cartilage tumors whose location in the distal phalanx (in contrast to more proximal bones) is rare but may be responsible for nail dystrophy (314).

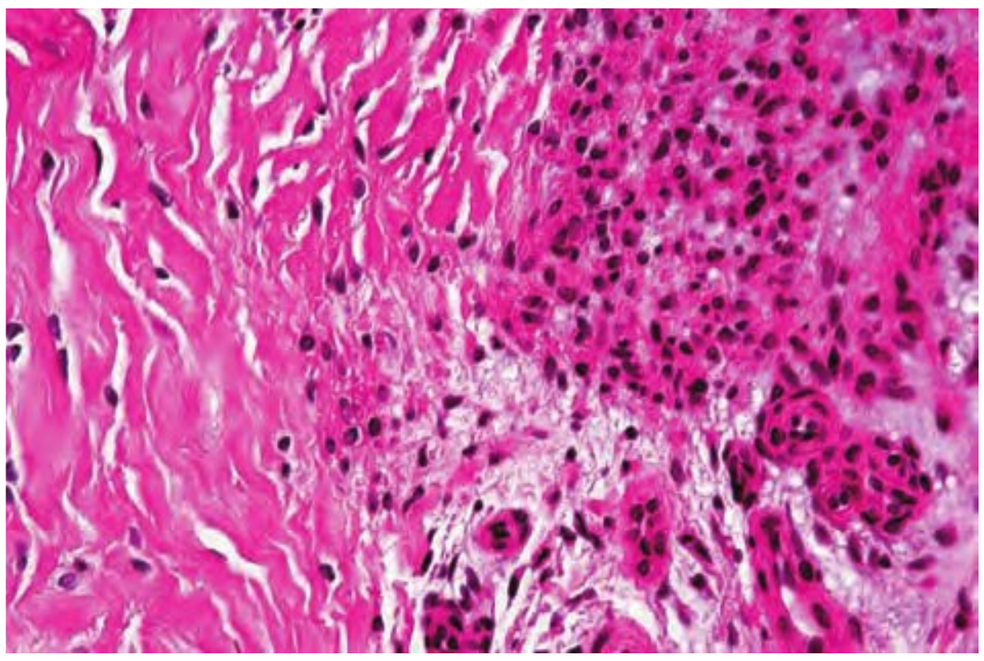
Histopathology. Soft tissue chondromas appear to develop and grow at their periphery by the metaplastic enlargement of fibroblasts into plump cells that inflate the preexisting structural fibrous tissue with mucopolysaccharides, creating hyalin cartilage (Fig. 34-38C). The plump chondrocytes frequently have distinctive reniform and elongated nuclei rather than the expected round shape in most cartilage (Fig. 34-38D). A minority exhibit central or peripheral (315) secondary stippled or heavy deposits of calcium pyrophosphate dihydrate (316) and hydroxyapatite crystals. The well-circumscribed, solid-appearing cartilage may exhibit focal fibrosis, enchondral ossification (soft tissue osteochondroma), myxoid change (myxochondroma), cystification, and/or hemorrhage. Hyaline globules, spherical intracytoplasmic eosinophilic droplets deemed secretory products of probable glycoprotein nature, are in a minority of soft tissue chondromas. Ultrastructurally, these are spherical, nonmembrane-bound bodies having complex architectural features associated with profiles of rough endoplasmic reticulum with electron probe x-ray microanalytic peaks of sulphur and calcium (317). Hypercellular soft tissue chondromas composed of enlarged chondrocytes within a variable amount of chondroid matrix that often demonstrate delicate calcifications and contain numerous osteoclast-like multinucleated giant cells closely resemble chondroblastoma of bone (318). There may be a granulomatous reaction ("chondrogranuloma") (319) with multinucleated giant cells along the margins and interlobular vascular channels (Fig. 34-38E). Interpretation should ignore substantial atypia in what is radiologically or clinically a small lesion to avoid unnecessarily disfiguring surgery. Plump, immature-appearing chondrocytes that are bi- or multinucleated are not uncommon and, as in bone lesions, do not necessarily connote malignancy (Fig. 34-38D); lesions associated with them behave no differently from the well-differentiated forms. Aspiration cytology of soft tissue chondroma presents myxofibrillary material and pleomorphic cells, the clinical, radiologic, and cytologic triad being critical for the correct cytologic diagnosis of soft tissue chondroma despite worrisome cell atypia (320). Immunohistochemically, most of the tumor cells except for multinucleated giant cells are positive for vimentin. Cells positive for S-100 protein will be scattered throughout the tumor. Ultrastructurally, the chondroblastic cells have a characteristic microvillous cell border (319).



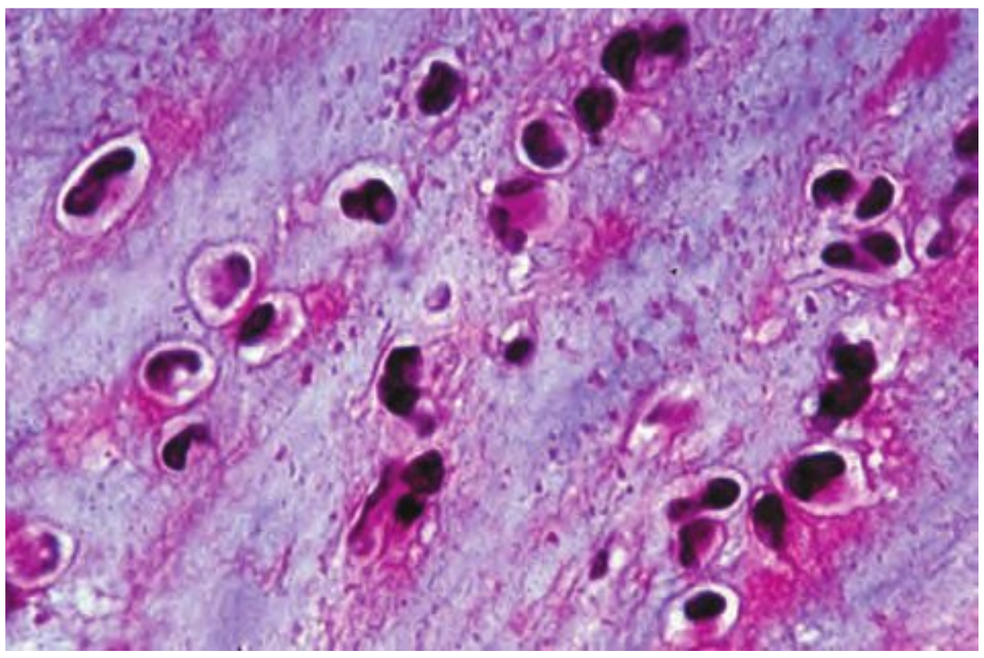
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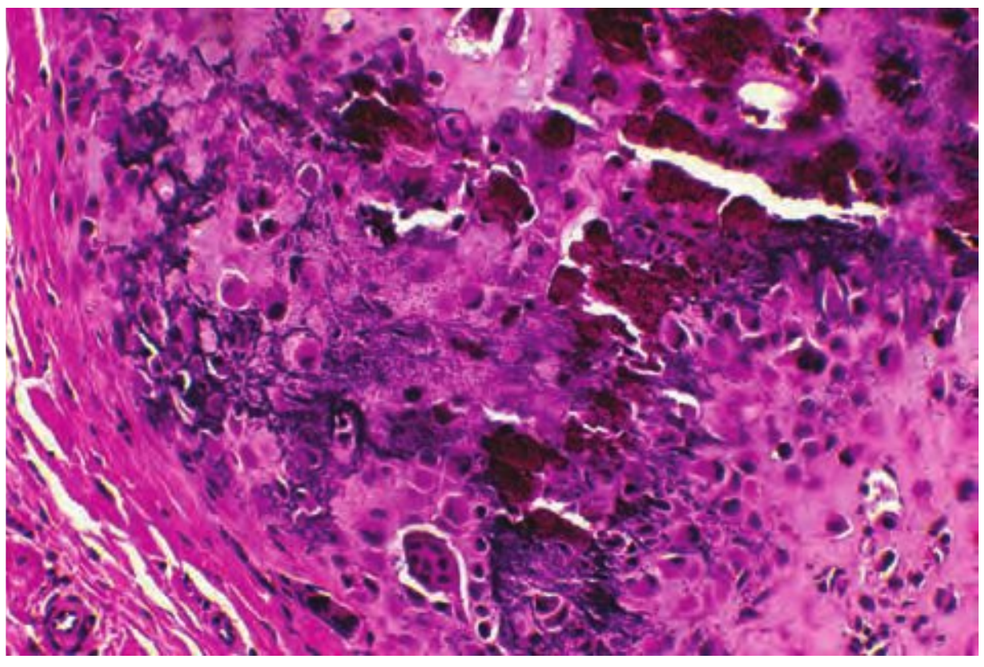
B



C



D



E

FIGURE 34-38. Extraskeletal (soft tissue) chondroma (62-year-old man; toe pain and swelling for 18 years). A: The plain film radiograph submitted with the specimen shows pressure erosion of all but 2 mm of the proximal end of the distal phalanx, which abuts a 1.4-cm diameter rounded unmineralized soft tissue mass at the tip of the toe. B: The tumor consists of a rounded mass of variably cellular, myxoid and hyaline cartilage. C: The gradual emergence of lesional chrondroid tissue from surrounding fibrous tissue suggests an in situ transformation of "fibroblasts," through the stage of chondroblasts, to become quiescent chondrocytes in lacunae. D: Chondrocytes in lacunae often have oblong nuclei, unlike the round nuclei of synovial and intraosseous chondromas. Nuclear size variation and binucleate cells are commonplace in this benign lesion. E: Particulate mineralizations and lacy basophilic mineral deposits around tumor cells in the matrix correlate with the speckled radiographic densities from another case that are seen in one third of these tumors.

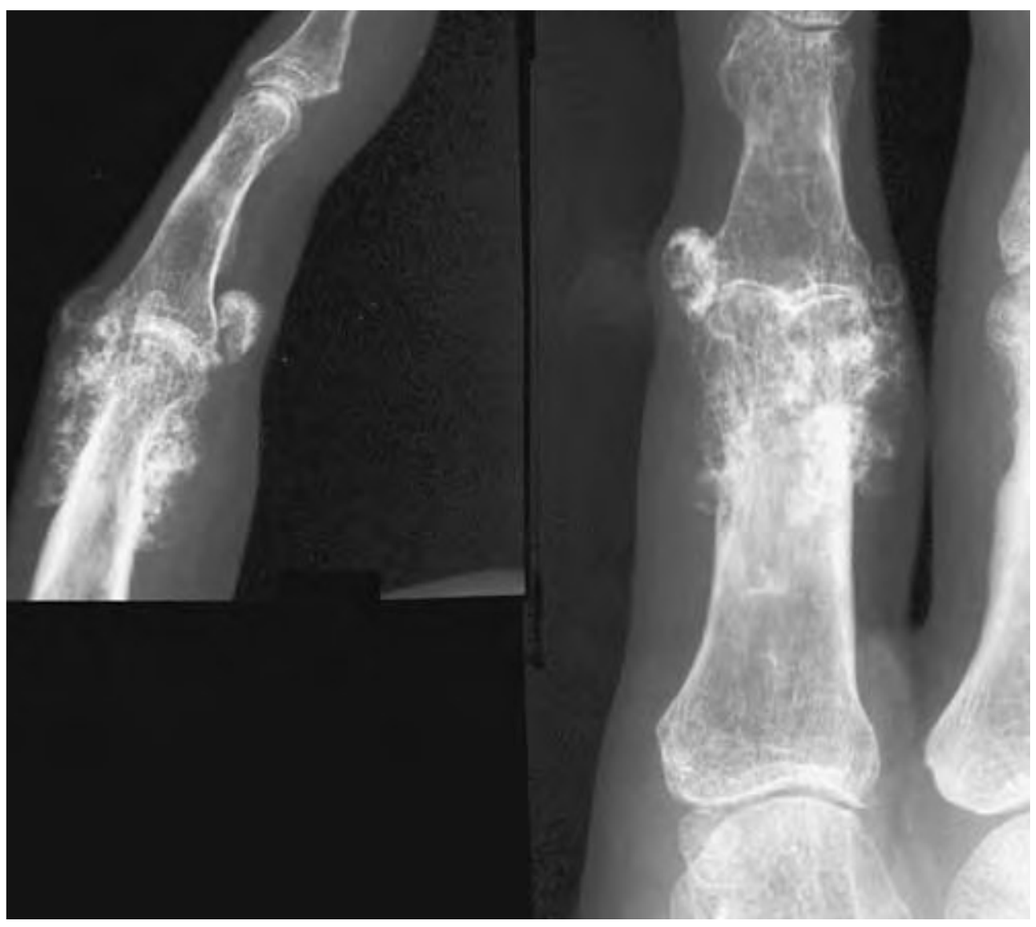
Differential Diagnosis. Chondromas of soft tissue are defined by an asymptomatic and harmless clinical course, lack of connection between the tumor and the underlying bone, slow tumor development, absence of age and sex predominance, and their characteristic tumor histologic picture (321). Extraskeletal chondromas are to be distinguished from developmental cartilaginous rests of branchial origin (usually in the lateral neck in children or infants). A superficial biopsy might retrieve a bit of hyalin cartilage from digital synovial (osteo)chondromatosis (Fig. 34-39). Several soft tissue processes may contain histologically disconcerting cartilage including mixed tumors (apocrine or eccrine), juvenile aponeurotic fibroma (Fig. 34-40), giant cell tumor of tendon sheath, fibromatosis, metaplastic cartilage in occasional lipoma varieties, (teno)synovial (osteo)chondromatosis, cartilage produced in myositis ossificans and fracture callus, metaplastic cartilage in and around tophaceous pseudogout, and soft tissue recurrence of a bone tumor (e.g., chondromyxoid fibroma) (322). Heavily calcified chondromas show granular areas with giant cell reaction resembling tumoral calcinosis or tenosynovial giant cell tumors. Radiographs can distinguish tumors extending from bone, such as osteochondroma or subungual exostosis (323). Extraskeletal chondromas with mineralization of the chondroid matrix will show on plain film radiographs (324), and the remainder can be imaged by MRI (325) or sonography (326).

Pathogenesis. Cytogenetic analyses of soft tissue chondroma report aberrations of chromosomes 6, 11, and 12q13-q15 (327).

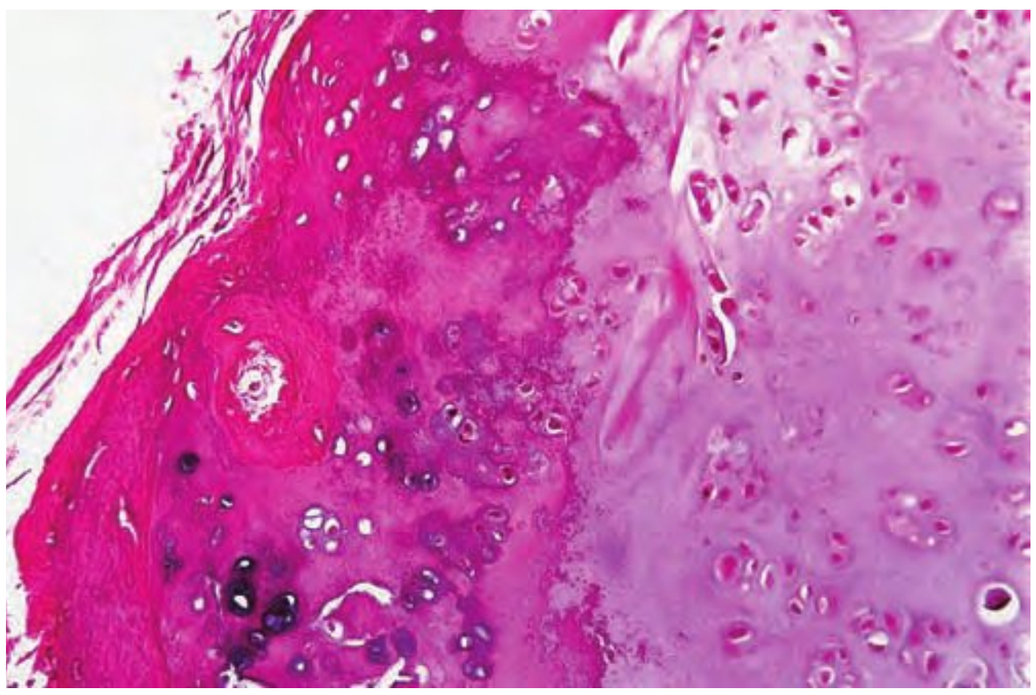
Calcifying (Juvenile) Aponeurotic Fibroma

Calcifying (juvenile) aponeurotic fibroma (CAF) is a rare benign tumor clinically presenting as a painless, mobile solitary mass with a strong predilection for the distal portion of the distal hands and feet of children and young adults (328). Uncommonly, it can occur in extraacral sites such as lumbosacral (329), back, knee region, thigh, forearm, elbow, and arm (330). Minute calcific foci may be evident grossly and on plain films (Fig. 34-40C). Often adherent to dense fibrous connective tissue (e.g., tendon, fascia, or periosteum), CAFs are 1 to 5 cm in maximum dimension, lobulated, and poorly circumscribed with a dense fibrous consistency. Histologically, in the periphery of each chondroid island (Fig. 34-40A) is the transition from rounded mononuclear and fibroblastic cells to chondrocytic cells. The intervening fibromatosis-like areas (Fig. 34-40B) consist of spindle-shaped fibroblastic cells and occasional myofibroblasts. The morphologic pattern of the tumor somewhat mimics embryonal chondrogenesis, and the fibromatosis-like areas may represent an overgrowth of the fibrous layer of the "perichondrium" around some chondroid islands. CAF may represent the cartilage analog of fibromatosis. It is possible to regard this as an organoid tumor having a capacity for bidirectional differentiation into cartilage and fibrous tissue.

CAF has been diagnosed by fine needle aspiration where cytologic examination reveals benign-appearing spindled cells, chondroid cells, multinucleated giant cells, and calcific debris (331). Immunoreactivity always finds vimentin positivity and



A



B

FIGURE 34-39. Synovial osteochondromatosis. (71-year-old man; 5-year history of postinjury finger enlargement). A: Multiple lobules of the lesion around a proximal interphalangeal joint have radiodense rims correlating with rims of enchondral bone. B: Between radiolucent, moderately cellular, solid-appearing hyaline cartilage (right) and the eosinophilic bone that rims it (left) is a basophilic zone of mineralized cartilage. (Courtesy of Newton Sampaio.)

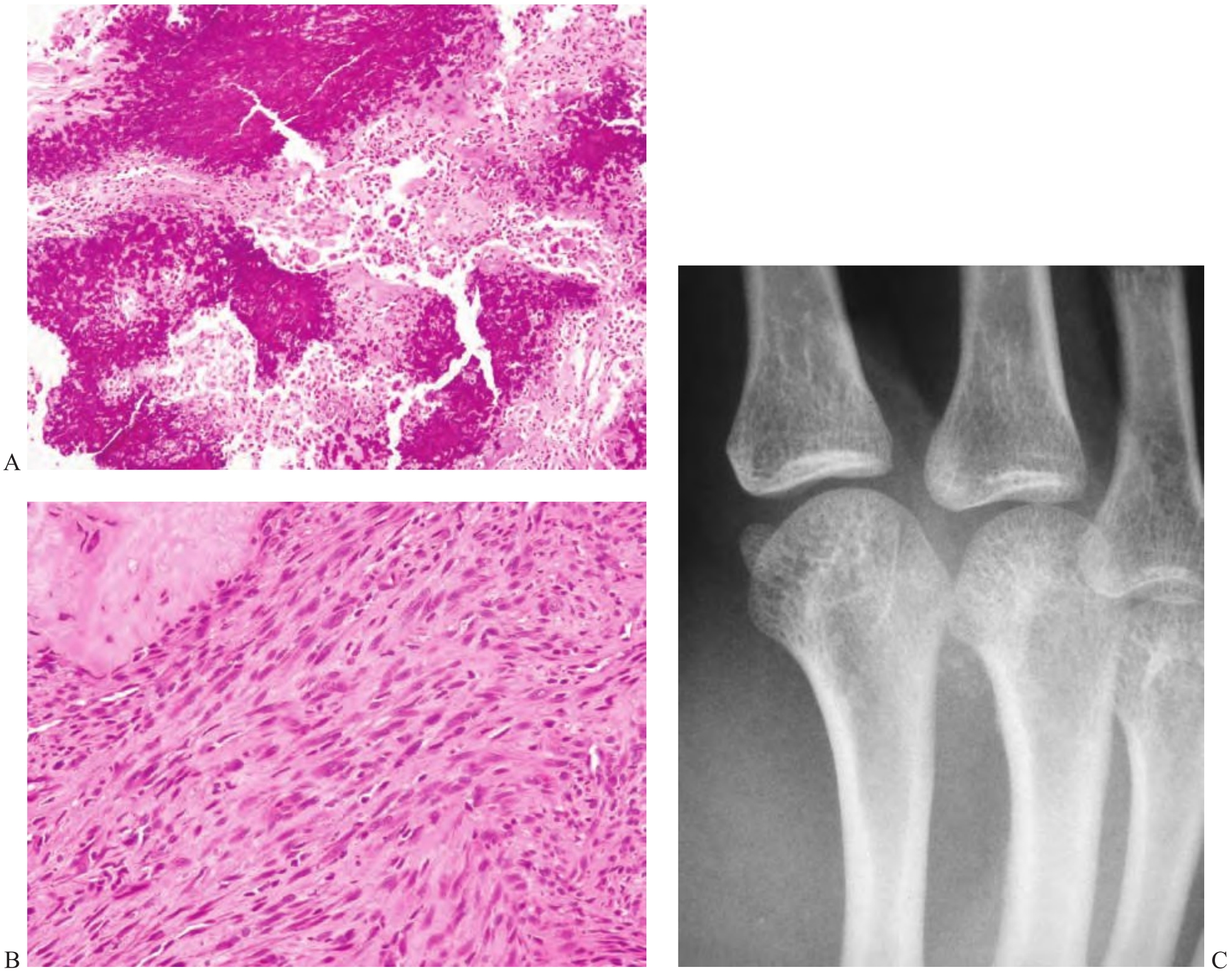


FIGURE 34-40. Calcifying (juvenile) aponeurotic fibroma (27-year-old man; palm). Cartilage islands with characteristic calcification (A) set in a fibromatosis-like background (B) explain the speckled densities in the plain film (C).

possibly also reactivity for muscle-specific actin, smooth muscle actin, CD99, CD34, EMA, S-100 protein, and CD68 (332).

According to Wick and colleagues (333), "[s]urgical management should be conservative for all tumors with the typical appearance of a CAF. In fact, excision and re-excision, if necessary, appear preferable to radical or mutilating surgical procedures to maintain function of the extremity." Fifty percent develop one or more recurrences. Rapidity of growth seems to slow down with increasing age. Various references state that no instances of metastasis have been reported, although others allude to rare malignant transformation (332).

Differential Diagnosis. Familiarity with this entity should help to avoid confusion with other processes, including infantile and extra-abdominal fibromatoses, chondroma of soft parts, and fibrous hamartoma of infancy (330). Unlike mesenchymal chondrosarcoma, which is a high-grade spindle cell sarcoma with islands of hyaline cartilage, mitoses are not obvious in the spindle cell component of the tumor, and a Ki-67 (proliferating cell antigen) reaction should label very few cells.

CHONDROSARCOMA

Extraskeletal Myxoid Chondrosarcoma

Extraskeletal myxoid chondrosarcoma is uncommon and known also as *chordoid sarcoma* because of the resemblance to chordoma (333). It usually affects adult males with a median age at the time of diagnosis in the fifth decade of life (334–336). Only a small minority have been reported in children (334,337,338). The tumor frequently arises in the deep soft tissues, especially of the lower extremity (334). A gradually enlarging mass may or may not be associated with pain (334). Radiographically, the neoplasm is a nodular, radiolucent mass rich in water. Most extraskeletal myxoid chondrosarcomas are

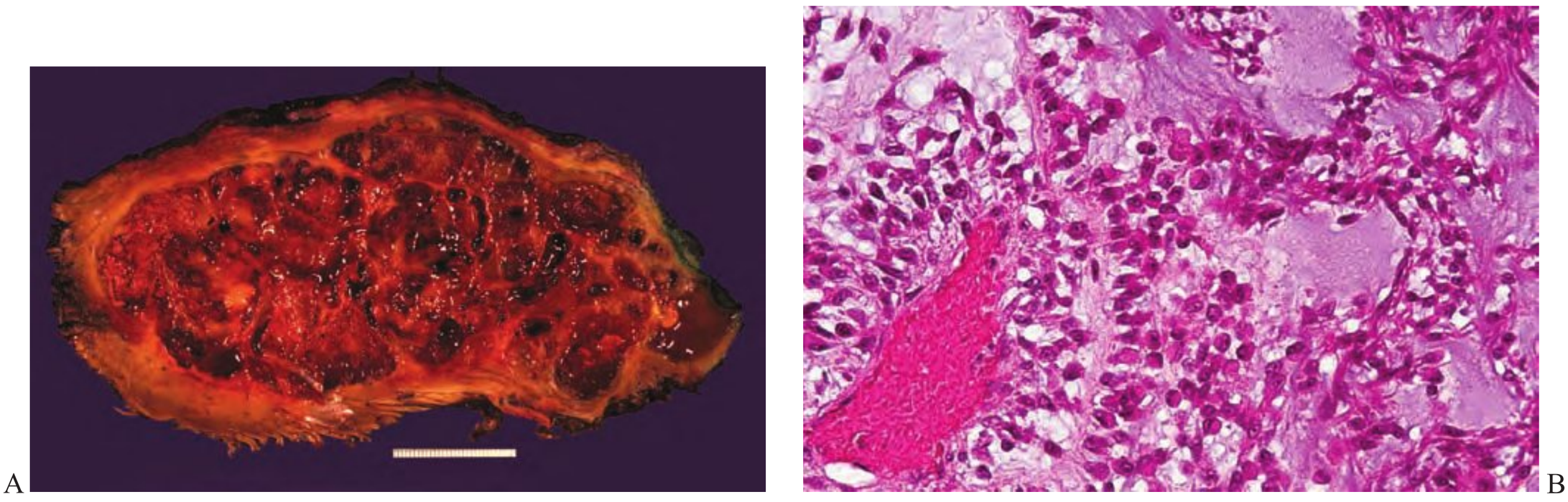


FIGURE 34-41. Extraskeletal myxoid chondrosarcoma (63-year-old man; 17 × 8 × 8-cm anterior thigh mass; death unrelated to tumor 28 months postoperative.) A: The tumor has a glistening myxoid and hemorrhagic cut surface. B: Ovoid and stellate tumor cells form perivascular arrays and cords in a basophilic myxoid background.

large, ovoid, pseudoencapsulated, well-circumscribed tumors with a lobular architecture. The cut surface is tan, gelatinous, and frequently hemorrhagic (Fig. 34-41A).

Histopathology. Extraskeletal myxoid chondrosarcoma is characterized by a proliferation of ovoid and bipolar cells that are enmeshed in a prominent myxoid matrix rich in chondroitin and keratin sulfate (334,339) (Fig. 34-41B). It has a repetitive lobular pattern and chains of neoplastic cells that seem to progress from the periphery toward the center of lobules. Hemorrhage and hemosiderin in the fibrous tissue surrounding the nodules is characteristic. The tumor cells have little to moderate amounts of eosinophilic cytoplasm, and the nuclei are uniform and not pleomorphic. Occasionally, individual tumor cells are surrounded by lacunar spaces; however, the formation of well-developed hyaline cartilage is uncommon. Mitoses are not numerous, and multinucleated giant cells are absent. There may be marked collagenization, spindling of tumor cells, and matrix-poor regions in which the tumor cells grow in solid sheets. Ultrastructurally, the tumor cells of myxoid chondrosarcoma resemble chondroblasts. They are round to elongate and frequently have microvilli. The cytoplasm contains abundant dilated rough endoplasmic reticulum, glycogen, free ribosomes, well-developed Golgi complexes, and mitochondria. Aggregates of microtubules within the rough endoplasmic reticulum are a distinguishing feature (340). The cells may connect by desmosome-like intercellular junctions or those of the macula adherens type (333). The extracellular matrix is rich in amorphous material, small electron-dense particles, and scattered collagen fibers. The neoplastic cells usually stain with antibodies to vimentin and S-100 protein (333,339–341). Some studies have shown that they also may be positive for Leu-7 and EMA. Uniformly, they have been negative for keratin. Extraskeletal myxoid chondrosarcoma is a unique entity defined by the presence of a fusion gene between the orphan nuclear receptor, CHN/NOR1, and a promiscuous partner, most commonly EWSR1 (342). Based on the types of collagen synthesized, the cellular phenotype of extraskeletal myxoid chondrosarcoma is not chondrocytic or prechondrocytic but rather is composed of primitive mesenchymal cells with focal, multidirectional differentiation (343).

Differential Diagnosis. Myxoid tumors of soft tissue encompass a heterogeneous group of lesions characterized by a marked abundance of extracellular mucoid (myxoid) matrix, with marked differences in biologic potential that generate diagnostic challenges for the clinician and pathologist alike (344). The differential diagnosis of extraskeletal myxoid chondrosarcoma is broad and includes many reactive processes and epithelial and mesenchymal neoplasms, chief among them, intramuscular myxoma, juxta-articular myxomas, neural neoplasms, cutaneous and soft tissue myoepitheliomas (345), benign polymorphous mesenchymal tumor of soft parts (346), myxoid liposarcoma, myxofibrosarcoma (myxoid malignant fibrous histiocytoma), metastatic carcinoma, metastatic melanoma with myxoid stroma, and chordoma. Myxoid chondrosarcoma does not have the vascular pattern typical of myxoid liposarcoma and lacks lipoblasts. Immunohistochemistry will help to sort it out.

Pathogenesis. Cytogenetic studies are few but so far have shown reciprocal translocations involving chromosomes 9 and 22 (347) and translocations between chromosomes 2 and 13. Behavior is as a low-grade sarcoma.

Mesenchymal Chondrosarcoma

Mesenchymal chondrosarcoma (348) represents the prototypic neoplasm of prechondrogenic undifferentiated cells undergoing multifocal chondrocytic differentiation (134) and can involve the skin (349). Chondroid-type calcifications and foci of low signal intensity within enhancing lobules reflect its dual histopathologic morphologic characteristics of differentiated

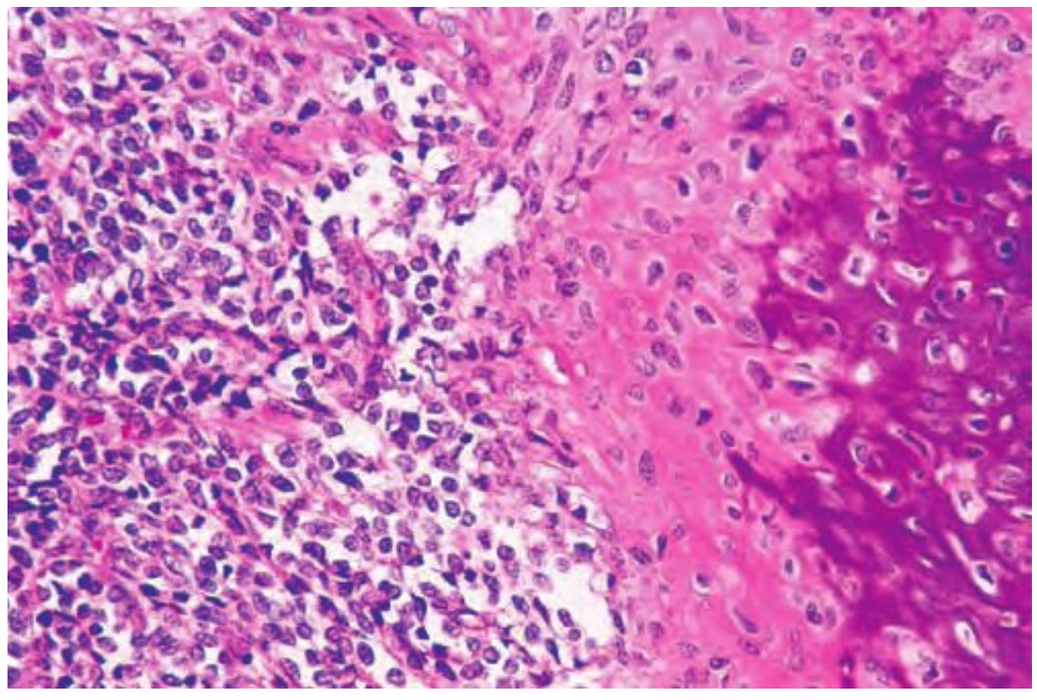


FIGURE 34-42. Mesenchymal chondrosarcoma. Small, round, undifferentiated cells (left) might easily be mistaken for Ewing's sarcoma or lymphoma were it not for the sporadic island of cartilaginous product (right).

cartilage islands interspersed within highly cellular undifferentiated mesenchyme (Fig. 34-42) (350). The cartilaginous areas are S-100 positive and exhibit strong CD99 reactivity in more than 50% of the small round blue cells with a distinct membrane pattern of staining (351). The expression of p30/32 (MIC2) is typically restricted to the small cell component. Positivity of small cells for desmin and/or smooth muscle actin may be seen; and in rare cases, more diffuse rhabdomyoblastic differentiation indicating mesenchymal chondrosarcoma is another primitive neoplasm with polyphenotypic differentiation and features that overlap those of other small cell malignancies of bone and soft tissue (352).

Differential Diagnosis. The cellular areas of mesenchymal chondrosarcoma can mimic fibrosarcoma, Ewing's sarcoma, malignant hemangiopericytoma, peripheral neuroectodermal tumor, and synovial sarcoma.

Pathogenesis. An identical robertsonian translocation involving chromosomes 13 and 21 [der(13;21)(q10;q10)] was detected in two cases of mesenchymal chondrosarcoma, possibly representing a characteristic rearrangement for this histopathologic entity (353).

OSSEOUS AND CHONDROID LESIONS, RARER STILL

Embryonic tissue and organ development are initiated from three embryonic germ layers: ectoderm (skin and neuron), mesoderm (blood, bone, muscle, cartilage, and fat), and endoderm (respiratory and digestive tracts). In former times, it was believed that cell types in each germ layer were specific and did not cross from one to another throughout life. A new finding is that one tissue lineage can differentiate across to another tissue lineage, and this is termed *transdifferentiation* (354). For example, skin-derived precursor cells (ectoderm) can transdifferentiate to osteoblastic cells (mesoderm), explaining the potential of skin appendage tumors to contain mesenchymal elements. Ossification in chondroid syringomas or mixed tumors of the skin employs the enchondral mechanism.

The appearance of cutaneous lesions in a patient with a prior history of chondrosarcoma should alert the clinician to the rare possibility of a *metastatic chondrosarcoma* (355). Such metastases preceding the diagnosis of primary chondrosarcoma are anecdotal. These metastases can be either single or multiple, with a slight predilection for the head and neck region (356).

Metaplastic carcinoma (a.k.a. carcinosarcoma, sarcomatoid carcinoma, malignant mixed tumor) is a biphasic tumor comprising malignant epithelial and heterologous mesenchymal elements (357). Mere vimentin reactivity alone is not enough. Leiomyosarcomatous areas have been the basis for a designation of metaplastic carcinoma (primary "carcinosarcoma") in a very few cases (357,358); better to hold out for a tumor product visible without immunohistochemistry (i.e., production of chondroid, osteoid or fat). In view of recent developments and progress in the understanding of the possible histogenesis of such tumors, *biphasic sarcomatoid carcinoma* or *metaplastic carcinoma* rather than carcinosarcoma are the most appropriate terms (357). Many conclude that the sarcomatous component of the tumor is best regarded as a metaplastic transformation of the carcinomatous component.

Primary carcinosarcoma of the skin is uncommon, and the count of exactly how many cases have been reported varies, even in three separate reports, all of which were published in 2005: Only 20 cases of primary cutaneous carcinosarcoma have been described in the world literature according to Ram and associates (359), 23 in the English literature according to Bigby and colleagues (358), and 38 according to Tran and coworkers (360). Most of these tumors were seen on the head and neck region of older individuals, both male and female. Microscopically, the more common carcinoma component is a squamous cell carcinoma followed by basal cell carcinoma, whereas the most common sarcoma component is osteosarcoma.

Tran's literature review in 2005 (360) identified 38 cases of cutaneous carcinosarcoma that could be broadly classified into two distinct groups. Epidermal-derived (basal or squamous cell carcinoma epithelial component with a sarcomatous component) carcinosarcomas arose on the sun-damaged skin of the head and neck of elderly males (mean age 72 years) and had a 70% 5-year disease-free survival. In contrast, adnexal carcinosarcomas (spiradenocarcinoma, porocarcinoma, proliferating trichilemmal cystic carcinoma, or matrical carcinoma) occurred in younger patients (mean age 58 years), showed recent growth in a long-standing nodule, and had a 25% 5-year disease-free survival. Malignant heterologous malignant mesenchymal elements included osteosarcoma, chondrosarcoma, leiomyosarcoma, and rhabdomyosarcoma. In contrast to metaplastic carcinomas arising in visceral sites, those primarily arising in the skin do not appear to behave in a very aggressive manner.

Although *dedifferentiated* is a concise term of which generations of pathologists have been exposed, it is not reflective of

actual tumor biology, nor is it entirely correct when applied to epithelial tumors, because the so-called dedifferentiated component is still recognizable as carcinoma and usually is an adenocarcinoma. In fact, this term is one of the most widely used misnomers in pathology jargon, because it merely reflects a type of tumor progression—a subpopulation of tumor cells within a low-grade tumor fails to differentiate along expected lines rather than transforming in a retrograde fashion toward a more protean morphology. Hence, high-grade transformation is a more appropriate description of this phenomenon (361).

Breast carcinoma is the most common origin of cutaneous metastasis in women but is usually a ductal or lobular histologic type. *Sarcomatoid (metaplastic) carcinoma* of the breast, although a well-established aggressive neoplasm, is very uncommon. Its metaplastic elements, derived from carcinomatous elements, span all types of mesenchymal differentiation. Skin metastasis from such lesions is extremely rare but can be chondrosarcomatous (362).

Malignant mesenchymoma, defined as a sarcoma with three or more lines of differentiation, can occur in skin (e.g., a tumor in an abdominal incision scar composed of leiomyosarcoma, chondrosarcoma, and osteosarcoma) (363).

Malignant melanomas showing foci of osteocartilaginous differentiation are extremely rare, with only 18 cases reported as of 1998 (364), a review that added two primary mucosal malignant melanomas (vagina and oral cavity). Chondroid change in the absence of osteogenic differentiation is extremely rare in malignant melanoma, but melanoma should be considered in the differential diagnosis of primary cutaneous neoplasms exhibiting cartilaginous differentiation (364). Oral mucosal melanomas with osteocartilaginous differentiation are to be distinguished from malignant change in a pleomorphic adenoma, sarcomatoid carcinoma, osteogenic sarcoma, and mesenchymal chondrosarcoma. Primary vaginal melanoma with cartilaginous differentiation must be distinguished from primary malignant mixed müllerian tumor (363).

Atypical fibroxanthoma can contain areas of chondroid differentiation that resemble chondrosarcoma and have S-100 positivity (366).

A gastrointestinal carcinoma metastasis is reported in cutaneous osseous metaplasia (367).

Pseudocyst of the auricle is a benign condition that presents as a fluctuant swelling of the ear, most commonly in young Asian males (368). Histologically, there is an intracartilaginous cyst with no epithelial lining, often with a sparse lymphocytic inflammatory response (Fig. 34-43).

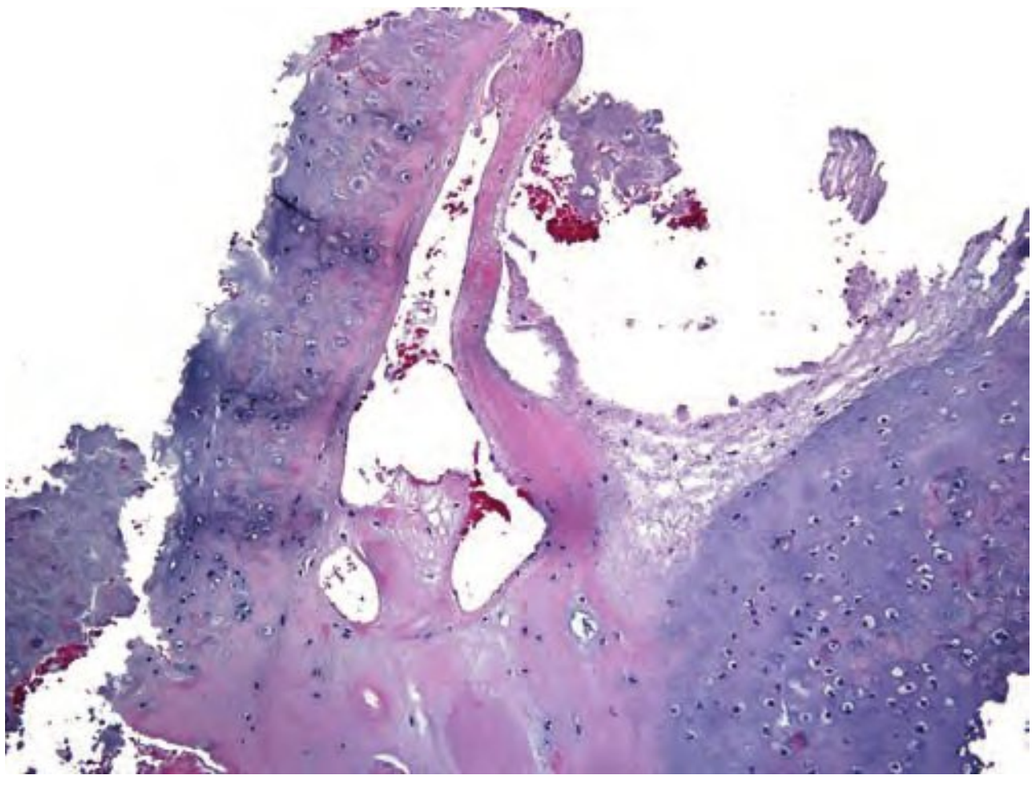


FIGURE 34-43. Pseudocyst of the auricle. There is a space in the auricular cartilage lined by chondroid tissue with a sparse inflammatory response. There is no epithelial lining, which is consistent with a pseudocyst.

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CHAPTER 35

Richard J. Reed
Donald R. Pulitzer

Tumors of Neural Tissue

GENERAL ANATOMIC RELATIONSHIPS STRUCTURAL COMPONENTS

A *nerve*, an anatomic unit, is composed of nerve fibers, endoneurium, and perineurium. *Nerve fibers*, the functioning elements, are aggregated to form axial bundles (parallel arrays of nerve fibers with longitudinal symmetry). Individually, each fiber consists of an axon, or axons, and related *Schwann cells* (1–4). *Axons* are cytoplasmic extensions from the perikaryon of *neurons* in the central nervous system or from ganglion cells in sympathetic ganglia. The peripheral portion of an axon, along its entire length from its origin to terminus, is enclosed by enveloping Schwann cells. Along nonmyelinated nerve fibers, a single Schwann cell encloses segments of several axons in cytoplasmic invaginations. Along myelinated nerve fibers, a single Schwann cell encloses a segment of an axon in concentric layers of its cytoplasmic membrane; where neighboring Schwann cells abut, end to end, a node of Ranvier is formed. In sympathetic ganglia, neurons are rimmed by satellite cells; Schwann cells are substituted for satellite cells along axons. Ultrastructurally, microfilaments, specialized intermediate (neural) filaments, and microtubules are components of axons. Schwann cells have complex cytoplasmic processes; they are surrounded by continuous basal lamina and contain densely packed intermediate filaments (4).

The *perineurium*, a tubular fibrous sheath, delimits each nerve. It extends from the pia-arachnoid of the central nervous system to the terminus of each nerve or to specialized sensory receptors. Slender, bipolar or tripolar cells (*perineurial cells*) are isolated among the concentric fibrous lamellae of the perineurium. Ultrastructurally, discontinuous basal lamina, numerous pinocytotic vesicles, and tight intercellular junctions are characteristics of the perineurial cells (4). The perineurium is a relatively impervious barrier.

The *endoneurium*, a delicate, mucinous matrix, is confined by the perineurium; it provides a cushion for the axial collection of nerve fibers. Components of the endoneurium include fibroblasts ($CD34^+$), mast cells, collagen, a myxoid matrix, and capillaries.

In proximal (axial) locations, several large nerves in bundles are encased in a dense fibrous matrix, the *epineurium* (a fibrous sheath that, at the junction of the spinal nerves with the central nervous system, is continuous with the dura mater). Individual nerves, at some place along their course, leave the bundles to continue without an epineurium. Near the terminus of each nerve, nerve fibers extend beyond an open-ended perineurium into the mesenchyme; naked axons even extend into epithelium. Ensheathed receptors of the skin include mucocutaneous corpuscles and the corpuscles of Vater-Pacini, Meissner, and Merkel. Meissner corpuscles are ovoid structures in which an axon is sinuously enclosed in stacks of distinctive cells. Pacinian corpuscles are spherical structures in soft tissue. In them, concentrically laminated, distinctive cells and fibrous lamellae are arranged around a centrally located axon (Fig. 35-1). The ultrastructural features of the laminated cells of both Meissner and pacinian corpuscles are perineurial cell-like, with the exception of the innermost cells that ensheathe the central axon (5).

ONTOGENY AND REACTIONS TO INJURY AS RELATED TO THE INTERPRETATION OF PHENOTYPIC EXPRESSIONS OR PATTERNS IN NEOPLASIA

Neurosustentacular cells of peripheral nerves, related cells of the peripheral ganglia, melanocytes, and even cells of some cranial mesenchyme are all of neurocristic origin.

In reactions of peripheral nerves to injury, reserve cells of neural origin proliferate; they subsequently express either a schwannian or a perineurial phenotype. Expressions of phenotype are fortuitous; the environs in which uncommitted reserve cells find themselves influence the expressions. The available options probably include a capacity to function facultatively as endoneurial fibroblasts (6).

Histologic interpretations are based on images, both real and virtual; the virtual images are evoked from the pathologist's mental stores; the richness of the stores is a reflection of the experience of the pathologist. Virtual images, once recalled and compared with real images, form the basis for histologic interpretations. Various patterns, some relating to the structural components of peripheral nerves, some to the embryologic development of their neurocristic precursors, and some to the reactions of normal nerves to injury, provide clues for the interpretation of the puzzling histologic patterns of nerve sheath tumors. In turn, the interpretations, often with an

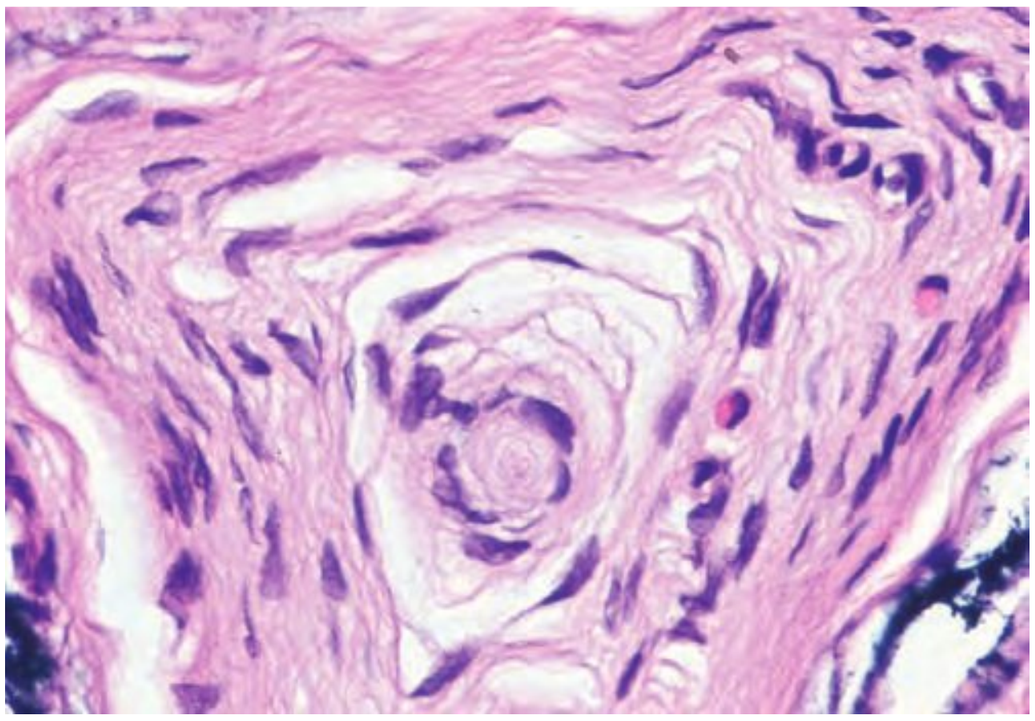


FIGURE 35-1. Pacinian corpuscle. This pacinian body has a distorted outline. At the periphery, there is a well-formed dense fibrous membrane. Elongated spindle cells are compressed among the compactly arranged collagen fibers. At the center, an acidophilic punctum is representative of a single axon. Cytoplasmic processes of sheath cells are clustered about the axon. There is an intermediate zone in which spindle cells are loosely spaced in a clear matrix. Regardless of the results of immunoreactions, the loosely spaced spindle cells have the morphologic features of perineurial cells. There is a morphologic continuum from periphery to, but not including, axon.

element of luck, can lead to the structuring of a proper histologic diagnosis. For example, the structure of Meissner corpuscles is recapitulated in the tactile corpuscle–like structures (tactoid bodies) of diffuse (extraneural) neurofibromas (3). Some of the features of wallerian degeneration (Fig. 35-2) are recapitulated in a most distorted manner in granular cell nerve sheath tumor. The intravaginal hyaline nodules of Renaut (3) may provide a model for the patterns manifested in nerve sheath myxomas.

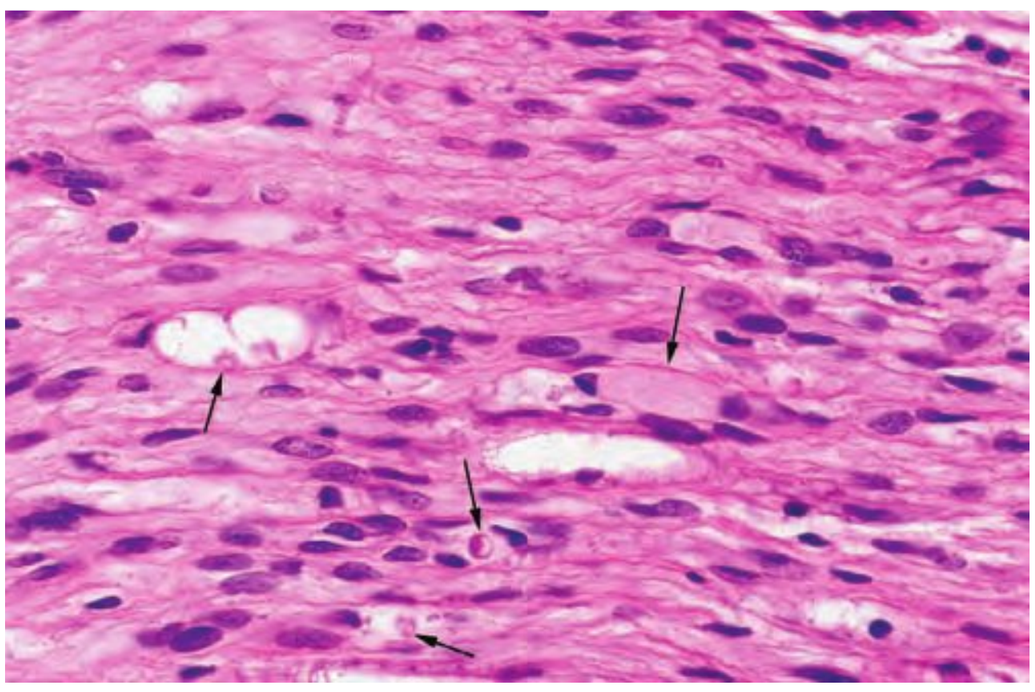


FIGURE 35-2. Wallerian degeneration. This peripheral nerve, bordering the site of an injury, shows poorly defined myelin sheaths; as a result, reticular fibers (basement membranes) of individual Schwann cells are more closely spaced. Scattered microcystic areas are representative of sites in which myelin sheaths have been disrupted. In some of the defects, there are globular deposits, some of which are concentrically laminated (black arrows); these "myelin figures" are collections of lipid membranes. Some of the Schwann cells are swollen and have pale, faintly granular cytoplasm.

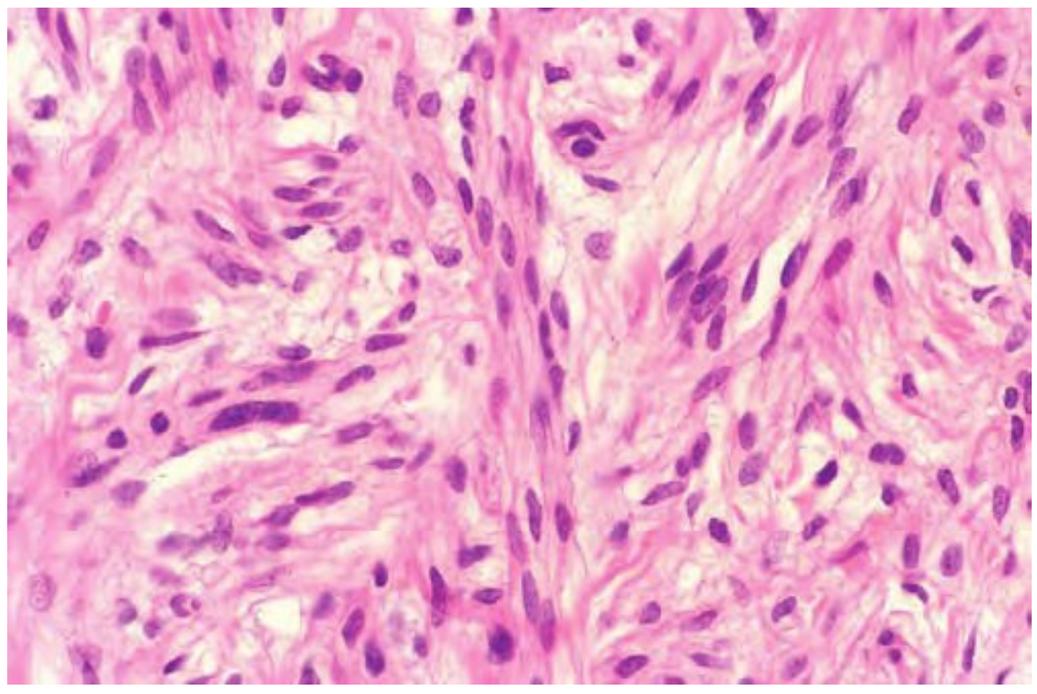


FIGURE 35-3. Extraneural neuroma. In this extraneural neuroma, Schwann cells cluster to form thin fascicles among collagen bundles of the preexisting soft tissue. Proliferating axons, as they extend in the process of repair into the fibrous tissue, provide a scaffold for proliferating Schwann cells.

When damaged, axons form multiple, sproutlike extensions (6). In the ensuing reparative process, newly formed Schwann cells accompany newly formed axons (Fig. 35-3). These patterns are incompletely recapitulated in spontaneous, intraneural neuromas. The distorted patterns that are manifested in intraneural neurofibromas, and even in some small schwannomas, may relate to a (temporary?) local excess of thin, nonmyelinated axons.

PHENOTYPES AND HISTOCHEMICAL AND IMMUNOHISTOCHEMICAL REACTIONS

Neurosustentacular cells, melanocytes, and even some mesenchymal cells, being of neurocristic origin, share a common progenitor. In tumors of peripheral nerves, the structural qualities of either Schwann cells or perineurial cells are commonly expressed, but the expression of either histologic cell type may, in turn, be associated with an immunohistochemical marker of a conflicting type. For example, the cells of tactile corpuscles mark with antibodies for S100 protein (as do Schwann cells) but have the ultrastructural features of perineurial cells.

S100 protein is a lightly acidic, calcium-binding protein of glial cells but also is expressed in a variety of other cells, including melanocytes, lipocytes, chondrocytes, some cells of sweat glands, and Schwann cells. Neuron-specific enolase (NSE) is a cytoplasmic product common to a variety of cells, including Schwann cells, and both neurons and their axons. An immunoreaction for the demonstration of neural filaments

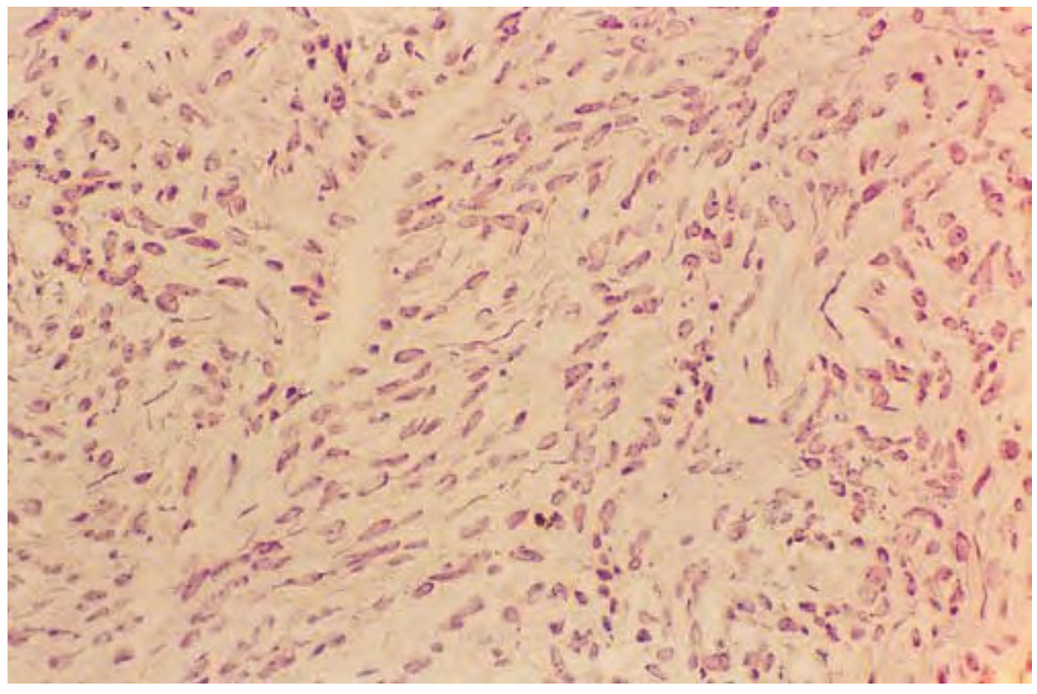


FIGURE 35-4. Extraneural neuroma (Bodian stain). The loosely spaced, delicate fibers are axons; axons are argyrophilic.

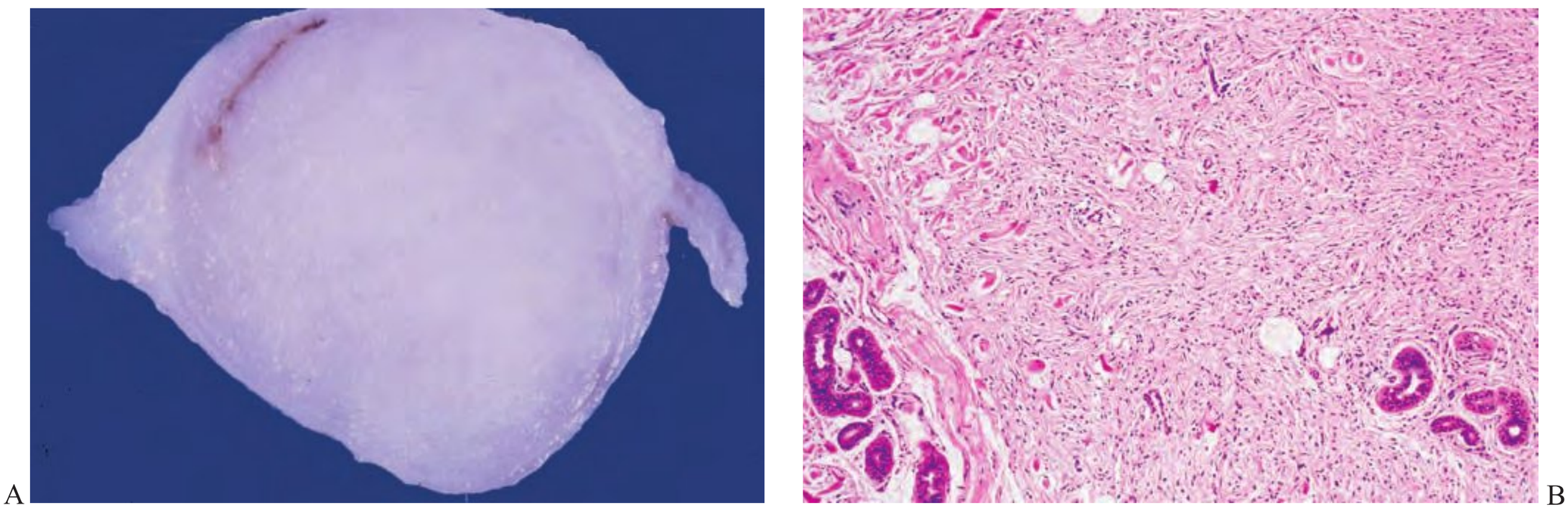
provides a pure demonstration of the reaction of axons. Silver impregnation techniques are the time-honored method of demonstrating axons (Fig. 35-4) but are less sensitive than immunohistochemical reactions; fewer axons are demonstrated. The Luxol-fast blue stain and antibodies for either myelin basic protein (MBP) or CD57 (Leu-7) antigen demonstrate myelin products. An immunoreaction for glial fibrillary acidic protein (GFAP) is positive in glial cells; it is also positive in some of the cells in some tumors of salivary glands. In some large schwannomas of soft tissue, neoplastic Schwann cells are immunoreactive for GFAP. Epithelial membrane antigen (EMA) is a cytoplasmic antigen commonly expressed in a variety of normal and neoplastic tissue, including cells of the perineurium and sebaceous cells.

Structural peculiarities take precedence over immunohistochemical findings; the commonness of a reaction for S100 protein does not take precedence over the morphologic distinctions between schwannoma and neurofibroma. The commonness of a reaction for EMA should not be the basis for a grouping of morphologically dissimilar lesions in a category of "perineurioma," a currently popular practice.

NEUROFIBROMAS (HAMARTOMAS WITH PHENOTYPIC DIVERSITY)

Extraneural sporadic cutaneous neurofibromas (ESCNs) (the common, sporadic neurofibromas) are soft, polypoid, and skin colored or slightly tan; they are small (rarely larger than 1 cm in diameter) (Fig. 35-5A). They usually arise in adulthood. The identification of as many as four small cutaneous neurofibromas in a single patient, in the absence of other confirmatory findings, would not qualify as stigmata of neurofibromatosis.

Histopathology: Under low magnification, most examples of ESCN are faintly eosinophilic. These small tumors of the reticular dermis are circumscribed but not encapsulated (Fig. 35-5B); they are extraneural (3,4). Thin spindle cells with elongated, wavy nuclei are regularly spaced among thin, wavy collagenous strands (Fig. 35-6). The strands are either closely spaced (homogeneous pattern) or loosely spaced in a clear matrix (loose pattern) (1); the two patterns often are intermixed in a single lesion. Rarely, ESCNs are composed of widely spaced spindle and stellate cells in a myxoid matrix. The regular spacing of cutaneous adnexa is relatively preserved in cutaneous neurofibromas (Fig. 35-5B). Small nerves that extend into a common cutaneous neurofibroma occasionally are



A B

FIGURE 35-5. A: Extraneural sporadic cutaneous neurofibroma. This symmetrically rounded, circumscribed tumor bulges into the subcutaneous fat. The cut surface is white and homogeneous. B: Extraneural sporadic cutaneous neurofibroma. A circumscribed, nonencapsulated tumor of the dermis is composed of loosely spaced spindle cells and wavy collagenous strands. Near the margin, collagen bundles of the dermis are entrapped in the lesion. A cluster of sweat glands also is present within the tumor; in this relationship, a defect in dermal mesenchyme has been inlaid with a neurocristic derivative.

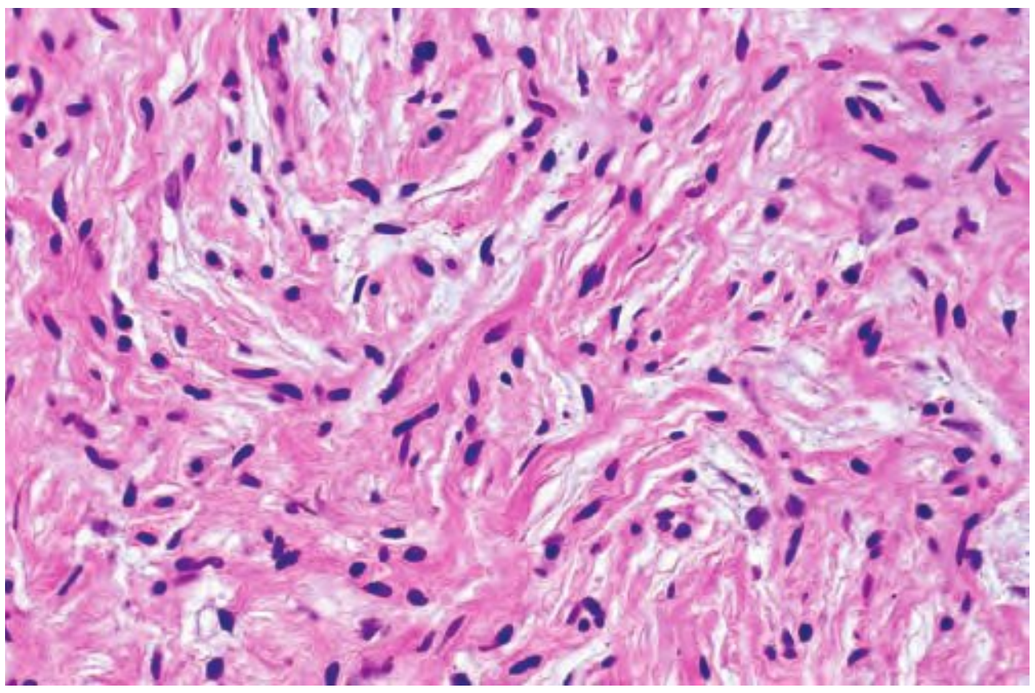


FIGURE 35-6. Extraneural sporadic cutaneous neurofibroma. Thin spindle cells are associated with thin, wavy collagen bundles. The cells and collagen bundles are loosely spaced in a clear or mucinous matrix.

enlarged and hypercellular. Tactoid (tactile corpuscle–like) bodies and pigmented, dendritic melanocytes are most uncommon (3).

Histogenesis. With silver impregnations (Bodian or Bielschowsky stain), only a few axons, mostly in small, embedded nerves, are demonstrable. Immunohistochemically, axons are more uniformly and generously represented. With monoclonal antibodies for NSE, the reaction of the axons of a cutaneous neurofibroma is intense; it is either punctate or fiber-like in a background of diffuse, but faint staining of the cytoplasm of the enveloping Schwann cells. A similar response, but without diffuse cytoplasmic staining, characterizes the reaction for neural filaments. Both of these immunochemical reactions and ultrastructural features have utility in the documentation of the schwannian (neurosustentacular) nature of the tumor cells in ESCN.

Differential Diagnosis. A schwannoma is intraneural (encapsulated); it usually does not contain axons (as demonstrated by antibodies to neurofilaments).

In a neurotized nevus, nests and fascicles of nevocytic cells usually can be identified in scattered foci. Tactile corpuscle–like bodies are common in neurotized nevi; they are rare in ESCN.

In the absence of an intraneural component, some cutaneous neurofibromas of neurofibromatosis are histologically indistinguishable from ESCN; cutaneous neurofibromas of neurofibromatosis, which in histologic patterns resemble sporadic variants, usually are larger than sporadic variants.

Some sporadic, cutaneous neurofibromas, including subcutaneous variants, differ in patterns from ESCN. Confined, at least in part, by the perineurium of the nerve of origin, they are circumscribed and variable intraneural (1–4). Their intraneural patterns are indistinguishable from the patterns variously manifested in the intraneural components of plexiform neurofibromas.

On rare occasions, the pattern of a dermatofibroma or that of a subcutaneous, spindle cell lipoma might be mistaken for that of a nerve sheath tumor.

NEUROFIBROMATOSIS (PHENOTYPIC DIVERSITY EXPRESSED IN GENETICALLY DETERMINED HAMARTOMAS AND NEOPLASMS)

Multiple cutaneous neurofibromas are characteristic of most, but not all, examples of neurofibromatosis (von Recklinghausen's disease). Other important stigmata include plexiform (intraneural) and deep, diffuse (extraneural) neurofibromas; multiple periareolar neurofibromas (Fig. 35-7); intraocular Lisch nodules; and macular, cutaneous hyperpigmentations (e.g., café-au-lait spots and bilateral axillary freckling) (7,8).

Neurofibromatosis type I (NF1) can arise as an autosomal dominant condition, but in nearly half of the patients, it arises by spontaneous mutation (9). In NF1, cutaneous neurofibromas usually appear first in late childhood or in adolescence; the disease progresses by showing gradual increases in the size and number of neurofibromas.

For NF1, the gene, which is huge, has been localized to the pericentromeric region of the long arm of chromosome 17 (10). A high spontaneous mutation rate, an attribute of huge genes, would account for the high incidence of sporadic cases. The gene shows functional and structural homology with guanosine triphosphatase–activating protein, which controls the ras oncogene. In turn, the role of the ras oncogene in growth, development, and differentiation may be aberrantly expressed in the NF1 phenotype (10). The protein product of the gene is called neurofibromin (11).

In NF1, superficial peripheral nerves, deep peripheral nerves, nerve roots, and the autonomic nerves of viscera and blood vessels may be affected. Large, pendulous plexiform neurofibromas have the flabby texture of a "bag of worms." Deep, diffuse neurofibromas are poorly defined at their limits with the adjacent soft tissue (3). Changes sometimes associated with large neurofibromas of the skin and subcutaneous fat provide an elephantiasic quality. Spinal nerve root tumors may cause compression of the spinal cord (9). Tumors of the central nervous system occur in 5% to 10% of the patients (7). A neurofibroma that is adjacent to bone or is intraosseous may erode the bone. Lesions that are variably associated with neurofibromatosis include

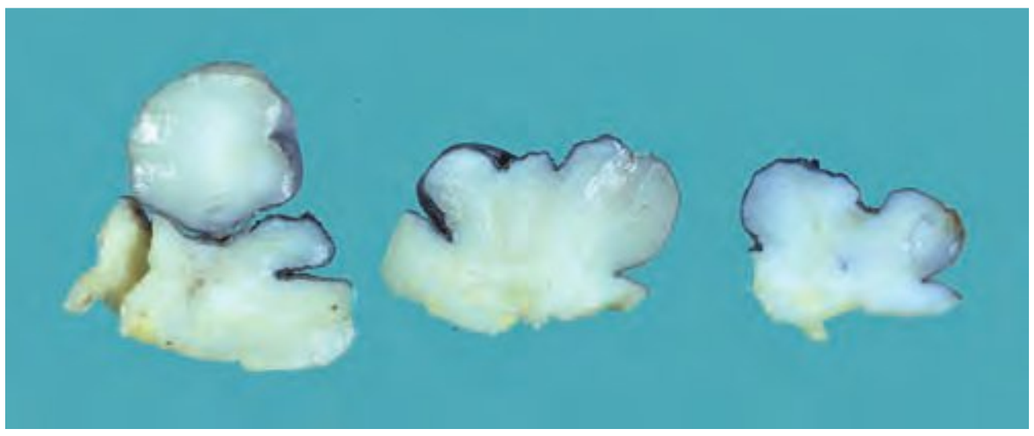


FIGURE 35-7. Periareolar neurofibroma. The lesion has been breadloafed. Multiple polypoid components project above the skin surface. The cut surface is white and glistening. The lesion diffusely involves the dermis and protrudes irregularly into the subcutaneous fat.



FIGURE 35-8. A: Acoustic neuroma (schwannoma involving the VIIIth cranial nerve and meningiomas). The schwannoma is expansile and white. Portions of a meningioma are also represented along the base of the brain; other portions had been surgically removed. The patient had neurofibromatosis. B: Acoustic nerve schwannoma (cut surface of brainstem at the level of the pons). On the right, an acoustic neuroma (schwannoma) involves the VIIIth cranial nerve. The cut surface focally is hemorrhagic. In other areas, the cut surface is tan, a coloration often seen in association with hemosiderin deposits.

kyphoscoliosis and an increase in the length of long bones. NF1, diffuse intestinal ganglioneuromatosis, and multiple endocrine neoplasia (MEN) type 2b are unpredictably associated (12,13). Gastrointestinal stromal tumors are more common in NF1 than in the general population (14). An association among juvenile xanthogranuloma, juvenile chronic myelogenous leukemia, and NF1 has been observed (15).

In localized or segmental neurofibromatosis, cutaneous neurofibromas are few in number, and the family history is negative (16–18).

In *neurofibromatosis type 2* (NF2) (a genetically distinct variant), café-au-lait spots, neurofibromas, schwannomas, and a variety of intracranial tumors, including bilateral schwannomas of the acoustic nerves, are manifestations (11) (Fig. 35-8). Meningioangiomatosis has been reported in association with NF2 (19). The gene locus has been linked to chromosome 22q11-q13. The protein gene product, called merlin, is similar to a group of cytoskeleton-linked proteins (11).

The syndrome of *multiple schwannomas* (schwannomatosis or neurilemmomatosis) (20) is characterized by multiple schwannomas and plexiform schwannomas. It has been characterized as a clinical entity, distinct from NF2 (21).

Café-au-lait spots occur in nearly all patients with neurofibromatosis. In the sequence in which clinical findings first appear, they usually precede cutaneous tumors (8). Although a few café-au-lait spots are occasionally seen in patients without neurofibromatosis, the presence of more than six spots, each exceeding 1.5 cm in diameter, is indicative of neurofibromatosis (7,9).

Histopathology. The histologic spectrum of neurofibromas in NF1 is broad. Cutaneous, extraneural variants (as manifested in ESCN), cutaneous or deep, circumscribed (intraneural) variants, plexiform (intraneural) variants (Fig. 35-9), deep, diffuse (extraneural) variants, and various combinations thereof are manifested in an array of histologic patterns.

In many deep, circumscribed (intraneural) neurofibromas and in most plexiform (intraneural) neurofibromas, axial bundles (which are composed of symmetrically arranged nerve fibers) are remnants of the axial bundle of the nerve of origin (Figs. 35-9 and 35-10) (3,4,22) Their role in the histogenesis of NF is uncertain. The axial bundle retains its symmetry in a field of distorted and asymmetric patterns (Fig. 35-10). In some axial bundles, Schwann cells are hyperplastic and tightly packed. In areas, these remnants of the nerve of origin focally evolve into micronodules composed of interlacing fascicles of Schwann cells; the micronodules qualify as *microscopic schwannomatosis* (3). Many of these cellular nidi (micronodules) may be independent of a true axial bundle, but all seem to function as growth centers (Fig. 35-11). Cells and collagenous strands stream from the periphery of these nidi (growth centers); they extend asymmetrically into the expanded, mucinous, endoneurial matrix. In some intraneural variants, similar patterns of streaming cells and collagenous strands blend with (or arise from) the perineurium; in such lesions, the perineurium appears to contribute to the tumor; the cells that stream from the perineurial components cytologically resemble perineurial cells.

In the evolution of a neurofibroma, the contributions from each anatomic component of a peripheral nerve are variable. The cells of *perineurial variants* are bipolar or tripolar with rigid processes; they are loosely spaced in either a myxoid or fibrous matrix (Figs. 35-12 and 35-13). *Endoneurial (schwannian) variants* are characterized by a thickened perineurium, one or several axial bundles, and isolated cells in an

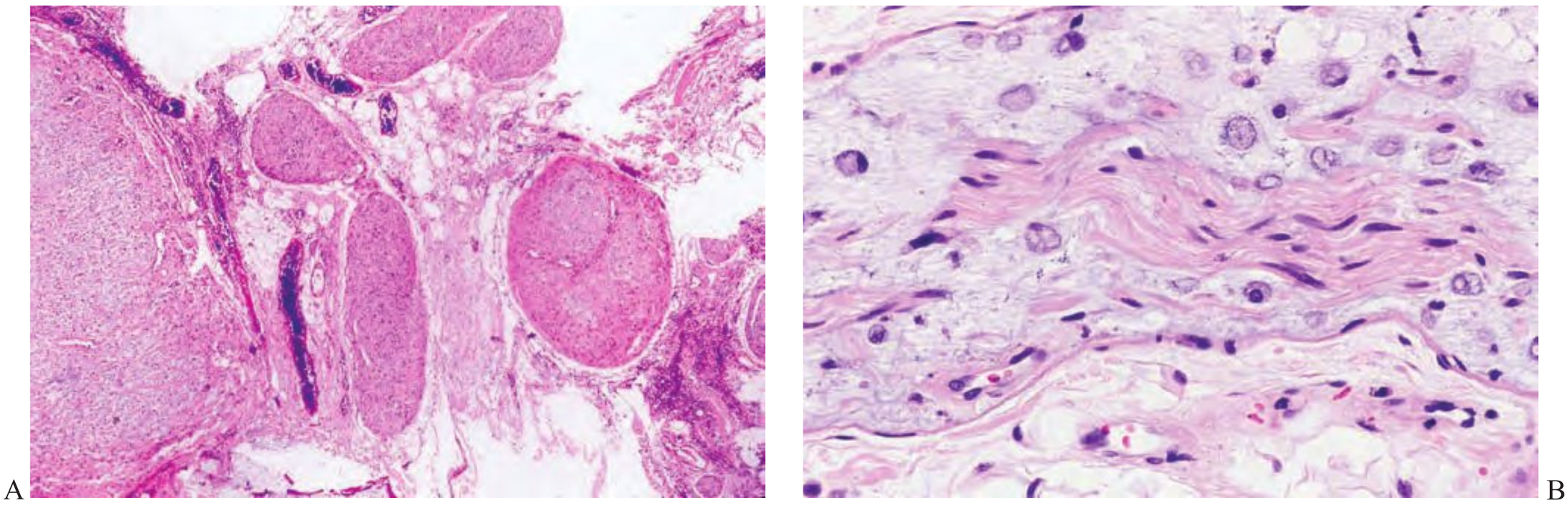


FIGURE 35-9. A: Components of a cutaneous, plexiform, intraneural neurofibroma. For the most part, components of the plexus in this field are cut in cross section. The tumor is intraneural; it sits in fibrofat without an extraneural component. Each component of the plexus is confined by a thickened perineurium. B: Plexiform intraneural neurofibroma; mucinous endoneurial type. This small branch of a large, cutaneous, plexiform neurofibroma shows a well-defined, central bundle of Schwann cells (an axial bundle). In this central bundle, Schwann cell fascicles of the preexisting nerve are symmetrically arranged along the long axis of the nerve. The endoneurial space is widened and mucinous. In it, distinctive rounded cells (endoneurial mucocytes) are loosely spaced. The expanding mucinous matrix has displaced some of the Schwann fascicles of the axial bundle away from their neighbors. The muciparous cells resemble the "cellules godronné" as seen in the "intravaginal hyaline system" of Renaut (6). The perineurium is delicate; it is a single layer of flattened cells.

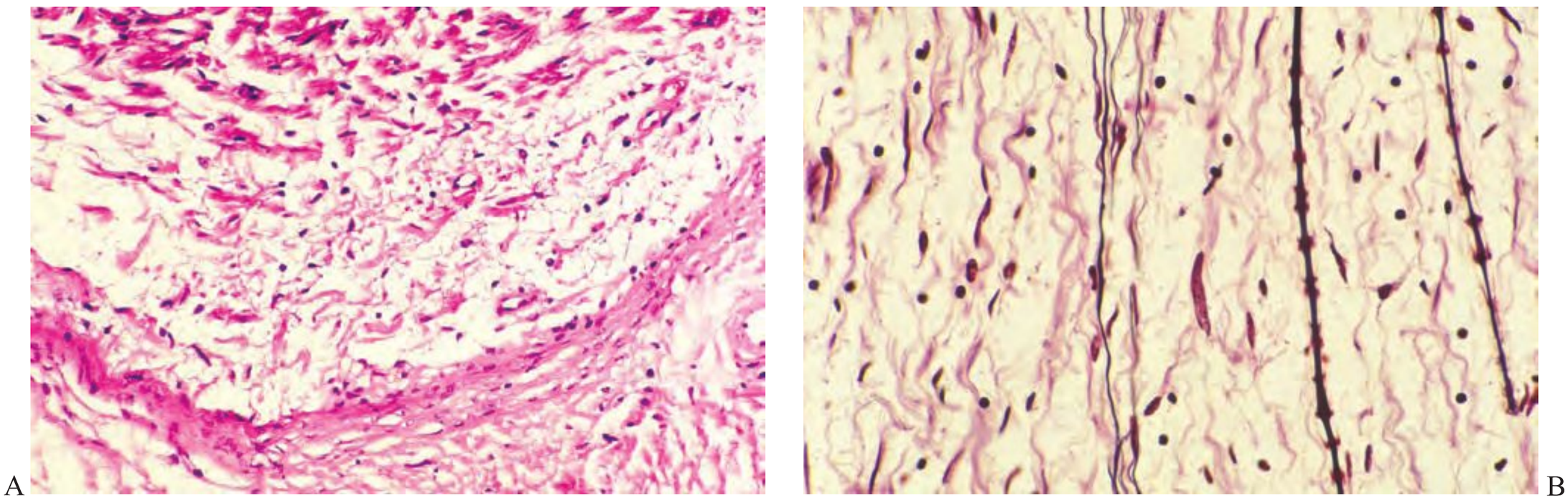


FIGURE 35-10. A: Intraneural neurofibroma; schwannian pattern of differentiation. A thickened perineurium forms a concave band near the bottom of the field; it defines the limits of the tumorous component at the interface with the adjacent soft tissue. At the top of the field, a distorted axial bundle (a remnant of the nerve of origin) is represented. The tumor is represented in the space between the perineurium and the distorted axial bundle; thin, pale collagen bundles are loosely and randomly spaced in a stringy, myxoid matrix. Thin spindle cells with elongated, wavy nuclei are closely associated with some of the collagen bundles. The fibrous component of the lesion is asymmetric in its relationships with both the long axis of the involved nerve and the central axial bundle. B: Intraneural neurofibroma; remnant of axial bundle (Bodian stain). Argyrophilic, myelinated and nonmyelinated axons are parallel; they have axial symmetry and are a remnant of the axial bundle. Wavy collagen bundles of the tumor are more asymmetric in orientation and distribution.

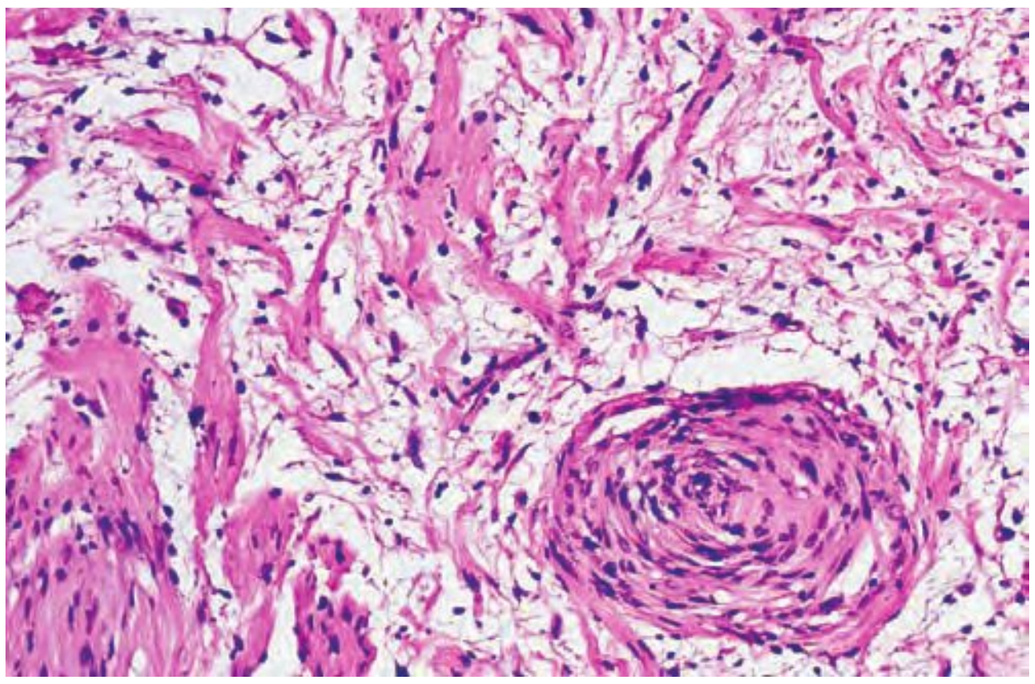


FIGURE 35-11. Intraneural neurofibroma; focal, microscopic schwannomatosis. Coarse collagen bundles are asymmetrically arranged in a loosely cellular, myxoid matrix. Near the right lower corner, collagen bundles and cells form a whorl; the whorl, as a nidus, is an example of microscopic schwannomatosis.

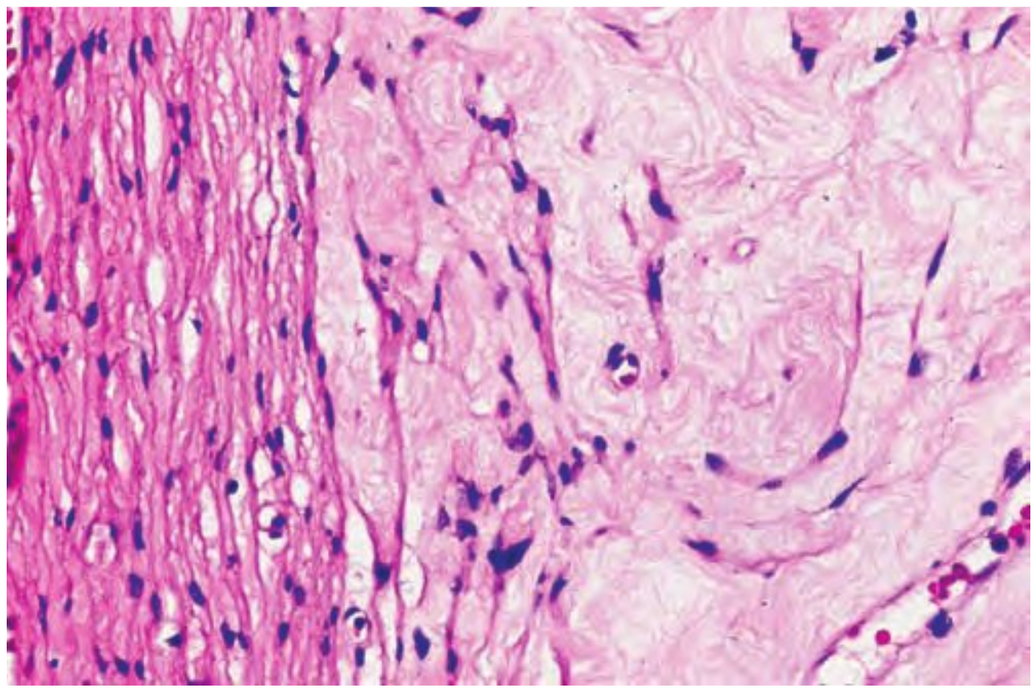


FIGURE 35-13. Intraneural neurofibroma; perineurial cell differentiation near the capsule of the tumor. The membrane to the left of the field is a thickened perineurium (capsule). In the fibrous matrix to the right of the perineurium, distinctive cells are loosely spaced; some blend with the inner surface of the perineurium. The loosely spaced cells have the morphologic features of perineurial cells.

expanded, mucinous endoneurial component (Fig. 35-14). In some examples, some of the cells in an expanded, mucinous matrix resemble the "cellules godronné" of Renaut [round cells with portions of the mucinous matrix that are either enclosed within the cytoplasm or focally partitioned (encircled and sequestered) by cytoplasmic processes] (Fig. 35-9B) (1,3,4,23). One or several axial bundles may be found among asymmetric collagen bundles of the tumor. In the expanded endoneurial component of both perineurial and endoneurial (schwannian) variants, the matrix is myxoid; it is rich in hyaluronic acid (Figs. 35-14 and 35-15) (3).

In a lesion in which the patterns of neurofibroma are otherwise preserved and mitotic activity is not a feature, spottily scattered cells with enlarged, atypical nuclei are not a significant finding (Figs. 35-14 and 35-16); as a variable to be assessed, cytologic atypia, in the absence of mitotic activity and necrosis, is comparable to the "ancient" (atypical) nuclear changes of some schwannomas (3,4).

At the interface of *extraneural (diffuse) neurofibromas* with soft tissue, margins are poorly defined (Fig. 35-17), and lipocytes are often present in the fibrous matrix of the tumor (4,24). The matrix of extraneural neurofibroma is either delicately fibrous

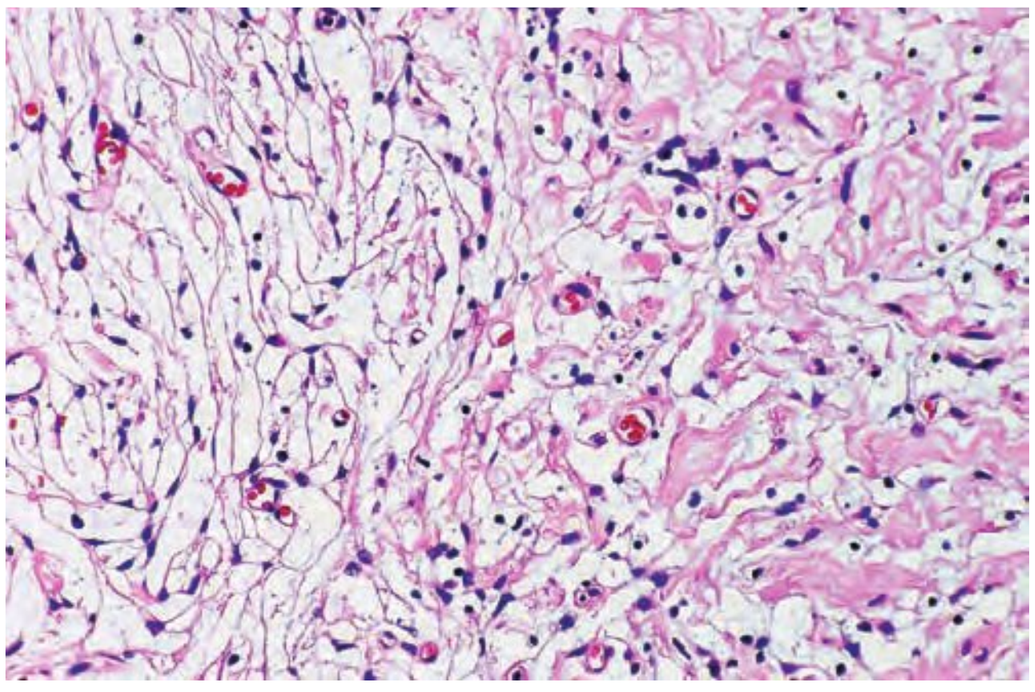


FIGURE 35-12. Intraneural neurofibroma; biphasic (perineurial and schwannian) patterns. To the right, wavy collagen bundles are loosely spaced; spindle cells are closely associated with the collagen bundles (schwannian pattern). To the left, distinctive bipolar and tripolar cells are loosely spaced in a clear or myxoid matrix; these distinctive cells have perineurial qualities.

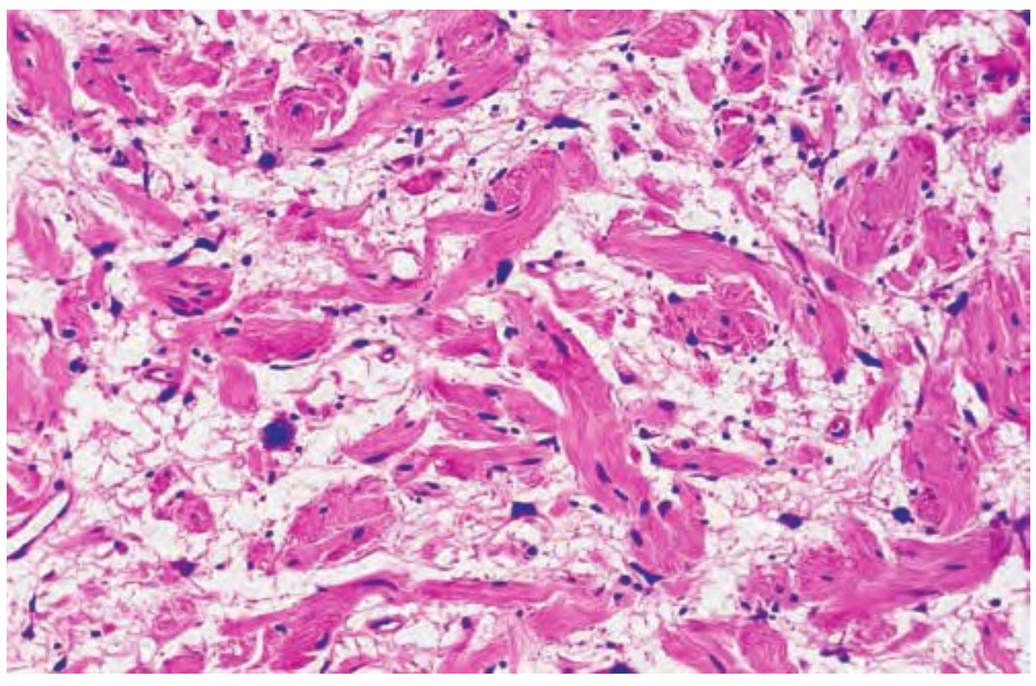


FIGURE 35-14. Intraneural neurofibroma; cytologic atypia. Coarse collagen bundles are loosely and randomly spaced in a myxoid matrix. Spindle cells are closely associated with the collagen bundles. Spindle and stellate cells are present among the collagen bundles in the myxoid matrix. Some of the cells in the myxoid matrix show nuclear atypism; they show variations in nuclear size and outline.

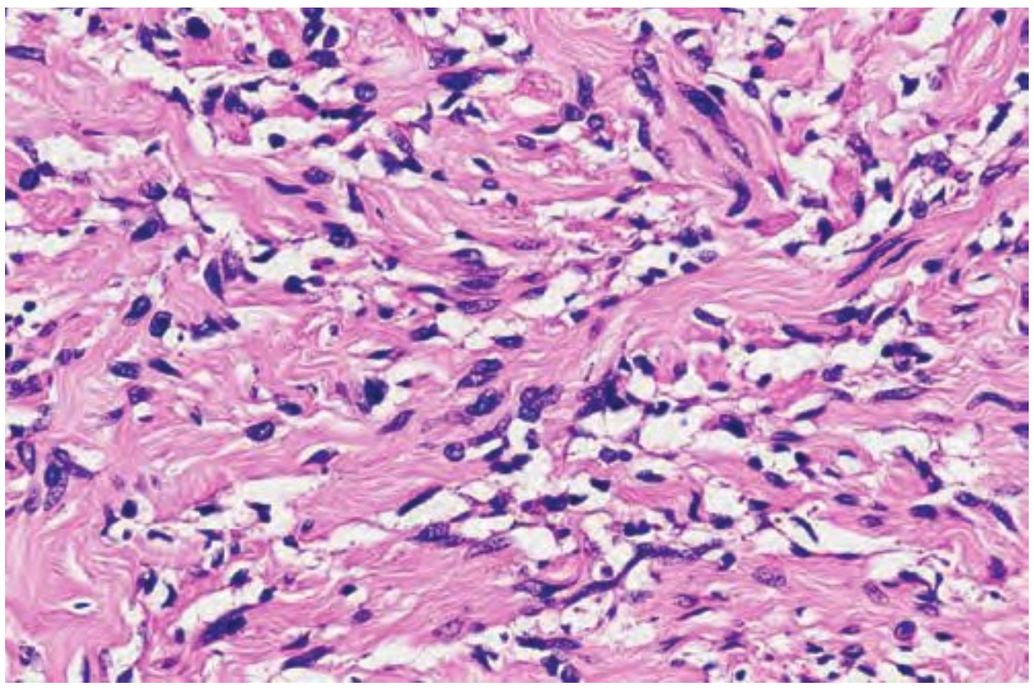


FIGURE 35-15. Intraneural neurofibroma; cellular pattern. Spindle cells are increased in number among the collagen bundles; focally, they are present within the collagen bundles. The cells have enlarged, wavy nuclei and scanty cytoplasm.

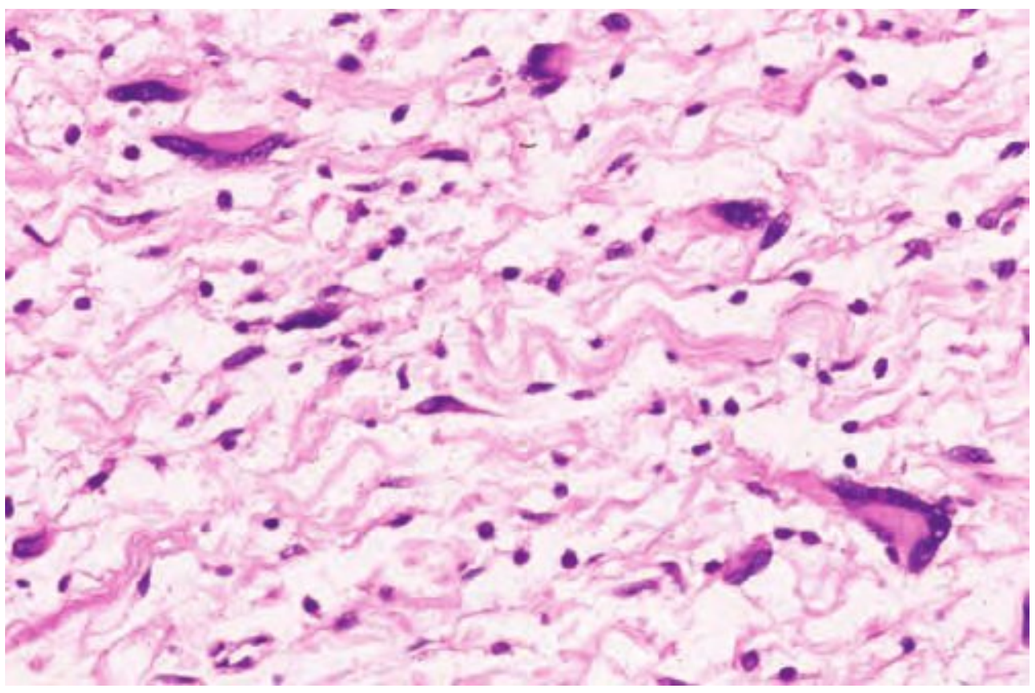


FIGURE 35-16. Intraneural neurofibroma; cellular atypia. Some of the cells among the collagen bundles are cytologically atypical; some of the atypical cells are multinucleated.

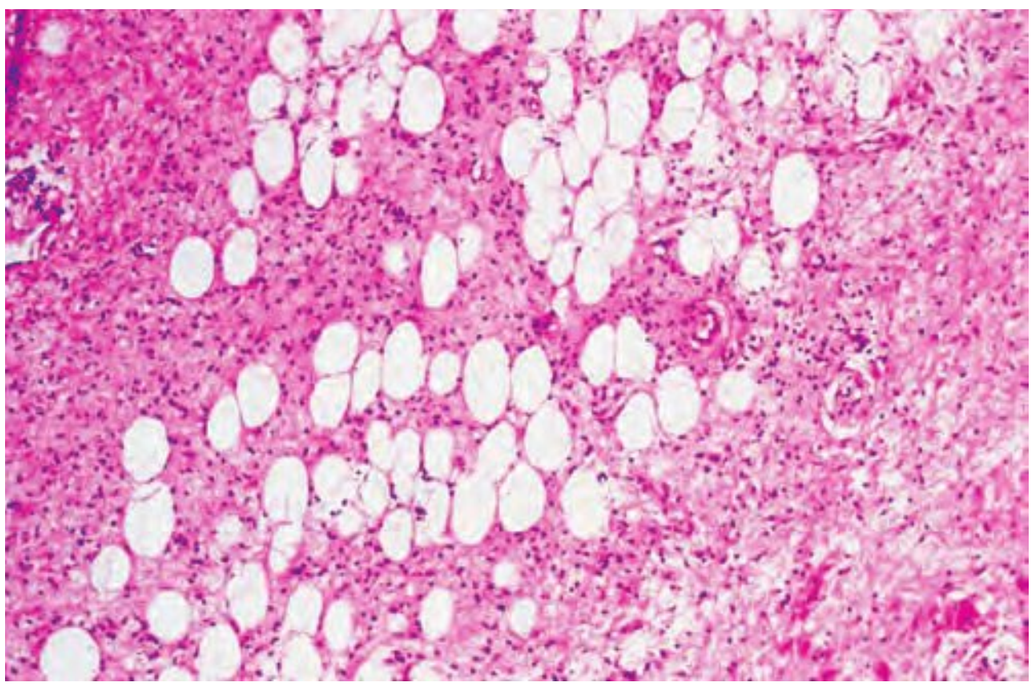


FIGURE 35-17. Extraneural (diffuse) neurofibroma. A delicately fibrous matrix is loosely cellular. The cells have scanty cytoplasm; they appear as naked nuclei. Lipocytes are entrapped.

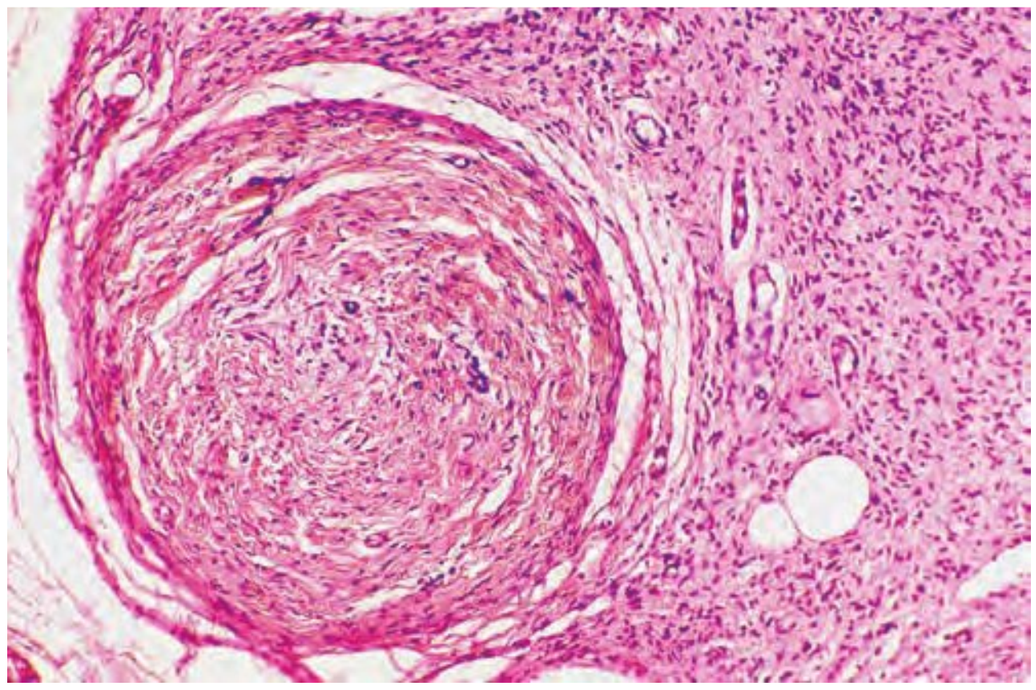


FIGURE 35-18. Diffuse and plexiform neurofibroma (paraneurofibroma). The round nodule to the left is a portion of an intraneural plexiform neurofibroma; it has been cut in cross section. The delicate fibrous matrix to the right is a portion of a diffuse (extraneural) component.

and faintly acidophilic or more coarsely fibrous and brightly acidophilic. In the absence of plexiform components, nerves within diffuse neurofibromas usually are small, internally symmetric, and hypercellular; perineuria of such nerves often are hyperplastic. In cross section, these nerves might be mistaken as evidence of pacinian corpuscle–like differentiation (25). Patterns of both a plexiform (intraneural) neurofibroma and a diffuse (extraneural) neurofibroma are combined in *paraneurofibroma* (Figs. 35-18 and 35-19) (3). Focal collections of structures resembling tactile corpuscles (tactoid bodies) (Fig. 35-20) and pigmented, dendritic melanocytes [a relatively

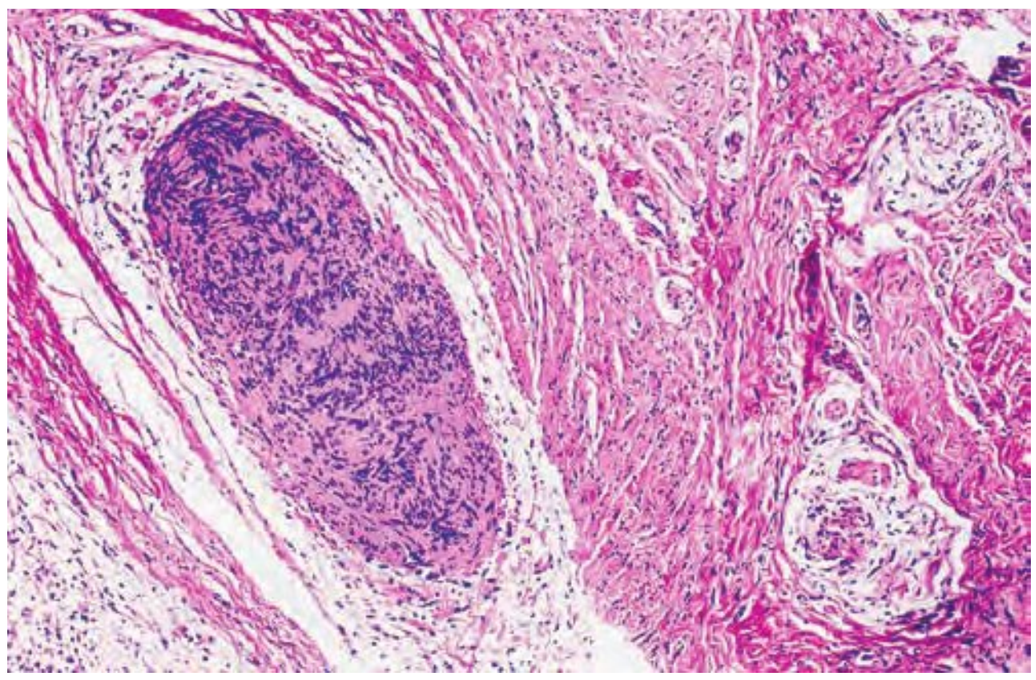


FIGURE 35-19. Diffuse and plexiform neurofibroma (paraneurofibroma) with focal microscopic schwannomatosis. The intraneural portions are pale, rounded, and faintly basophilic; in these components, wavy collagen bundles are loosely spaced. The extraneural component is a uniformly cellular fibrous matrix. Near the center of the field, a cellular nodule is confined within the intraneural matrix; in this cellular nodule, nuclei are arranged in palisades. The nodule is an example of microscopic schwannomatosis. The patterns of Verocay bodies are represented.

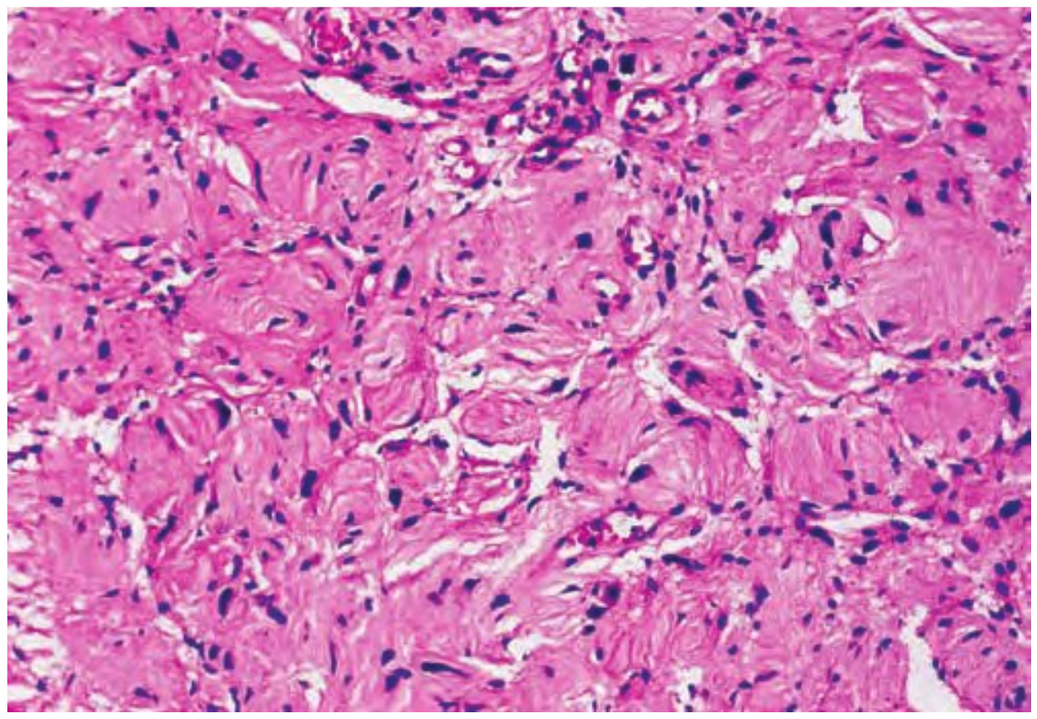


FIGURE 35-20. Extraneural neurofibroma; tactile corpuscle–like patterns. As a regional variation in this extraneural neurofibroma, spindle cells, in stacked lamellae, form tactile corpuscle–like structures.

common feature of deep, extraneural (diffuse) neurofibromas] are rare in the intraneural components of plexiform, or circumscribed, intraneural neurofibromas (3).

Ultrastructurally, the cells of neurofibromas (including those of tactoid bodies) mostly resemble perineurial cells (26), but cells with the characteristics of Schwann cells, as well as endoneurial fibroblasts, also have been identified; a morphologic continuum of neurosustentacular cells is manifested (3,27). Endoneurial fibroblasts, like common mesenchymal fibroblasts, do not have basal lamina. The average diameter of their collagen fibrils lies well below that of dermal collagen fibrils, which is about 100 nm (28).

Histogenesis. The immunohistochemical profile of neurofibroma is as follows: S100 protein (+), with variable expression of CD57 (Leu-7) antigen (+) and myelin basic protein (+). In extraneural cutaneous neurofibromas, axons, as demonstrated with NSE, or with antibodies to neurofilaments, are fairly uniform in distribution among collagen bundles. This finding is less consistent in deep, intraneural neurofibromas. Endoneurial fibroblasts are $CD34^{+}$ (29).

The ultrastructural features of neurofibromas [i.e., a preponderance of cells that resemble perineurial cells (26)] and the respective immunohistochemical findings (i.e., $S100^{+}$ and EMA^{-}) are discordant qualities.

Schwann cells with enclosed axons, as demonstrated with monoclonal antibodies for either NSE or neural filaments, are variably distributed in cutaneous neurofibromas. They have been characterized as an integral part of neurofibromas or simply as a consequence of the entrapment of uninvolved nerve fibers (26). Nonplexiform but circumscribed neurofibromas of von Recklinghausen's disease contain abundant, peptide-rich nerve fibers (30). Similar associations undoubtedly exist in plexiform variants. The innervation of neurofibromas of NF1 apparently is much richer than was appreciated in the past.

The extraneural distribution of the common dermal neurofibroma may be a manifestation of the extension of tumor through the open-ended terminal of perineurial sheaths or through the thin perineurium of small dermal nerves (22). Deep, extraneural neurofibroma may represent a diffuse, neurocristic dysplasia that is expressed in mesenchymal patterns (3,31). In this approach, the presence of lipocytes within such a tumor may be evidence of mesenchymal differentiation rather than simple entrapment.

Hybrid peripheral nerve sheath tumors have been described (32). In this study, in which certain lesions were classified as schwannoma-perineurioma or neurofibroma-perineurioma, histopathologic and immunohistochemical findings were emphasized; the characterization for one case was supplemented with ultrastructural findings. In one case, a point mutation was detected in exon 15 of the NF2 gene (32).

Differential Diagnosis. Plexiform (and pseudoplexiform) lesions of the skin and subcutaneous tissue include plexiform schwannoma (3), plexiform neuroma (33), the neuromas of the mucosal neuroma syndrome (34), nerve sheath myxoma (1,35), and plexiform fibrous histiocytoma (36). A plexiform variant of perineurioma (all of its current guises apparently being insufficient) has been described (37). Currently, there is a tendency to classify fasciculated melanocytic tumors as "plexiform" lesions.

Dendritic cell neurofibroma with pseudorosettes is a poorly documented, benign, "plexiform" lesion of the skin (38,39). Two cell types are represented: large dendritic cells and small, dark cells. The dark cells tend to cluster in palisades about the large dendritic cells. The tumor cells are immunoreactive for S100 protein. The large cells are not neurons. In a reply to a letter to the editor, Michal et al. provided additional photomicrographs (40). Their Fig. 1A shows a tumor that is both extraneural and intraneural (both diffuse and plexiform). With these photomicrographs as an aid, one can see that the lesion has the qualities of a variant of a plexiform and diffuse neurofibroma. As photographically documented, the dendritic cells are intraneural. The large dendritic cell is sheltered from the small-cell component by a complex of cell processes; as represented in the illustrations, the complex resembles neuropil. The histologic features of the population of small cells can be compared to those of the small cells in some examples of "epithelioid" small-cell populations in some variants of schwannoma. These variant schwannomas are of the type associated with zones of radial sclerosis. In neither category of nerve sheath tumor do the small cells have the cytologic features of a population of "blast" cells. To borrow an old designation, but to alter its definition, the patterns of differentiation in the small cell population might qualify as "neuroglial" differentiation. Having made such a concession, it would be difficult to define features that might qualify the "dendritic cell neurofibroma" as an example of a malignant small blue cell tumor, thus legitimizing the rubric "neuroblastoma-like."

Subcutaneous, extraneural (diffuse) neurofibromas may be confused with the deep component of *dermatofibrosarcoma*

protuberans. The confounding patterns account for the characterization of pigmented dermatofibrosarcoma protuberans as *pigmented storiform neurofibroma* (25,41). In infancy, "plexiform" fibrous hamartoma also might be considered in the differential diagnosis of an extraneural neurofibroma.

The nodular myxoid components of a low-grade *malignant myxoid fibrous histiocytoma* might be misinterpreted as the pattern of a "plexiform" nerve sheath tumor.

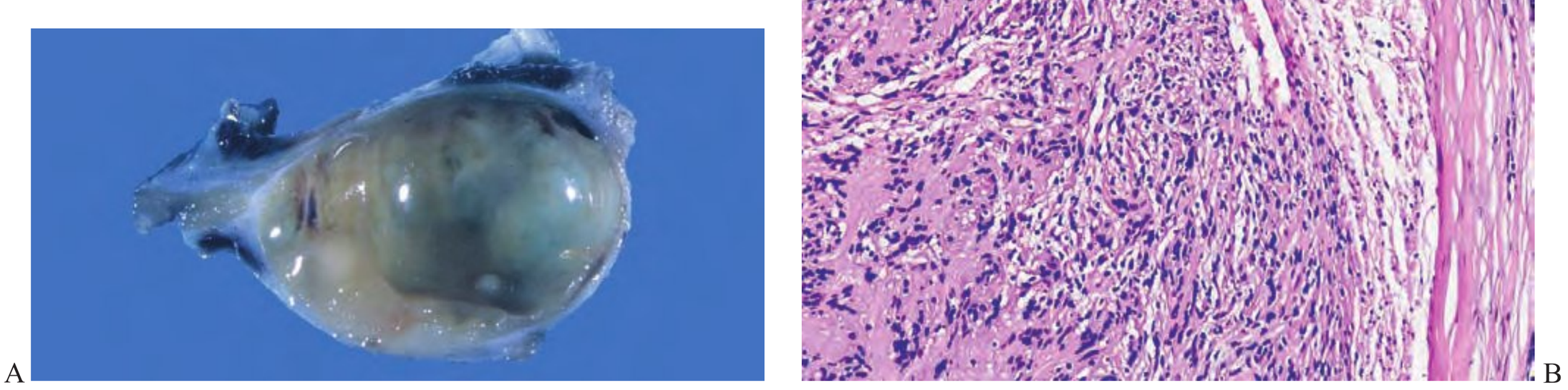
Mucinous and proliferative endarteritis and aneurysms are occasional features in the setting of NF1; they affect mainly muscular renal vessels, but similar changes can be manifested in other sites (3,42,43). Aneurysmal changes have been a prominent feature of muscular vessels in some examples of extraneural neurofibromas of the skin and soft tissue, particularly in the distribution of the trigeminal nerve (3). Such lesions clinically may be mistaken for *hemangioma*.

TRUE NEOPLASMS OF SCHWANN CELLS (ULTRASTRUCTURALLY DISTINCTIVE CELLS THAT ARE IMMUNOREACTIVE FOR S100 PROTEIN), SCHWANNOMAS

Schwannomas (neurilemmomas; anaxonal, intraneural, Schwann cell tumors; "peripheral neurogliomas") are benign, expansile neoplasms (1,26,44). The cells of schwannomas mostly have the characteristics of Schwann cells. Schwann cells are specialized sustentacular cells normally distributed as a single layer about and along one or more axons. In a sense, the insulation that they provide along normal nerve fibers favors proper propagation of nerve impulses. In schwannomas, the population of Schwann cells exists independent of a plexus of axons. As solitary, skin-colored tumors along the course of peripheral or cranial nerves, their usual size is between 2 and 4 cm; their usual location is the head or the flexor aspect of the extremities (Fig. 35-21). Schwannomas are rare in the subcutaneous tissue; they are even less common in the dermis. In deep soft tissue, they may be large (45). In the central nervous system, the VIIIth cranial nerve is the favorite site. Internal viscera (46) and bones may be involved. When small, most schwannomas are asymptomatic, but pain, localized to the tumor or radiating along the nerve of origin, can be a complaint.

Histopathology. Schwannomas, with the exception of infiltrating, fascicular variants, are intraneural and symmetrically expansile; they are confined by the perineurium of the nerve of origin (Fig. 35-21B). Most of the symmetrically bundled nerve fibers of the nerve of origin are displaced eccentrically; if identified in a histologic section, they usually are found between the tumor and the perineurium (Fig. 35-21B) (3,44). At the interface with the nerve of origin, some of the nerve fibers may extend from the compressed, eccentric axial bundle into the tumor. The observations of Russell and Rubinstein (47) contradict the dictum that schwannomas are universally devoid of axons. Loosely and randomly spaced nonmyelinated axons have been observed in small peripheral schwannomas and in small and medium-sized acoustic nerve schwannomas (47).

Two variant patterns, namely *Antoni A* and *Antoni B* types, have been described (4,48). In the Antoni type A tissue, uniform spindle cells are arranged back to back (Fig. 35-22); each cell is outlined by delicate, rigid, reticular fibers (basement membranes). The cells tend to cluster in stacks, and the respective nuclei often form palisades. Two neighboring palisades, the intervening cytoplasms of Schwann cells, and associated reticular



A B

FIGURE 35-21. A: Schwannoma. The lesion is circumscribed and encapsulated. The lesion bulges over a portion of the cut surface,. B: Schwannoma and nerve of origin. This schwannoma is uniformly cellular; the Schwann cells focally form nuclear palisades and Verocay bodies. To the right, a thickened perineurium, at its interface with the neighboring soft tissue, defines the limits of the tumor. The loosely cellular zone between the perineurium and the tumor is a compressed nerve of origin; the nerve maintains its identity at the periphery of the tumor; it is not enclosed within the substance of the tumor.

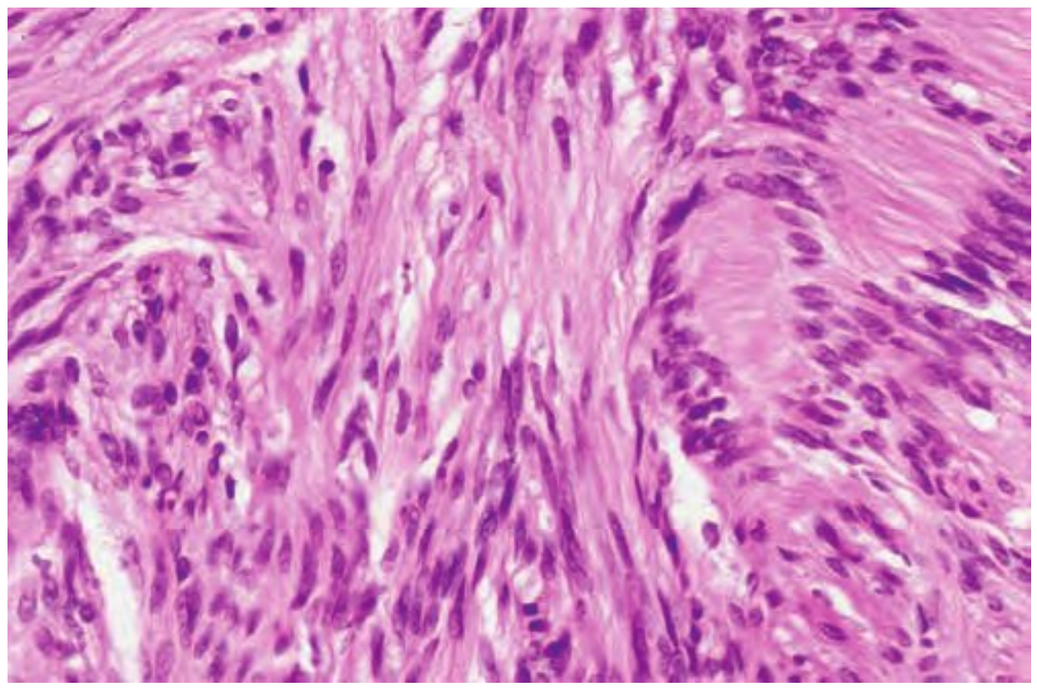


FIGURE 35-22. Schwannoma; Antoni A patterns. Pale spindle cells with elongated, wavy nuclei are arranged in fascicular patterns. To the right of the field, nuclear palisades are regularly spaced; two nuclear palisades and the enclosed cytoplasmic processes comprise a Verocay body. Cellular components of this type qualify as Antoni A tissue.

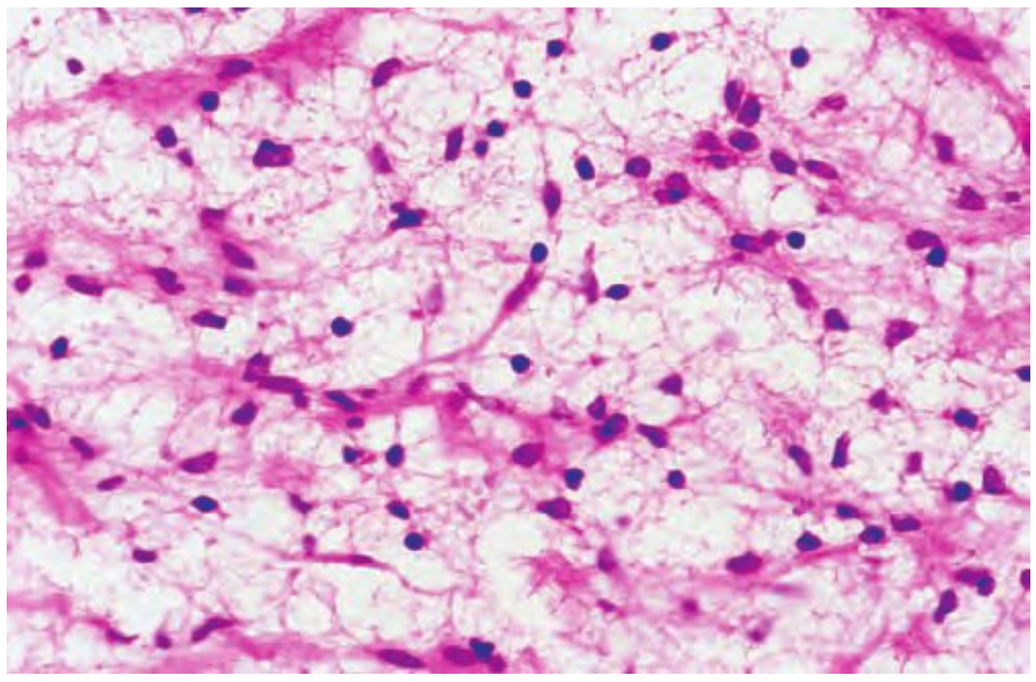


FIGURE 35-24. Schwannoma; Antoni B patterns. In this example, the cells of an Antoni B component are small with complex, delicate cytoplasmic processes. The cytologic features have a glial cell–like quality.

fibers, all in combination, constitute a *Verocay body* (Figs. 35-22 and 35-23).

In Antoni type B tissue, files of elongated "Schwann" cells arranged end to end and individual "Schwann" cells are loosely spaced in a clear, watery, or myxoid matrix (Figs. 35-23 to 35-25) (1,49); in some examples, the cells somewhat resemble glial cells; in other examples, they resemble perineurial cells.

Clusters of dilated, congested vessels are a characteristic feature (4). Fibrinoid necrosis or hyalinization, thrombi, and subendothelial collections of foam cells, in various combinations, often are features of the thick-walled vessels (Fig. 35-26) (49). The vascular changes can be found in both Antoni A and Antoni B tissue. Cystic changes (Fig. 35-27) (3,49), extravasated erythrocytes, and hemosiderin deposits are variable features.

Ultrastructurally, the tumor cells of a schwannoma manifest the features of Schwann cells (26). Axons usually are not a component. Long-spacing collagen may be represented (48).

The patterns in Antoni type B tissue are degenerative in nature; at the level of the light microscope, they have been characterized as "ancient change" (49). "Ancient change" also characterizes the nuclear atypia often seen in some schwannomas (4). Ultrastructurally, tumor cells are widely separated by an electron-lucid, homogeneous matrix containing strands of fibrin and detached segments of basement membrane. Autophagic lysosomes, some containing myelin figures, are seen in many cells (i.e., a "histiocytic" quality). The cellular changes include extensive loss of basement membrane, disruption of cell membrane, and nuclear degenerative changes (50).

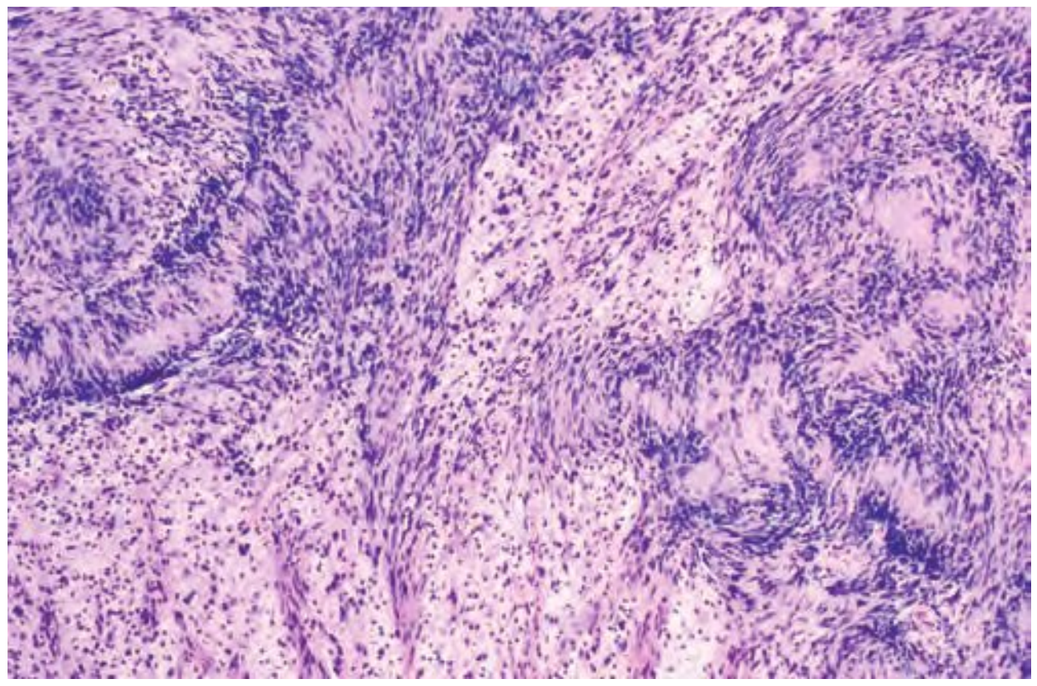


FIGURE 35-23. Schwannoma; mixed Antoni A and Antoni B patterns. The Antoni A component is cellular; Verocay bodies are a prominent feature. The loosely cellular, pale zones are Antoni B patterns. In the Antoni B component, there is some variation in nuclear size and staining.

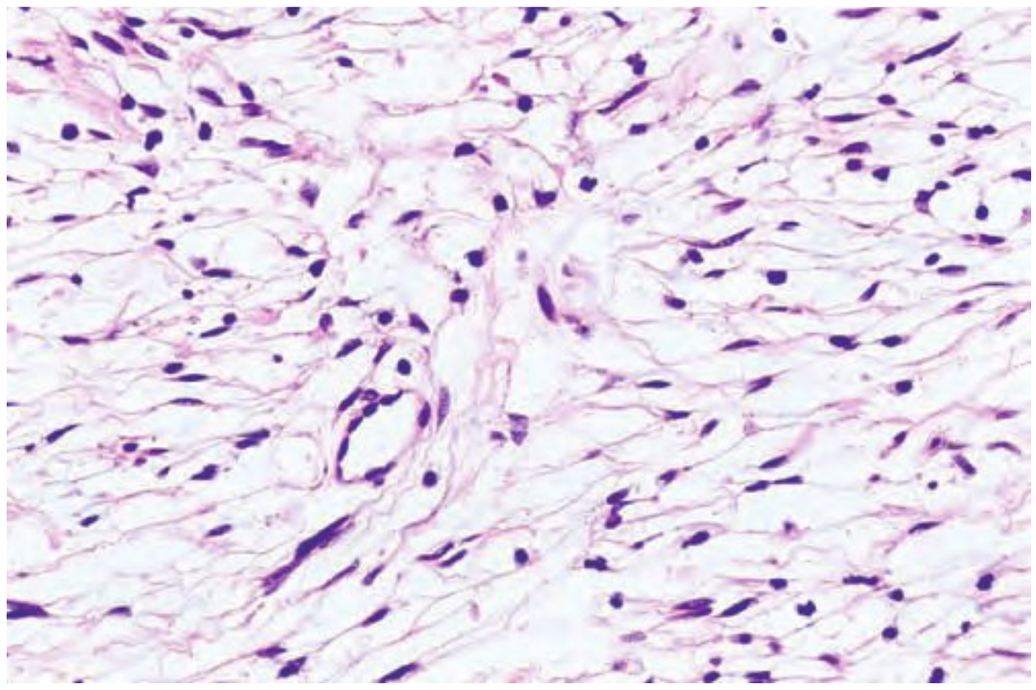


FIGURE 35-25. Schwannoma; Antoni B Patterns. In this example, the cells of an Antoni B component are bi- or tripolar; the cytoplasmic processes are elongated and straight; the cells cytologically resemble perineurial cells.

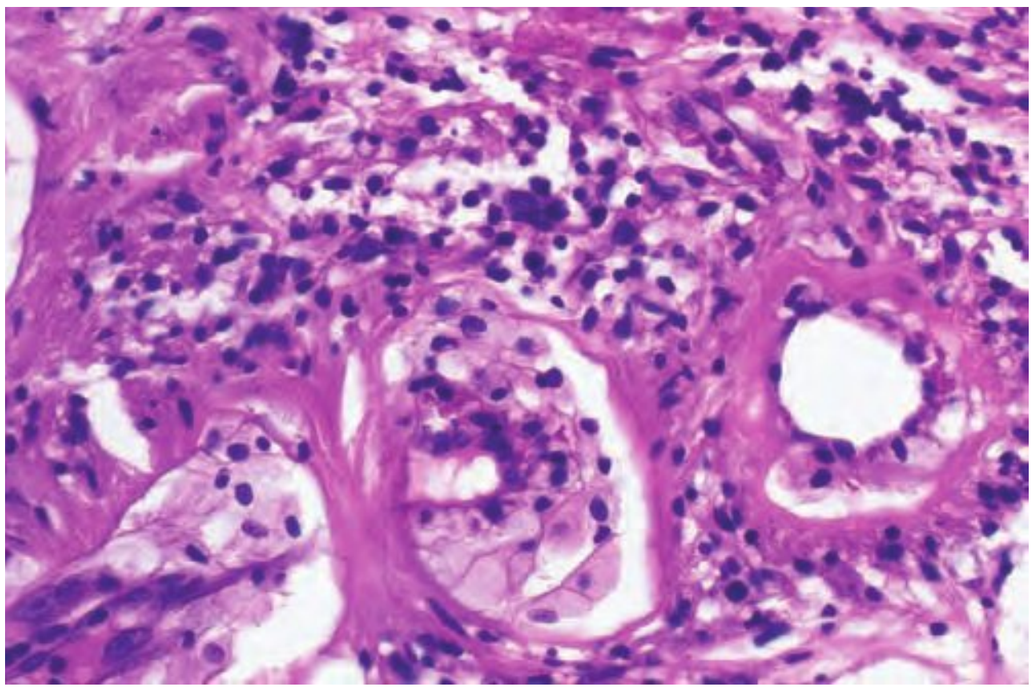


FIGURE 35-26. Schwannoma; Antoni B component, vascular changes. In this Antoni B component, several vessels are loosely clustered. They have thickened, hyalinized walls. There are prominent, subintimal collections of foam cells. Loose infiltrates of lymphoid cells are adjacent to the vessels and among the foamy histiocytes. In part, the hyalin represents a stage in the organization of fibrinoid; fibrinoid degeneration and thrombosis are common vascular changes in some schwannomas.

Histogenesis. The immunohistochemical profile is positive for S100 protein and collagen type IV and laminin. In the capsule, cells are EMA$^+$. A Bodian stain and an immunoreaction for the demonstration of neural filaments reveal few or no axons, except in and near the peripherally displaced axial bundle.

Apoptosis is a deletion of selected cells in both physiologic and pathologic processes (51,52). A modification of apoptosis may be operative in the expression of Antoni B patterns in a schwannoma.

Differential Diagnosis. If a nerve sheath tumor involves a significant sensory or motor nerve, the distinctions between intraneural neurofibroma and schwannoma become important considerations for a surgeon. For a functionally significant nerve, the intact but displaced symmetric axial bundle (Fig. 35-21) of a schwannoma (4) often can be preserved during surgical dissections. On the other hand, excision of an intraneural neurofibroma requires sacrifice of the nerve of origin (i.e., the axial bundle, being confined within the tumor, must be sacrificed).

Palisaded and encapsulated neuroma (PEN) should be considered in the differential diagnosis of schwannoma. A demonstration of axons within the fascicles of tumor cells is sufficient evidence from which the distinctions between PEN and schwannoma can be made.

Variant Types of Schwannomas

Cellular Schwannoma

In cellular schwannoma (CS), as defined by Harkin and Reed (4), the cellular arrangements mostly resembled those of Antoni A type tissue; Schwann cells were closely aggregated with scanty intercellular matrix. If other common features were preserved, scattered cells having large, hyperchromatic nuclei (Fig. 35-28) were of no significance. Increased cellularity per unit area, a preponderance of type A patterns, and a low mitotic rate were, in part, requisites for the diagnosis of "cellular schwannoma" (Fig. 35-29). Areas of atypia were acceptable in the definition. The definition of "cellular schwannoma" recently has been expanded (1). In this expanded definition, a wide range of features, some of which overlap with those of malignant peripheral nerve sheath tumor (MPNST), are acceptable. The criteria that currently are being promoted for the diagnosis of "cellular schwannoma" are of a type that generally would define borderline categories in other neoplastic systems. The designation has found a degree of legitimacy in several retrospective studies in which a "favorable" prognosis

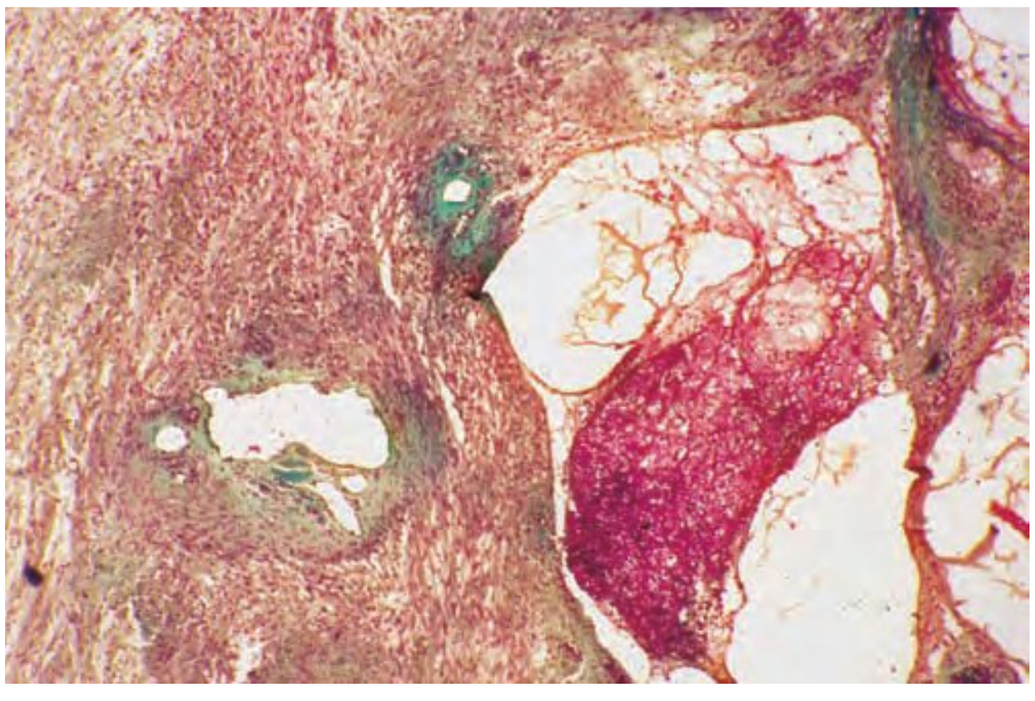


FIGURE 35-27. Schwannoma; microcystic and vascular changes. With this connective tissue stain, cells have a reddish tinge and connective tissue is green. Vessels are dilated; their walls are fibrous and irregularly thickened. To the right, multiple small cysts contain a loose meshwork of fibrin.

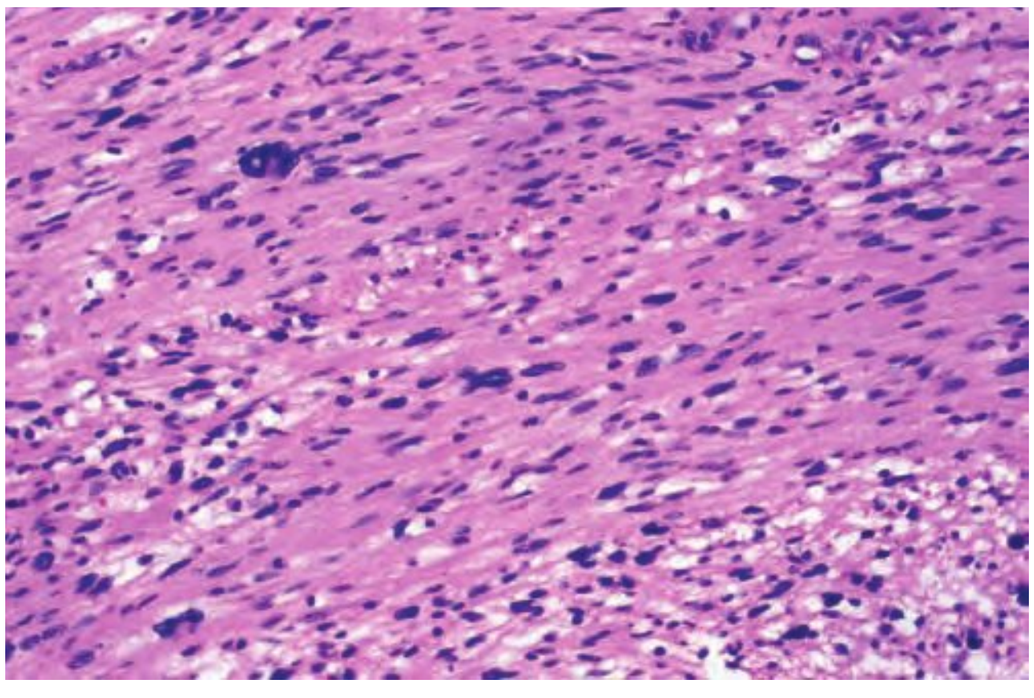


FIGURE 35-28. Schwannoma; cytologic atypia (ancient change of cytologic type). Spindle cells form interlacing fascicles. The cells show variations in nuclear size, staining, and outlines; in many of the nuclei, chromatin is dense and smudgy. Mitoses are not a feature of "ancient change."

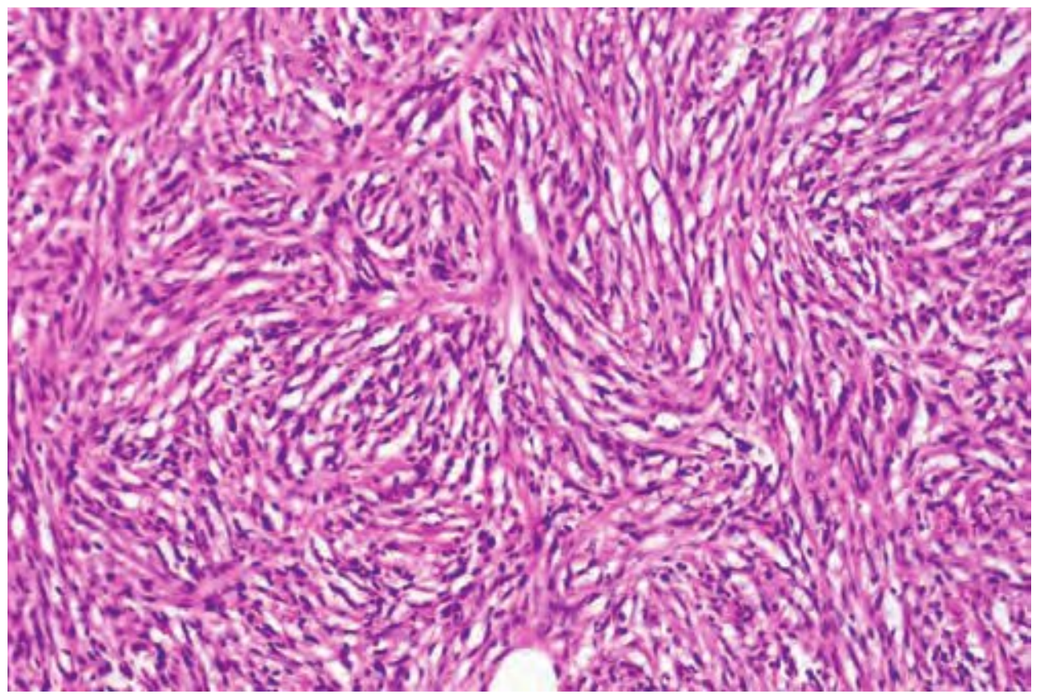


FIGURE 35-29. Schwannoma; cellular variant (CS1). In this schwannoma, patterns are uniformly cellular (Antoni A type). Uniform spindle cells are arranged in the pattern of interlacing fascicles. In this example, mitotic activity is not a significant feature.

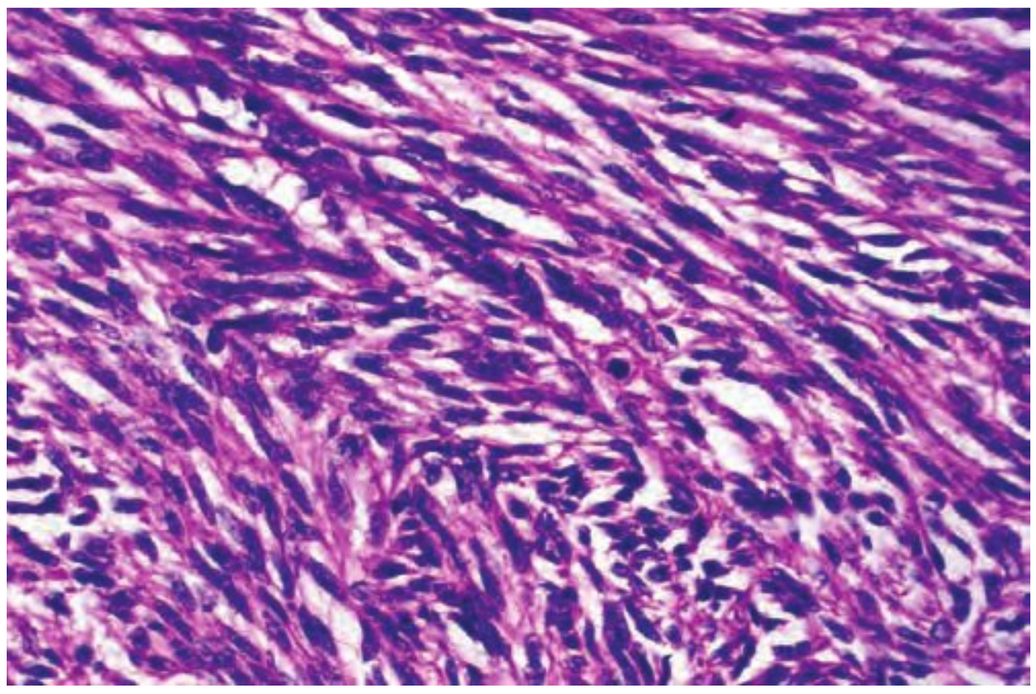


FIGURE 35-30. Schwannoma; cellular variant with mitotic activity (CS2). In this example of cellular schwannoma, the fascicles are hypercellular; nuclei are enlarged and show hyperchromatism. There are scattered mitotic figures.

has been documented (1). The dichotomy in the approaches to "cellular" schwannoma is given recognition herein by the definition of two classes: CS1 and CS2.

In *CS1* [a restricted application of the designation in the manner of Harkin and Reed (4)], most examples are large tumors of the retroperitoneum and mediastinum (and may incidentally show immunoreactivity for GFAP) (53,54). The lesions of CS1 are mostly cellular with patternless areas in which cells form solid sheets alternating with areas in which intersecting fascicles of spindle cells (Fig. 35-29) produce storiform patterns (4). The basic patterns of a variant of schwannoma, such as those of a common schwannoma or an epithelioid schwannoma, are preserved, but in some examples most of the cells are cytologically atypical (Fig. 35-30). Cellular pleomorphism is acceptable. In some examples, nuclear atypia is uniform and extensive. By definition, mitoses are infrequent (less than 2 per 10 high-power fields [hpf]). A background population of small lymphocytes also may contribute to the cellularity (3). Nuclear palisades, Verocay bodies, and Antoni type B components tend to be inconspicuous (4); zones of necrosis in palisaded patterns are not included in the definition.

In *CS2* [*cellular schwannoma* of Woodruff et al. (55); *transformed schwannoma* of Reed and Harkin (3)], some features are histologically worrisome. Increased cell density, storiform patterns, mitotic activity (even up to 20 or more mitoses per 10 hpf), zones of necrosis, and cytologic atypia might be cited as worrisome features (1,54–59). Some have argued that these lesions are unequivocally benign, but the prospective studies, which would certify CS2 as something other than a low-grade, intraneural malignant schwannoma [transformed schwannoma of Reed and Harkin (3)], are not available. The patterns are of a type that, in other organ systems, would be consistent with a transition from benignancy to low-grade malignancy (Fig. 35-30). In practice, most of these lesions are amenable to local surgery. In making a distinction between these lesions and infiltrating low-grade malignant schwannomas, confinement by the perineurium of the nerve of origin may be prognostically and therapeutically important (55).

Differential Diagnosis. The differential diagnosis of CS1 includes *leiomyoma*, low-grade *leiomyosarcoma*, and *gastrointestinal stromal tumor*. In the evaluation of a problematic lesion, an intense reaction for S100 protein and a negative reaction for both smooth muscle antigen (SMA) and desmin would offer support for a diagnosis of schwannoma. Smooth muscle cells, in turn, react with antibodies to SMA and desmin. In gastrointestinal stromal tumors, divergent phenotypes may be expressed, but CD117 (c-kit) is the commonly expressed antigen. Immunoreactivity for CD117 has been noted in MPNST (60). Variants of soft tissue sarcoma must be included in the differential diagnosis of CS1 and CS2.

Epithelioid Schwannoma

In the rare *epithelioid schwannoma* (with or without radial sclerosis) (3,61–63), spindle and round cells are clustered in epithelioid patterns; the nuclei often are round (Figs. 35-31 and 35-32). Nuclear atypia and dense nuclear chromatin are common features. In some examples, the cells have acidophilic cytoplasm. In one variation, in which cells have round nuclei and scanty cytoplasm, some of the cells are radially arranged in palisades around distinctive zones of sclerosis (3,64–67). In the zones of sclerosis, fibrous lamellae are radially oriented; they interdigitate with cytoplasmic projections of the surrounding tumor cells (67). Such lesions have been characterized as epithelioid schwannoma with radial sclerosis (3), "collagenous spherulosis" in a schwannoma (66), rosetoid schwannoma (67), and "neuroblastoma-like" epithelioid schwannoma (64,65). The designation neuroblastoma-like schwannoma gives recognition to a lymphocyte-like pattern; the nuclei of the small, blue tumor cells resemble those of lymphocytes in

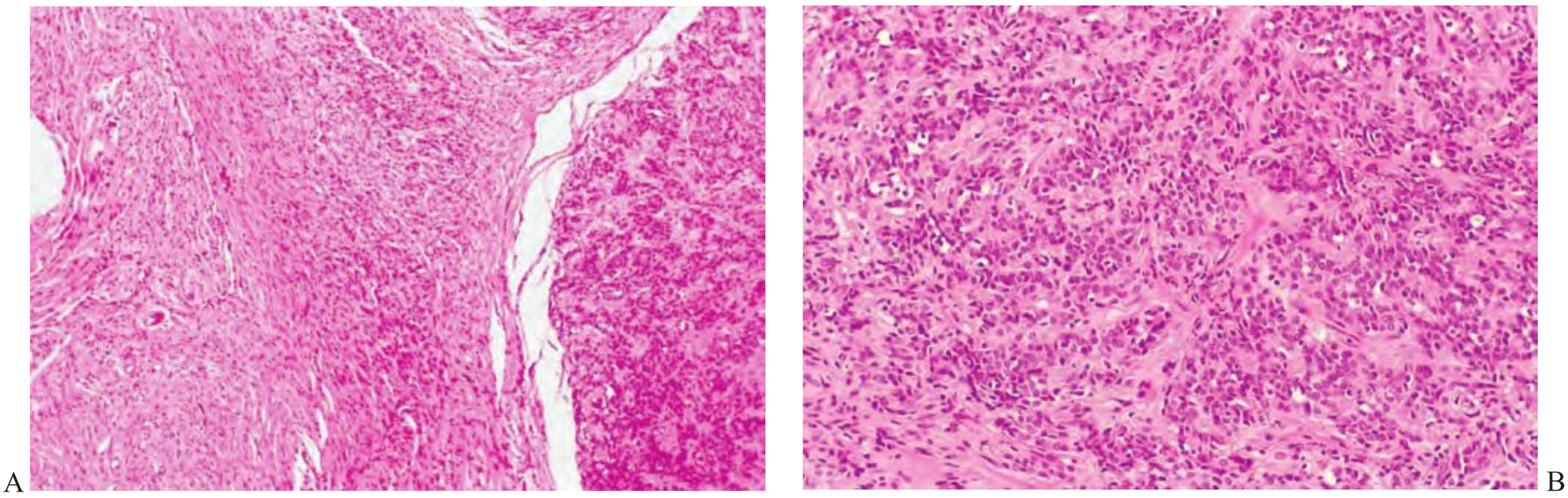


FIGURE 35-31. Plexiform epithelioid schwannoma, arising in extraneural neurofibroma. A: To the right, a portion of a plexiform lesion presents a sharp interface with an extraneural (diffuse) neurofibroma. Fascicles of uniform, epithelioid cells are loosely and regularly spaced in the plexiform component. B: At higher magnification, the fascicles of uniform, small epithelioid cells are loosely spaced in a fibrous matrix.

size and staining. The small-cell component may be extensive or a focal variation in what is otherwise a typical schwannoma. The small cells tend to cluster in rosette-like patterns about vessels and spherical zones of radial sclerosis. Neither the histologic patterns and the cytologic features nor the clinical behavior of these lesions justifies a characterization of the small, dark cells about radial zones of sclerosis as "neuroblastoma-like" (67). Collagenous spherulosis, as originally defined for breast lesions, is distinct from the patterns of radial sclerosis, as manifested in nerve sheath tumors (68). Some examples of epithelioid schwannoma have been characterized as cellular. Some epithelioid schwannomas are also plexiform (Figs. 35-31 and 35-32).

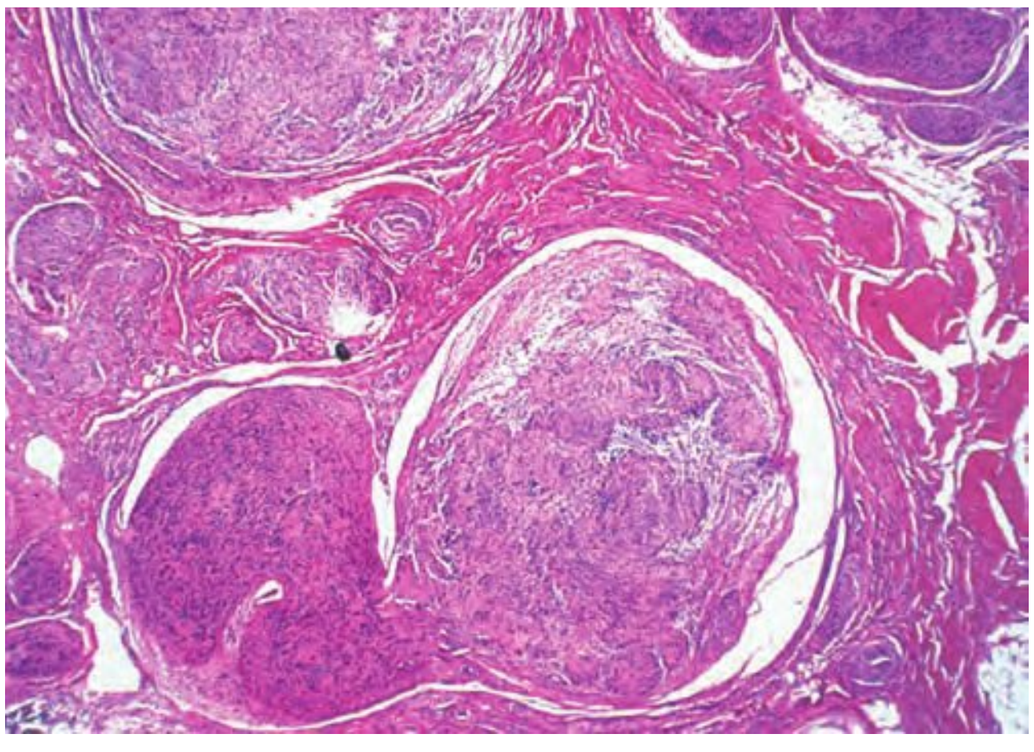


FIGURE 35-32. Plexiform schwannoma. Components of the plexus are mostly cut in cross section; they are supported by a dense fibrous matrix. Within some of the components, both Antoni A and Antoni B patterns are represented.

Glandular Schwannoma

Glands having the features of sweat glands are occasionally found within subcutaneous schwannomas (69–72). A demonstration of a component of myoepithelial cells has fostered a proposal that the glands are nothing more than entrapped sweat glands (70–72). Yoshida and Toot (71) proposed *divergent differentiation* as an alternate explanation for the glandular inclusions. Glandular patterns of a different type are a feature of some malignant schwannomas; they also have been observed in a benign neurofibroma (70). Cysts that contain mucoid material are a feature of some schwannomas; they are outlined by palisades of Schwann cells. Such lesions have been classified as pseudoglandular schwannomas (73).

Plexiform Schwannoma

Plexiform schwannomas occur mostly in the subcutaneous tissue; they rarely are confined to the dermis (3,21,74–80). They may be a feature of the syndrome of *multiple schwannomas* (clinical schwannomatosis or neurilemmomatosis) (77,81), or they may be solitary (79). The gene of NF2 and that of multiple schwannomas may be identical (82,83).

Histopathology. Plexiform schwannoma is intraneural. Spindle cells, often in solid Antoni A patterns, fill the expanded endoneurial space of a limited segment of a neural plexus; each column and nodule of the tumor is surrounded by perineurium. The vascular changes and Antoni type B tissue of a common schwannoma are variable features. Cystic changes are uncommon. In some examples, fascicles of Schwann cells extend for a short distance beyond the confines of the perineurium into the neighboring mesenchyme. These limited patterns, when encountered in the adjacent soft tissue, resemble those of a small, circumferential, extraneural neuroma (75).

Some plexiform schwannomas are "cellular;" some are epithelioid. Plexiform schwannomas of the deep soft tissue

frequently show the worrisome histologic features of CS2 (84). In one series, the atypical features included increased cellularity, pleomorphism, and mitotic activity; tumor necrosis and myxoid change were less common. Females were more commonly affected than males; none of the patients had stigmata of neurofibromatosis. Two of six patients with follow-up had two local recurrences, and one patient had one local recurrence. At last follow-up, all six patients were free of disease (84).

The category of plexiform schwannoma may be heterogeneous. In a single case, Kao et al. (79) documented a relationship between neurofibroma and plexiform schwannoma. In our experience, plexiform schwannoma may be associated with a background of diffuse neurofibroma (Figs. 35-31 and 35-32).

Schwannoma Arising in Neurofibroma (With Emphasis on Relationships With Intraneural Microscopic Schwannomatosis)

Schwannomas in continuity with neurofibromas have been documented (85,86). *Intraneural microscopic schwannomatosis* (Figs. 35-11 and 35-19) (3), a proliferative change affecting axial bundles of nerve fibers in intraneural neurofibromas, might, with progression, become *schwannoma ex neurofibroma* (18). Rarely, remnants of an intraneural neurofibroma are found at the periphery of a cellular schwannoma (CS1).

Borderline Variants

Infiltrating (Extraneural) Fascicular Schwann Cell Tumor of Infancy and Childhood

Infiltrating (extraneural) fascicular Schwann cell tumor (IFSCT) [*plexiform malignant peripheral nerve sheath tumor of infancy and childhood* (87); *congenital hamartoma of nerve*] is a rare Schwann cell neoplasm most often affecting an extremity (88). In contrast to all variants of schwannoma, IFSCT is chiefly extraneural. True plexiform patterns (intraneural by definition) are not a prominent feature. In common usage, a schwannoma is a benign, intraneural (encapsulated) tumor of Schwann cells. IFSCT is obviously something other than a variant schwannoma. It also lacks the organoid qualities of a hamartoma.

Histopathology. Uniform spindle cells form tortuous, interlacing fascicles; the fascicles vary in size. In some of the thin fascicles, spindle cells tend to cluster in palisades; anuclear collections of cytoplasm separate the neighboring palisades. The lesion infiltrates skin and soft tissue and, in some examples, erodes bone.

Histogenesis. The most characteristic feature of IFSCT is its extraneural invasion of soft tissue in fascicular patterns. The tumor cells of IFSCT are clearly identifiable, both immunohistochemically and ultrastructurally, as Schwann cells.

Prognosis. In one published collection, four of the six patients with follow-up had local recurrences (87). In addition, one patient, who had an invasive lesion of the orbit, died. Woodruff et al. reported six cases (89). The patients ranged in age from 2 to 15 months. There was no association with NF1. Three of the tumors were well circumscribed; the lesions were not encapsulated. All of the tumors recurred locally. With the exception of one case that was lost to follow-up, all of the children were alive and free of disease. Rapid growth, locally aggressive behavior, hypercellularity, and increased mitotic activity are worrisome features.

The documented behavior of reported examples has not convincingly established the nature of the lesion. The histologic patterns, if not the cytologic features, overlap with those of infiltrating and fascicular epithelioid malignant schwannoma (IFEMS, page 1124); they even share some features with neurotropic melanoma.

The nature of IFSCT is controversial. To assign IFSCT, in the face of controversy, to the category of malignant nerve sheath tumor would only mask its undefined biological nature. A malignant nerve sheath tumor unequivocally behaves in a malignant fashion, with a predictable capacity for local recurrence and metastasis. Assignment of IFSCT to the category of either cellular or plexiform schwannoma would be an unwarranted extension of what is already too broadly defined. In the category of cellular schwannoma, as defined by Woodruff et al. (55), some examples share the histologic features of malignant peripheral nerve sheath tumor, but in the available retrospective studies, all examples, *by definition*, have been biologically benign (examples with local recurrences excluded). IFSCT should be characterized as a borderline lesion of indeterminate malignant potential until its nature is better documented.

Psammomatous Melanotic Schwannoma

This uncommon tumor may be either sporadic or a stigma of a complex (i.e., *Carney's complex*). The complex includes some or all of the following: myxomas (including trichogenic and cardiac variants) (90), spotty pigmentation, pigmented adrenal cortical hyperplasia, large-cell calcifying Sertoli cell tumor (91), and endocrine overactivity (including Cushing's syndrome) (92,93). Some examples of psammomatous melanotic schwannoma (PMS) have behaved in a malignant fashion (94).

Histologically, psammoma bodies and pigmented, dendritic melanocytes are features. Most examples of PMS are quite distinctive, but some examples show nuclear palisades and Verocay bodies (92,95). Zhang et al. studied 13 cases of nonpsammomatous melanotic schwannoma (94). Positive immunohistochemical staining includes S100, Leu-7, HMB-45, Melan-A, and vimentin. The product, in linear patterns, of immunoreactions for laminin and collagen IV correlate with the Schwann cell nature of the tumor cells. Ultrastructural features also are those of Schwann cells (94).

Transformed (Borderline) Schwannoma (CS2)

This borderline lesion of uncertain malignant potential is, like its benign counterpart, intraneural (confined by an expanded perineurium) (3). Its internal patterns, but not its setting, are reminiscent of patterns seen in minimal-deviation (low-grade) malignant schwannomas (MPNST) of neurofibromatosis (a lesion that is not confined by the perineurium of the nerve of origin). Some examples of transformed (borderline) schwannoma (TBS) contain scattered globular deposits of melanotic pigment (3).

TBS, as defined by Reed and Harkin (3), shares many features with cellular schwannoma as defined by Woodruff et al. (55). Herein, *cellular schwannoma of Woodruff* is identified as cellular schwannoma, class 2 (CS2).

Malignant transformation of benign schwannoma is a rarely documented event (96–98). In one report, only histologically "high-grade" variants were represented (99). "High-grade," transformed malignant schwannomas, in contrast to TBS, show a greater degree of cellular atypia and pleomorphism and a higher mitotic rate. They may show infiltrative growth beyond the confines of the perineurium (99), a quality that excludes TBS.

MALIGNANT PERIPHERAL NERVE SHEATH TUMOR OF COMMON TYPE

Malignant peripheral nerve sheath tumor of common type (*neurofibrosarcoma*; *malignant schwannoma*; *MPNST*; *neurogenic sarcoma*) is expressed in a variety of phenotypes but, most commonly, the immunohistochemical profile is that of $S100^+$. These lesions may be sporadic, they may be associated with neurofibroma, or they may be associated with NF 1.

Malignant peripheral nerve sheath tumor of the common type is the characteristic malignancy arising in neurofibromatosis type 1 (Fig. 35-33). Related malignancies may be *de novo* or may be transformations in other neurocristic neoplasms, such as schwannoma or ganglioneuroma. The criteria for the diagnosis of MPNST include some, or all, of the following: origin from, or continuity with, a major nerve or neurofibroma; association with classic stigmata of neurofibromatosis; identification of characteristic histologic patterns and demonstration of immunohistochemical profile of $S100^+$; or ultrastructural features of Schwann cells (and/or perineurial cells) (100). It has been argued that, because most "malignant schwannomas" arise in association with neurofibromas of neurofibromatosis and malignant schwannoma ex schwannoma is rare, the designation "malignant schwannoma" has limited application. The designation "malignant peripheral nerve sheath tumor," an alternative lacking discrimination, provides no distinctions between the common malignancy of neurofibromatosis and an uncommon lesion such as peripheral neuroepithelioma (primitive neuroectodermal tumor). It provides no distinctions between Schwann cell variants and perineurial variants. Epithelioid variants and mesenchymal variants are not distinguished in the promotion of the designation "malignant peripheral nerve sheath tumor."

MPNST (*sheath* or *Schwann cell type*: $S100^+$) is the common malignant tumor of peripheral nerves (1,3,4,26,101–107). Its association with neurofibromatosis 1 is established, but it is uncommon even in this setting. In a series of 678 patients with neurofibromatosis, MPNST was observed in only 21 (3.1%) of the patients (104). In only 2 of the 678 patients did MPNST primarily involve the skin and subcutaneous fat. Allison et al. reviewed the clinicopathologic features of five examples of MPNST involving the skin or subcutaneous tissue (106). Four of the lesions occurred in women. One patient had a diagnosis of type 1 neurofibromatosis. Four of the lesions were associated with a cutaneous neurofibroma; for the remaining case the tumor involved a superficial peripheral nerve. Four of the cases were of a common type, whereas the remaining case was an epithelioid variant. There were no local recurrences, but three patients died of metastatic disease.

MPNST usually arises contiguous to either an extraneural or intraneural component of a neurofibroma: In turn, it may be intraneural or extraneural. In the deep soft tissue, involvement of a large nerve trunk, such as a femoral, tibial, or intercostal

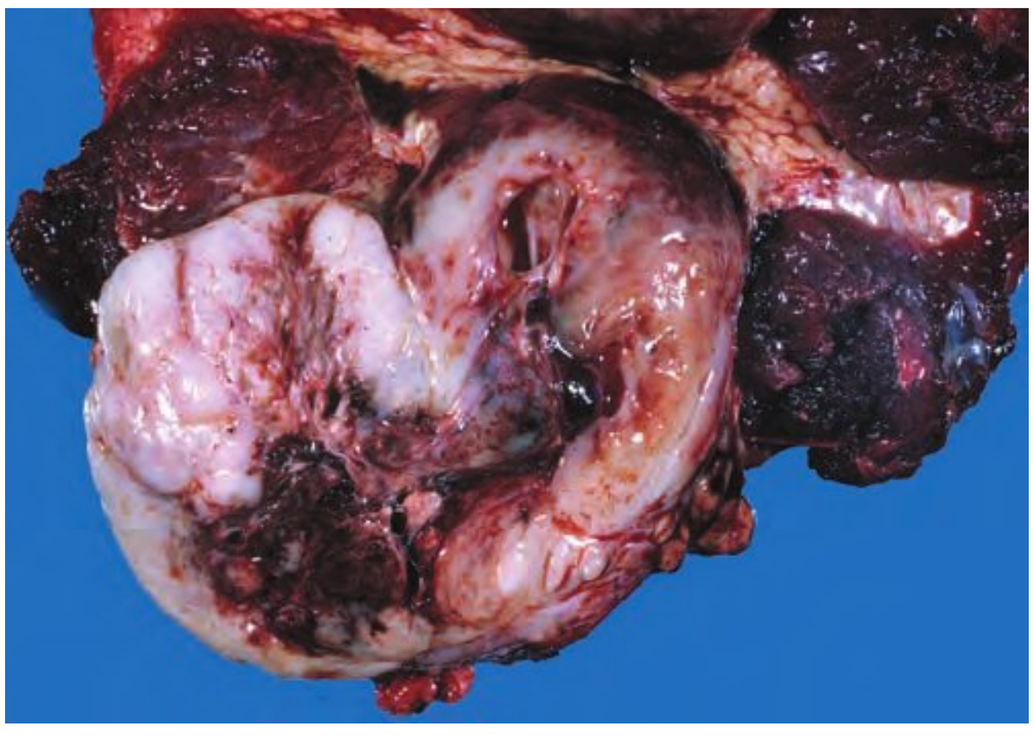


FIGURE 35-33. Malignant peripheral nerve sheath tumor. The tumor is expansile and circumscribed. The cut surface has a fish-flesh quality. A central, degenerative cyst contains blood clot.

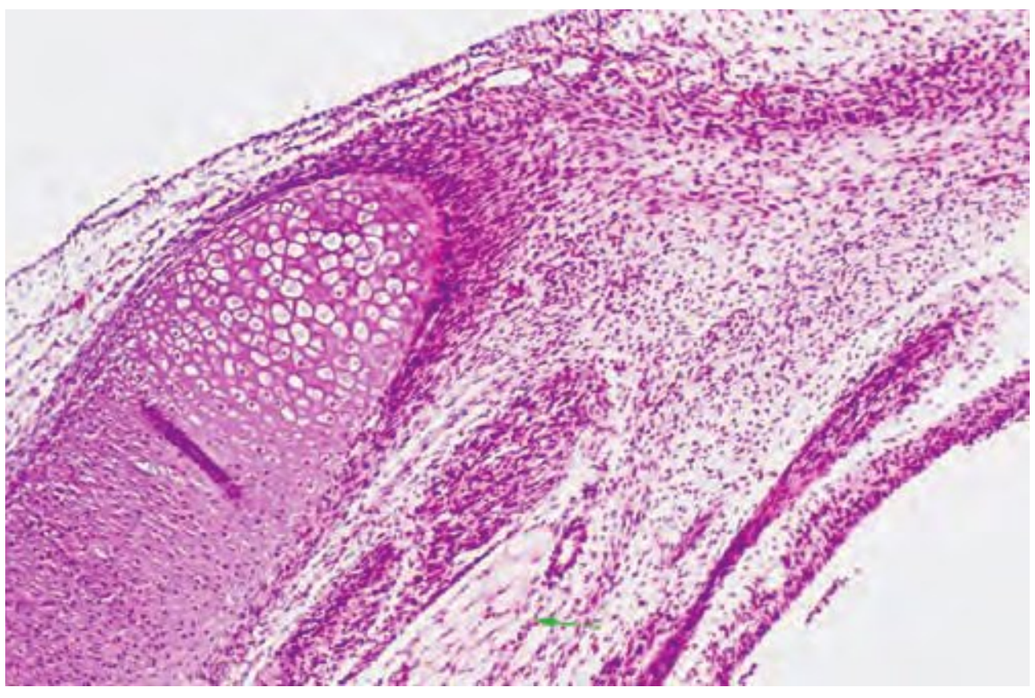


FIGURE 35-34. Fetal mesenchyme. Fetal mesenchyme shows varying patterns of differentiation. An island of immature cartilage is represented. In the neighboring mesenchyme, there are patterns of alternating light and dark fascicles. One fascicle of developing skeletal muscle fibers (green arrow) is represented in the myxoid matrix at the bottom of the field. These patterns are recapitulated, in neoplastic distortions, in many examples of malignant peripheral nerve sheath tumor.

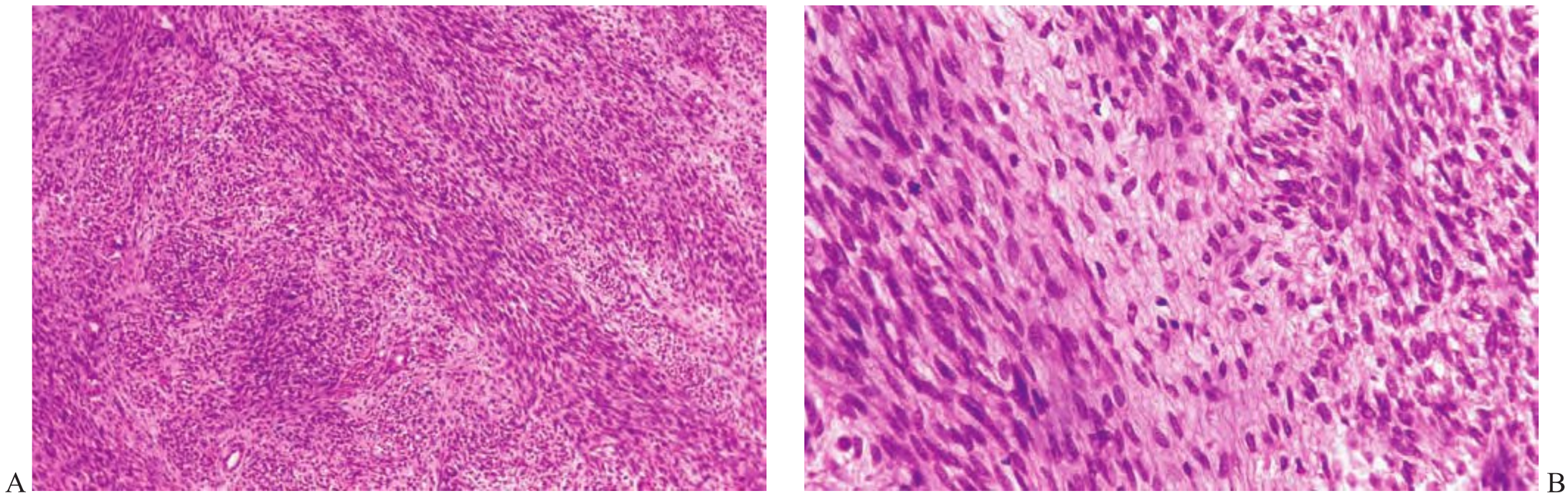


FIGURE 35-35. Malignant peripheral nerve sheath tumor; spindle cell variant. A: Atypical spindle cells form intersecting fascicles; the fascicles alternately are light and dark. B: At higher magnification, spindle cells are cytologically atypical, but cytologic features are uniform.

nerve, is characteristic, but in some instances no such connections are apparent. MPNST also can arise as a sporadic or *de novo* lesion (i.e., not associated with neurofibromatosis) (105). An origin in a benign schwannoma rarely has been reported as a documented phenomenon (99). For many examples of MPNST (sheath cell type), the patterns are expressive of the patterns of differentiation in embryonic mesenchyme (Fig. 35-34). The expressions can include, singly or in various combinations, fascicles of cells, often alternatingly light and dark (Fig. 35-35A, B), or elements such as chondroid matrix, osteoid (Fig. 35-36A), and rhabdomyoid cells (Fig. 35-36B) (107,108). MPNST of perineurial type has been promoted as a variant, with the predictable proposal that such a lesion is a malignant perineurioma, but without evidence that there is a relationship between any of the benign "perineurioma" variants and MPNST of any type (109–111). The biological potential of the perineurial variants has not been adequately defined.

Histopathology. The variable patterns of differentiation in MPNST include mesenchymal [fibrosarcomatous, osteosarcomatous, and chondrosarcomatous (3), rhabdomyosarcomatous (1,107,108), and even liposarcomatous] patterns; glandular (entodermal) patterns (70); epithelioid patterns in which individual spindle and round cells often have acidophilic cytoplasm (3,112,113) and are closely spaced in nests, fascicles, and sheets; and neuroepithelioma-like patterns (114).

Histologically, *mesenchymal patterns* are preponderant in the setting of MPNST that arise in patients with neurofibromatosis (4). Thin spindle cells are arranged in interlacing fascicles in a fibromyxoid matrix. The fascicles are straight, enabling an

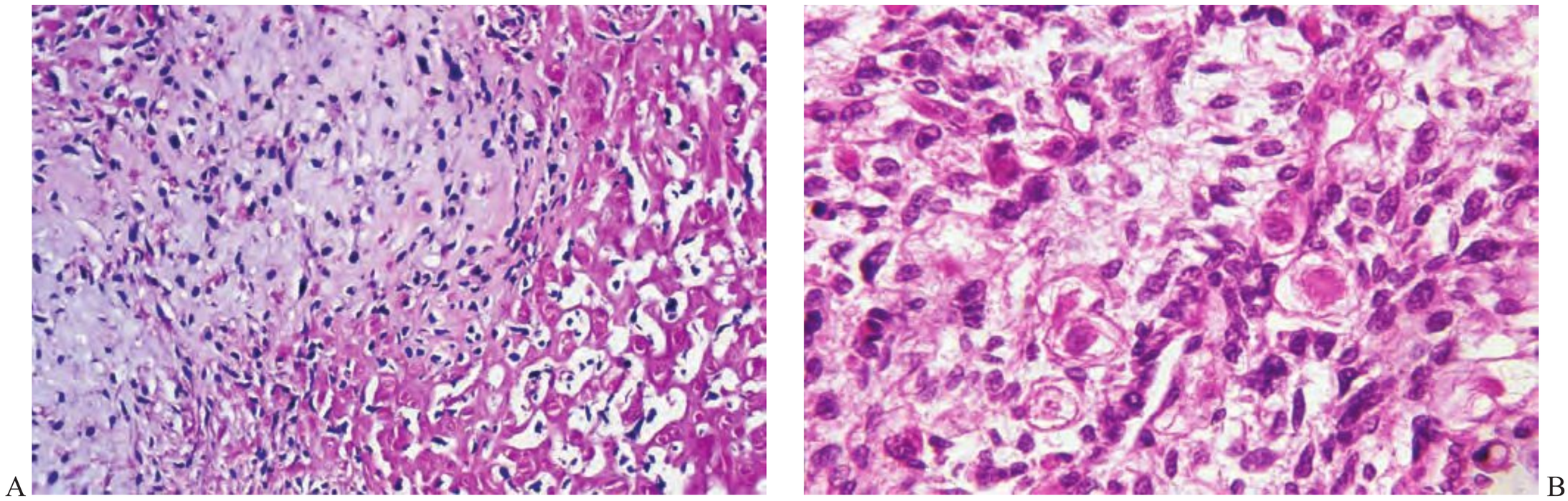


FIGURE 35-36. Mesenchymal differentiation in malignant peripheral nerve sheath tumor. A: Chondro-osseous differentiation. Chondroid differentiation is represented to the left of the center of the field; to the right, the patterns are those of neoplastic osteoid. B: Rhabdomyoblastic differentiation. In this field of undifferentiated small cells, there are scattered, rounded cells with plump, round nuclei; these round cells show concentrically arranged cytoplasmic myofibrils.

observer to trace them across low-power fields. They are alternatingly light (pale) and dark (more intensely stained). Often the spindle cells are remarkably uniform (Fig. 35-35A, B). Neoplastic cells tend to be concentrically or radially arranged about vessels, particularly near areas of necrosis. Having identified these basic features, an additional search for, and the identification of, specific expressions of mesenchymal differentiation provide strong support for a diagnosis of MPNST (Fig. 35-36A, B). Patterns of specific mesenchymal differentiation, when found, usually are spotty in distribution. Having identified one specific pattern of mesenchymal differentiation, it is often possible for the observer to then find others. The mitotic rate provides a correlate for the diagnosis of MPNST. It is not a prime determinant of biological potential. In the setting of neurofibromatosis, rates may be low (fewer than 10 per 10 hpf) or high (more than 50 per 10 hpf), and the outcome for either category may be poor, depending on other factors, such as the size and location of the lesions and the age of the patient.

Epithelioid patterns are a variant expression of MPNST in the setting of neurofibromatosis (4). *De novo* malignant schwannomas (105) and "high-grade" MPNST arising in benign schwannomas (*malignant transformed schwannoma*) (99) tend to be intraneural in origin and be manifested in "epithelioid" patterns (112,113). The study of Hruban et al. does not support this generalization but is compromised by including, as *de novo* variants, examples of both neuroepithelioma and MPNST arising in neurofibroma (114).

In epithelioid variants, plump tumor cells in nests and sheets are closely spaced with scanty intercellular matrix (Figs. 35-37 and 35-38) (112,113). Nuclei are large and often rounded. In pleomorphic variants, tumor giant cells are common. Specific patterns of mesenchymal differentiation are variant features. In some examples, the cells form nests and cords in a sparsely cellular, myxoid or hyaline matrix. The "purely epithelioid" (epithelial) MPNST, a lesion with no "sarcomatous" component, is rare (115). In some "epithelial" examples, plump, acidophilic tumor cells manifest a striking cytoplasmic argyrophilia (Fig. 35-39) (3); such examples may represent large-cell neuroendocrine carcinoma.

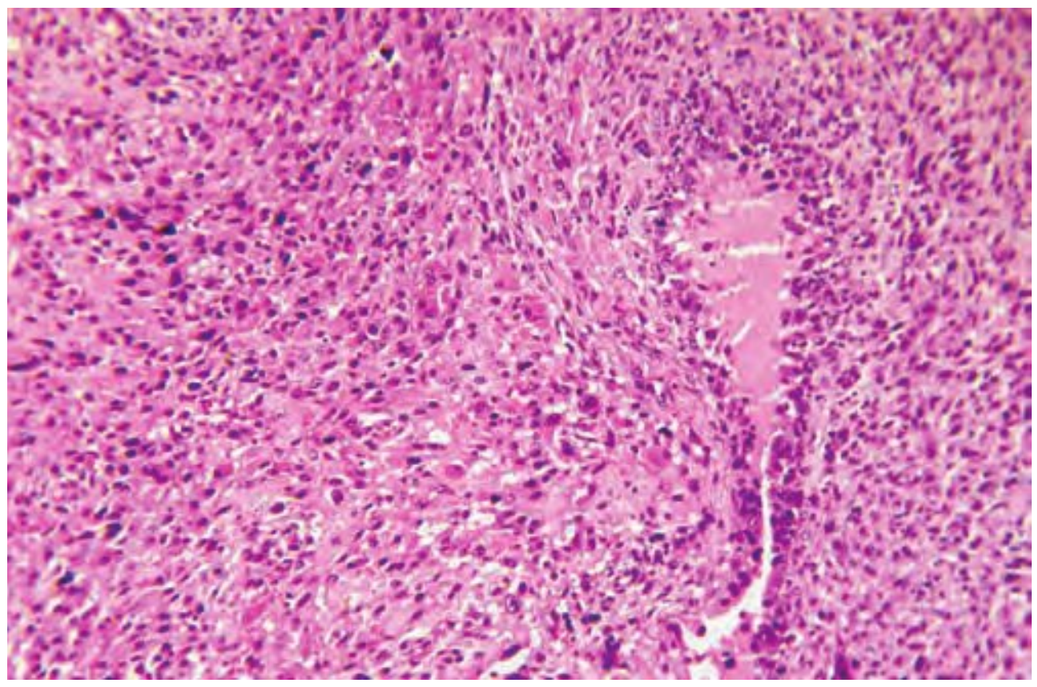


FIGURE 35-38. Epithelioid malignant peripheral nerve sheath tumor. Plump, rounded cells are arranged in patterns of ill-defined nests. Nuclei show variations in size and staining. A cleft to the right of the center of the field is outlined by palisades of tumor cells.

Malignant epithelioid peripheral nerve sheath tumors, some of which appear to have had their origin from, and are in continuity with, a peripheral nerve, may manifest extraneural, infiltrating, and fascicular patterns (25,112); they qualify as infiltrating and fascicular epithelioid malignant schwannoma (IFEMS). In the skin and subcutis, such a lesion, in recurrences, might be histologically indistinguishable from desmoplastic and neurotropic melanoma (Fig. 35-40).

The designation MPNST without additional qualifications constitutes a category without discrimination; in the epithelioid category, the designation MPNST of epithelioid sheath cell type is more appropriate.

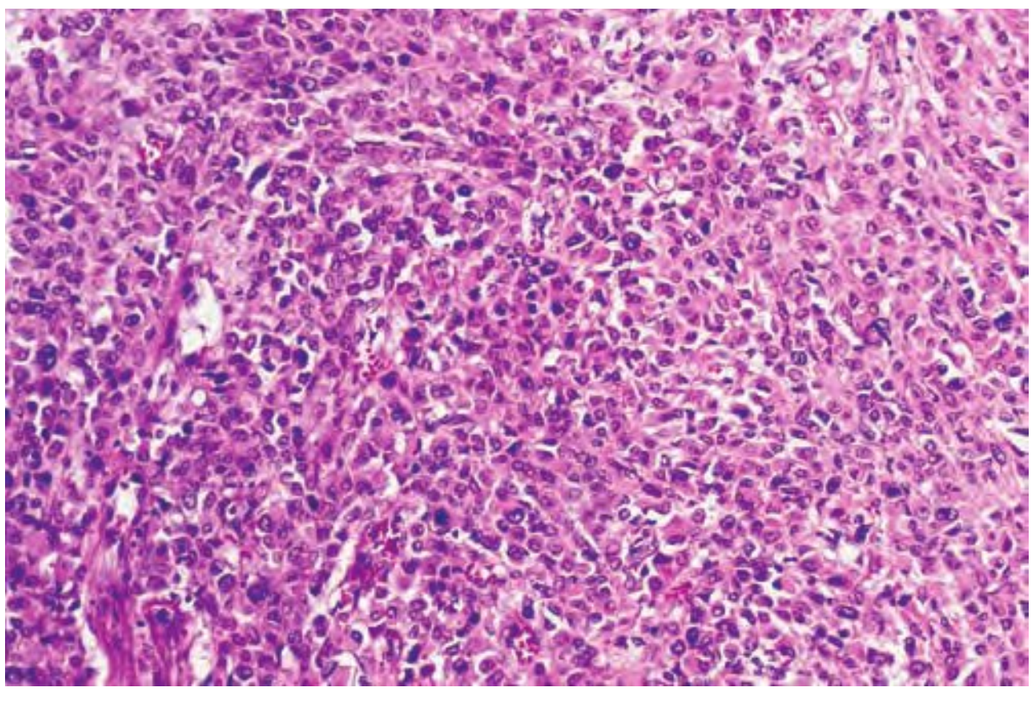


FIGURE 35-37. Epithelioid malignant peripheral nerve sheath tumor. Plump, atypical, spindle and epithelioid cells form solid sheets. Intercellular matrix is scanty.

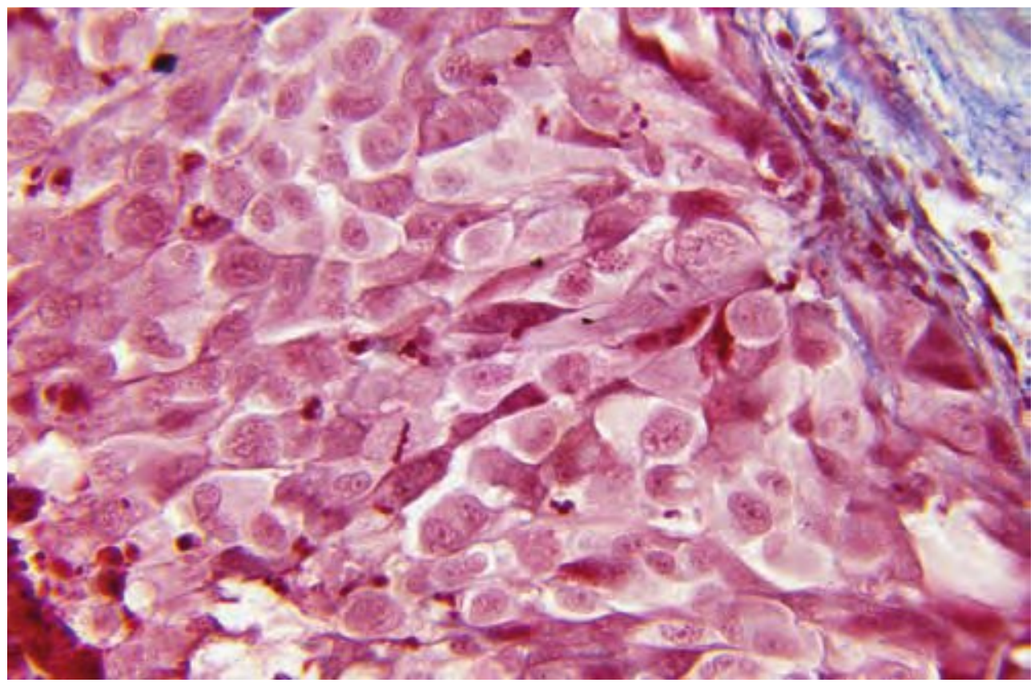


FIGURE 35-39. Neuroendocrine malignant peripheral nerve sheath tumor (Masson trichrome stain). Large atypical cells are closely clustered; they form distinct nests in a fibrous matrix. The preponderant cells have pale cytoplasm. Dark cells with dendritic processes are compressed among the pale cells. The dark cells are argyrophilic.

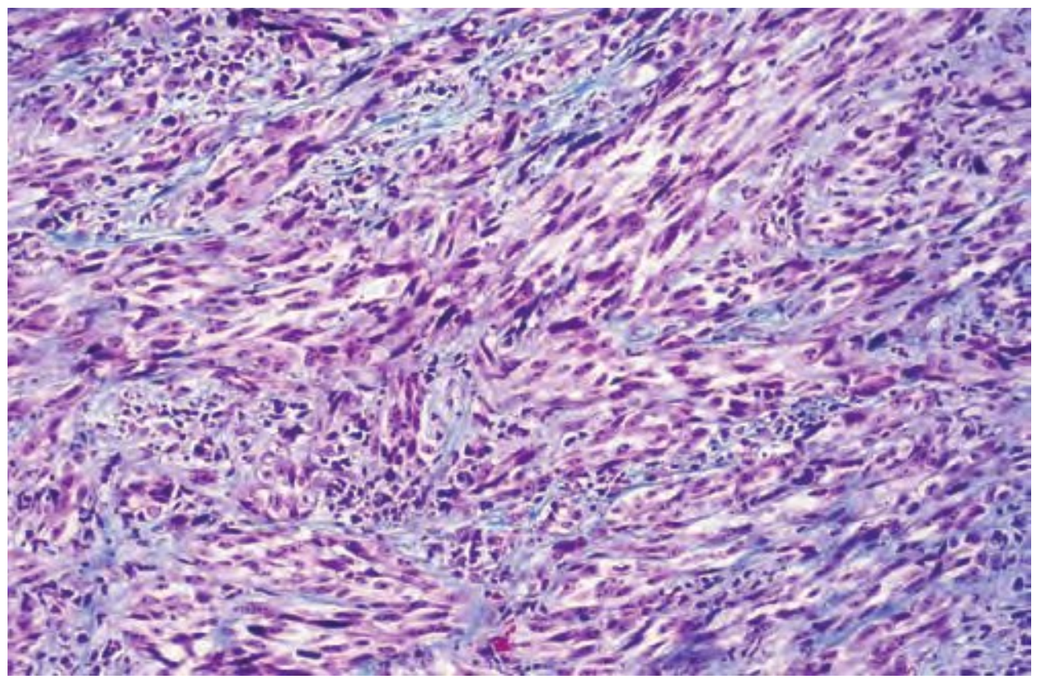


FIGURE 35-40. Fasciculated, malignant epithelioid peripheral nerve sheath tumor (both melanoma-like and neurotropic). Broad fascicles of atypical spindle cells infiltrate a fibrous matrix; portions of this soft tissue lesion were intraneural.

Zones of necrosis with peripheral palisades of tumor cells, a feature of both mesenchymal and epithelioid variants (4), are reminiscent of patterns in high-grade gliomas of the central nervous system.

For both the *de novo* variants and the transformed variants, attempts to predict an association with neurofibromatosis made simply on the basis of histologic findings in the malignant component usually are defeated by common expressions of overlaps in patterns of differentiation in the *de novo* and the transformed categories.

Of the many peripheral stigmata in neurofibromatosis, neurofibromas are the most predisposed to malignant transformations.

Ultrastructure. A light microscopic diagnosis of MPNST of sheath (Schwann) cell type is supported by a variety of features. Slender, overlapping cytoplasmic processes that envelop other processes or cell bodies may be connected by intercellular junctions. Granular, flocculent material, preferably along and parallel to the plasma membrane, may occasionally assume the linear form of basal lamina. Fine intracytoplasmic filaments should be absent or relative scanty (100).

Histogenesis. In this section, the figures reflect the whims of authors as they select or reject examples of "MPNST" for their studies. In 40% to 80% of cases of MPNST (25,115,116), the tumor cells are immunoreactive for S100 protein. CD57 can be detected in 30% to 40% of the cases (116). Myelin basic protein is less commonly detected (10%) (117). Laminin and collagen type IV are found in about 25% to 30% of cases. A high Ki67 labeling index (LI) has been correlated with a reduced survival rate; in addition, a significant correlation between Ki67 LI and the immunohistochemical expression of p53 or MDM2 has been reported (118). A positive reaction for S100 protein has taken on the aura of primacy in the classification of nerve sheath tumors. In turn, a malignant peripheral nerve sheath tumor ($S100^{+}$) might then be characterized as malignant schwannoma.

Patterns of diverse differentiation have been noted in MPNSTs (102). In the latter study, immunohistochemistry and ultrastructure were emphasized in documenting evidence of diverse differentiation; schwannian, perineurial and endoneurial, and mesenchymal categories were defined. Some MPNSTs had a high component of cells immunoreactive for S100 protein; for this group, perineurial and mesenchymal features were not associations. In a second category, less than 50% of tumor cells were reactive for S100 protein, and, in a third category, the cells did not react for S100 protein; for these two groups, patterns of heterologous (mesenchymal) and/or perineurial differentiation were observed.

Differential Diagnosis. In the absence of discernible stigmata of neurofibromatosis, differentiation of MPNST from fibrosarcoma is difficult. Patterns of interlacing fascicles that are alternately light and dark are characteristic of malignant schwannoma. In a mesenchymal variant of MPNST with patterns of specific differentiation but with no history or stigmata of neurofibromatosis, a diagnosis of malignant mesenchymoma would be a consideration.

Monophasic synovial sarcoma should be considered in the differential diagnosis (119). Its genetic profile includes t(X;18). For MPNST, the common changes are a loss of NF1 locus and a loss of the band containing gene p53; the changes are not specific. In 50% of monophasic synovial sarcomas, the cells are immunoreactive for cytokeratins and EMA. With the exception of one study, MPNSTs are t(X;18) (SYT-SSX)–negative "sarcomas" (119).

For deep epithelioid variants of MPNST, malignant fibrous histiocytoma (120), rhabdomyosarcoma, leiomyosarcoma, and malignant melanoma are considerations.

If one is confronted with infiltrating and fascicular patterns in a tumor of the skin, it might be impossible to distinguish between neurotropic melanoma (3,121) and cutaneous primary infiltrating and fascicular epithelioid MPNST in the absence of lentiginous and junctional, melanocytic patterns in the overlying or adjacent epidermis. Fortunately, the distinction as to whether such a lesion is one or the other has no major therapeutic or prognostic implications: The management is similar for both lesions. Patterns of radial sclerosis, as seen in rare epithelioid schwannomas, occasionally are a feature of dermal lesions in this overlap category of malignant fascicular epithelioid schwannoma and neurotropic melanoma.

Infiltrating fascicular Schwann cell tumor of infancy, in its histologic but not its cytologic patterns, shows overlaps with the patterns of both IFEMS and neurotropic melanoma (121).

Glandular, entoderm-like patterns (Fig. 35-41) may be more commonly associated with epithelioid than with mesenchymal variants of MPNST. If glandular patterns are represented in a problematic lesion, then carcinosarcoma might be a consideration. Entoderm-like glandular patterns, in the absence of sarcomatous components, rarely are encountered in the soft tissue in the setting of neurofibromatosis; a lesion showing such patterns may represent a primary neuroendocrine carcinoma (122).

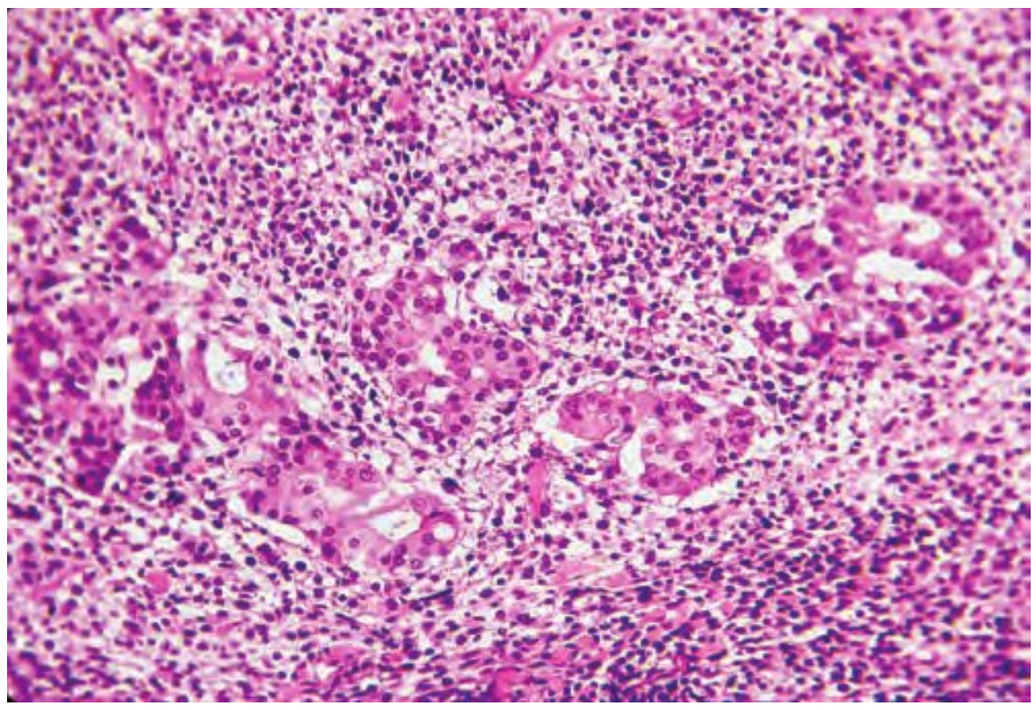


FIGURE 35-41. Small epithelioid cell malignant peripheral nerve sheath tumor; divergent glandular differentiation. Plump, columnar cells form solid nests and glandular patterns; the cells have small, round nuclei with uniform nuclear characteristics. The glandular spaces contain basophilic mucin. The glandular component is a random manifestation in an epithelioid malignant peripheral nerve sheath tumor.

Ganglioneuroma of the deep soft tissue has been the rare site of origin for a MPNST (31,123,124).

Prognostication and Treatment. A moderate increase in cellularity, focal storiform patterns, mild nuclear atypia, and the presence of mitoses (fewer than 10 per 10 hpf) may be the only features that distinguish low-grade MPNST from neurofibroma (3,57,125,126). Such examples qualify as *minimal deviation variants of indeterminate malignant potential*; local surgery is an option in treatment.

In the setting of neurofibromatosis, MPNST, in its many guises, generally has a poor prognosis. High-grade tumors show high mitotic rates (as many as 50 per 10 hpf), dense cellularity, scanty stroma, marked nuclear atypia, pleomorphism, and palisaded zones of necrosis. For intraneural, high-grade MPNST ex schwannoma (confined by the perineurium of the nerve of origin), confinement favorably modifies the significance of the "high grade." In one series of epithelioid MPNST, superficial location (skin and subcutis) and small size were favorable prognostic parameters (112). In general, adverse prognostic factors include large tumor size, age greater than or equal to 7 years, tumor necrosis greater than or equal to 25%, and von Recklinghausen's disease (127,128). A high mitotic rate and the need for resection by amputation have also been cited as factors related to a poor prognosis (114). Aggressive surgical treatment is required for high-grade tumors with extensive spread along the involved nerve (129).

TUMORS OF UNCERTAIN NATURE WITH NERVE SHEATH–LIKE FEATURES

Nerve sheath myxoma was originally defined by Harkin and Reed (3). Gallager and Helwig, under the designation *neurothekeoma,* described a series of tumors that they interpreted as nerve sheath tumors; the histologic patterns of neurothekeomas shared some general features with those of nerve sheath myxoma (130). As a result, there has been confusion regarding a relationship between the two categories.

Herein, the designation *nerve sheath myxoma* (NSM) (a myxoid and loosely cellular lesion that mostly appears micronodular) recognizes the classic nerve sheath myxoma as defined by Harkin and Reed (3,4). A larger group, the *neurothekeomas* of Gallager and Helwig (NTK) (130), includes both a cellular, or epithelioid and fascicular, neurothekeoma and a variant of neurothekeoma in which epithelioid and myxoid patterns are mixed (131,132).

NSM has an "immunohistochemical profile" that more clearly identifies nerve sheath qualities (i.e., $S100^{+}$); immunohistochemical distinctions have come to define the apparent separateness of NSM and NTK. In the face of immunohistochemical properties, which are of value in defining neural tumors but are weak or negative in NTK, attempts to find definitive immunohistochemical neural markers for NTK have found only brief support—witness the initial enthusiasm for PGP 9.5 in NTK (133).

In all variations, NSM and NTK are mostly neoplasms of the dermis. Similar lesions are rarely encountered in the soft tissue. NSM, in all its expressions, has been benign, although in cases of incomplete removal, rare examples have recurred. Neither neurofibromatosis nor multiple mucosal neuroma syndrome has been a documented association of either NSM or NTK.

Mature Nerve Sheath Myxoma

The relationship, if any, between nerve sheath myxoma (NSM) and neurothekeoma is controversial. In 1985, Pulitzer and Reed (134) expanded the concept of NSM and, in the process, fed the controversy. In 2005, Fetsch et al. (135) analyzed their material with emphasis on those cases that would immunohistochemically and clinicopathologically correspond to classic NSM. Their results offer strong support for the neural character of classic NSM. The nature of classic neurothekeoma has remained a mystery, although some of the findings, which initially had been cited as offering support for a neural origin, now could also be interpreted as favoring a fibrohistiocytic origin (136).

Classic (micronodular) NSM (Pulitzer and Reed) is most common in middle-aged adults, with a male-to-female ratio of approximately 1:2 (3,4,134,135); mean age has been variously reported as 21.6 and 36 years. Characteristically, it is an asymptomatic, soft, skin-colored or translucent papule or nodule ranging from 0.5 to 1.0 cm in diameter (35,134). It is typically located on the face and the upper extremities but can occur anywhere on the body; in the material from the Armed Forces Institute of Pathology, acral locations were preponderant (135).

Histopathology. Symmetrically expansile, myxoid micronodules are loosely clustered in a fibrous matrix in the reticular

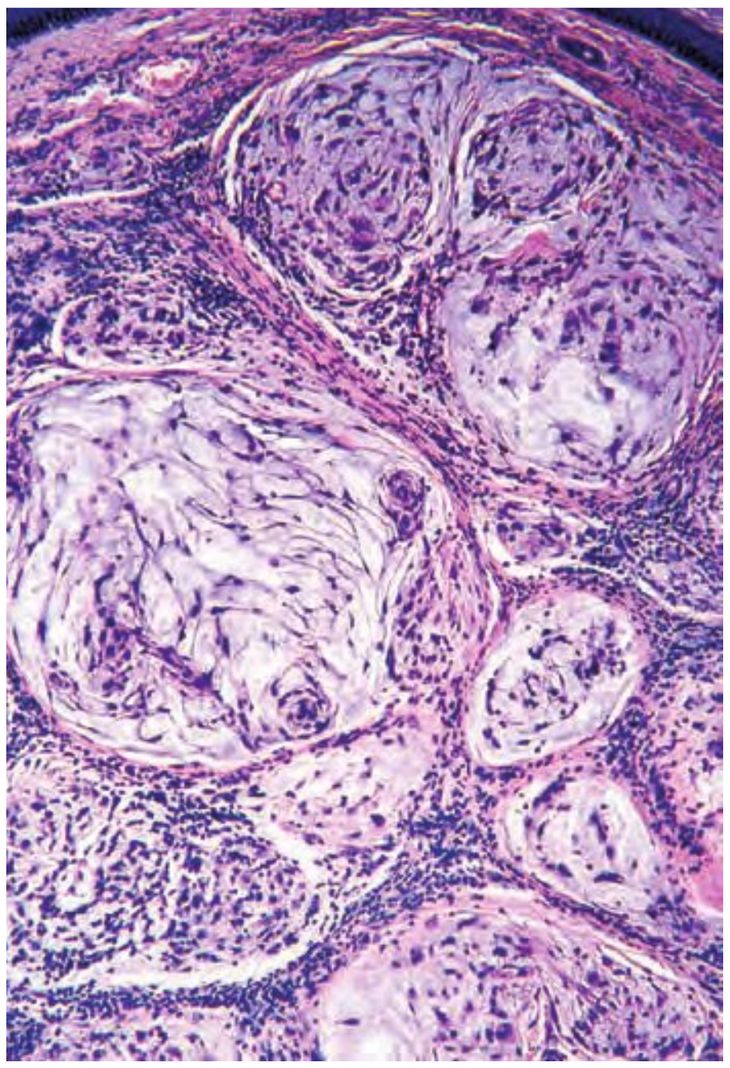


FIGURE 35-42. Mature nerve sheath myxoma. The lesion is plexiform; fascicles are represented in both longitudinal and cross sections. Some of the fascicles are outlined by thin sheaths of condensed fibrous tissue. Tumor cells are loosely spaced in a prominent myxoid matrix. Some of the tumor cells have thin polar extensions of cytoplasm; they morphologically resemble perineurial cells. Some are plump and epithelioid. Some of the thin cells form whorls about blood vessels of the fascicles. In this example, lymphoid infiltrates are prominent in the stroma.

dermis; they vary in size. In aggregate, they form a multilobulated mass that is often poorly circumscribed and not always symmetric (Fig. 35-42). The myxoid matrix is rich in acid mucopolysaccharides (sulfated glycosaminoglycans). In it, bipolar and tripolar cells are widely and fairly regularly spaced (Fig. 35-43). Nuclei are elongated and often angulated, with inconspicuous nucleoli and uniformly distributed, dense chromatin. Cytoplasms are pale, and cell membranes are sharply defined. Centrally in the micronodules, cells tend to be arranged in loose whorls. Each micronodule is partially or completely outlined, in perineurium-like patterns, by a thin condensation of fibrous tissue. Continuity with adjacent nerves is rarely identified (3,130,134,135).

Ultrastructurally in lesions of NSM, a continuous basal lamina outlines most cells, but in some reports, discontinuous basal lamina and pinocytotic vesicles have been features (134,137). Engulfment of collagen fibers in the manner of Schwann cells has been observed. Fibroblasts and mast cells are also represented.

Histogenesis. The most consistent immunohistochemical profile is S100$^+$, collagen type IV$^+$, GFAP$^+$, and vimentin$^+$ (35,136). A smaller number of cells are EMA$^+$ (35).

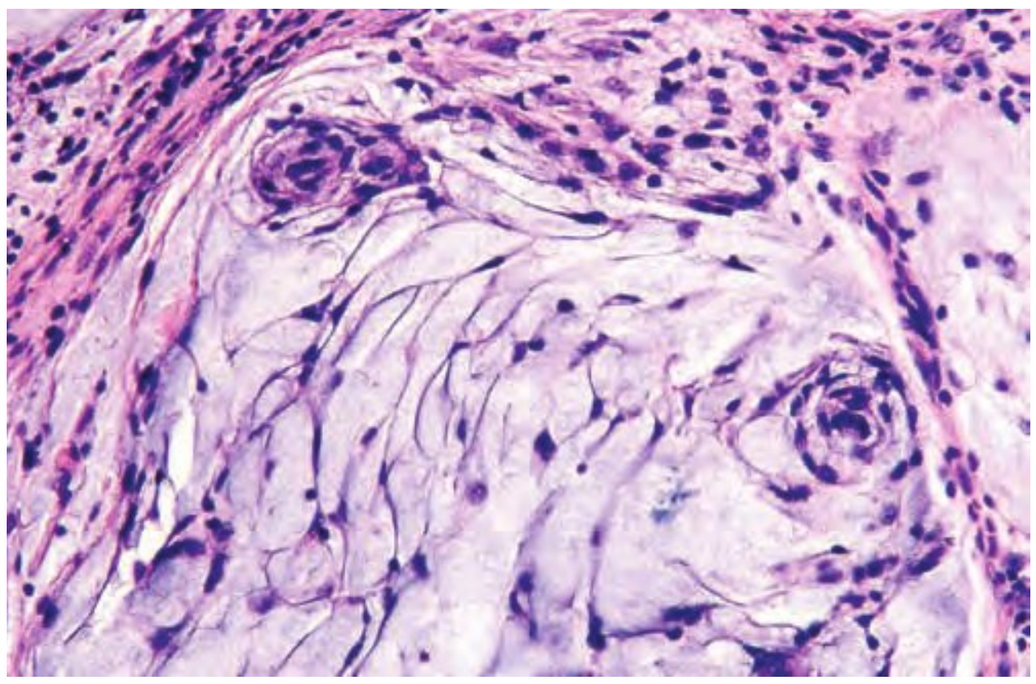


FIGURE 35-43. Mature nerve sheath myxoma. At higher magnification, many of the tumor cells have "perineurial cell–like" qualities. Some of the distinctive cells form whorls about vessels.

Neurothekeoma [Cellular, Epithelioid, and Fascicular (Nerve Sheath Tumor–Like) Neoplasm, Questionably of Nerve Sheath Origin: Cellular Neurothekeoma; NTK]

The lesions of this category should be classified as *neurothekeoma* (NTK); the designation *cellular neurothekeoma* was and is, in large part, a political accommodation that has been rendered superfluous. The category includes two variants. For one variant (*NTKA*), the patterns are uniformly cellular and fasciculated. For the second variant (*NTKB*), cellular and fascicular patterns are admixed with myxoid components (i.e., focal histologic qualities that might be confused with those of classic nerve sheath myxoma).

In NTK, the mean age is 24 years, but examples have been reported in children. The upper body is the favored site. Women are more commonly affected (136). The lesions are firm, pink, red-brown papules or nodules measuring 0.5 to 3.0 cm; some may produce symptoms (137).

Histopathology. In the variant *NTKA*, fascicles of cells tend to be rather uniform in diameter, and their margins are poorly defined. They are arranged in infiltrating (dissecting) patterns among collagen bundles of the reticular dermis or are supported by a fibrous matrix (Fig. 35-44A, B); they often extend into the subcutis. Exclusive of the fascicular component, individual tumor cells and small, irregular clusters of tumor cells may infiltrate the reticular dermis; they may even extend into arrector muscles. In the fascicles, the cells are closely spaced; they tend to be polygonal, but in rare examples they are plump and spindle shaped. Cytoplasm is conspicuous and tends to be acidophilic. Rigid cytoplasmic processes are prominent. The nuclei are plump and rounded or elongated and somewhat irregular in outline. Nuclear chromatin is stippled, and nuclear membranes are heavy.

In the variant *NTKB*, some of the aggregates become locally expanded to form broad fascicles and nodules in which

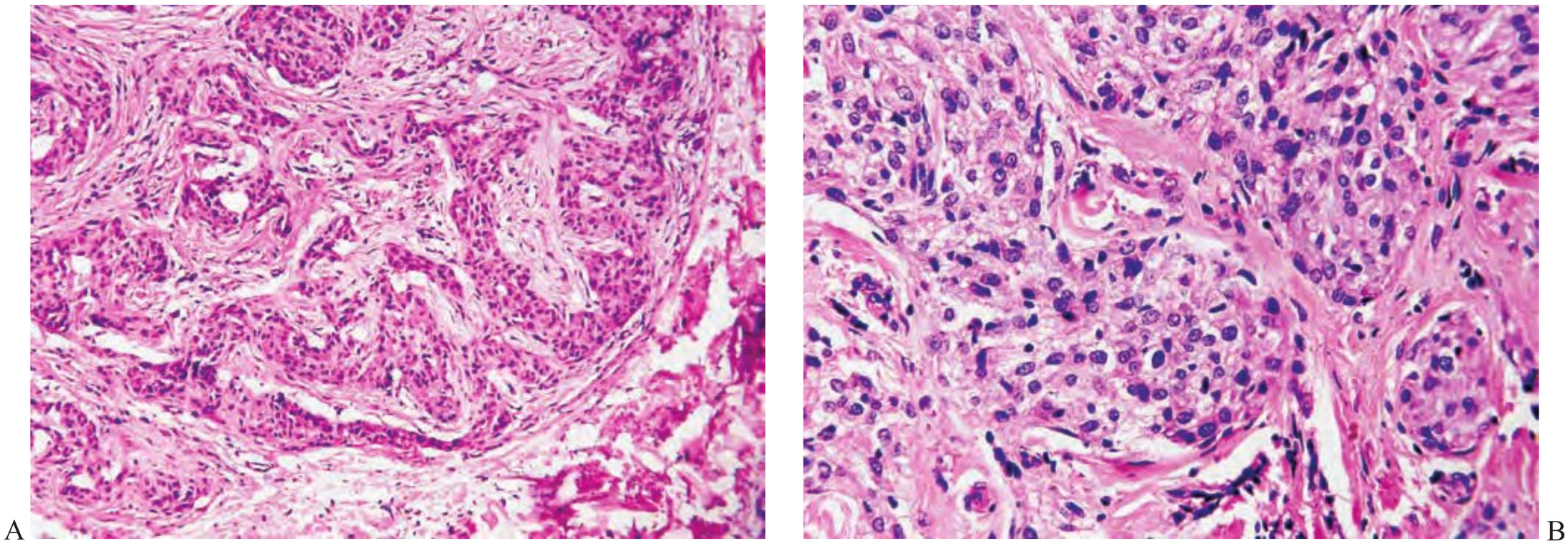


FIGURE 35-44. Neurothekeoma. A: Pale, acidophilic epithelioid cells from tortuous, interconnected fascicles in a well-defined fibromyxoid matrix; the lesion is sharply circumscribed. In the fascicles, myxoid matrix is scanty. B: At higher magnification, the epithelioid cells of the fascicles are loosely attached to their neighbors. Defects among the tumor cells contain a mucinous matrix. The tumor cells show regular, round nuclei with well-defined nuclear membranes and stippled chromatin; nuclei are small.

both cellular and myxoid patterns are represented (Fig. 35-45). In the myxoid zones, stellate cells are loosely spaced: Their cytoplasmic processes are broader and more irregular in diameter than those of the cells of classic NSM. The myxoid patterns tend to be represented at the periphery of broad fascicles and nodules. Compact whorls of cells are focally prominent in all variations of NTK. Spotty, incomplete condensations of fibrous tissue are observed at the periphery of the broad fascicles and nodules.

In some examples of NTK, the stroma consists of a sclerotic, fibrous matrix with no preservation of the interwoven fiber patterns of the reticular dermis (Fig. 35-44A).

Mitoses are not a prominent feature in most examples of both variants of NTK. Atypical variants are characterized by nuclear atypia and pleomorphism with scattered mitoses (Figs. 35-46 and 35-47), some of which may be atypical (134,138).

In some examples of NTK, histiocytic, multinucleated giant cells are represented among the tumor cells. In lesions showing a component of such cells, the patterns somewhat overlap with those of plexiform fibrous histiocytoma (Fig. 35-48).

Rarely in lesions of NTK, cells of the tumor can be found within small nerves in the adjacent dermis.

Ultrastructurally, NTKA and NTKB are composed preponderantly of undistinguished cells. Focal densities of the cell

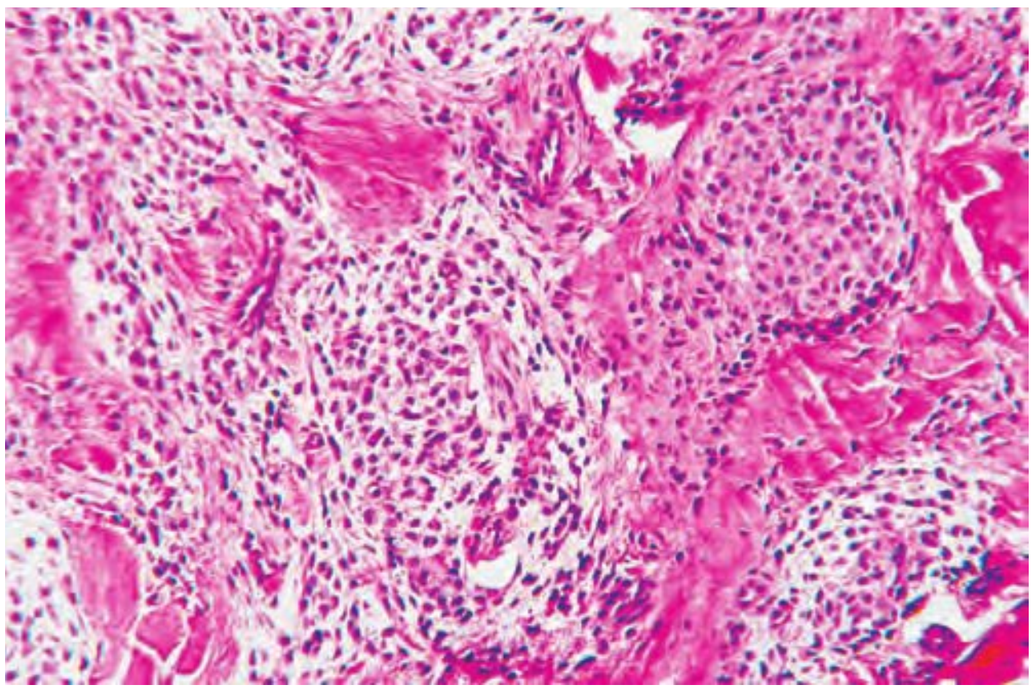


FIGURE 35-45. Neurothekeoma; intermediate variant. In this example, cellular zones merge with myxoid zones; the lesion is fasciculated; the fascicles extend among collagen bundles of the reticular dermis without inducing a tumor stroma.

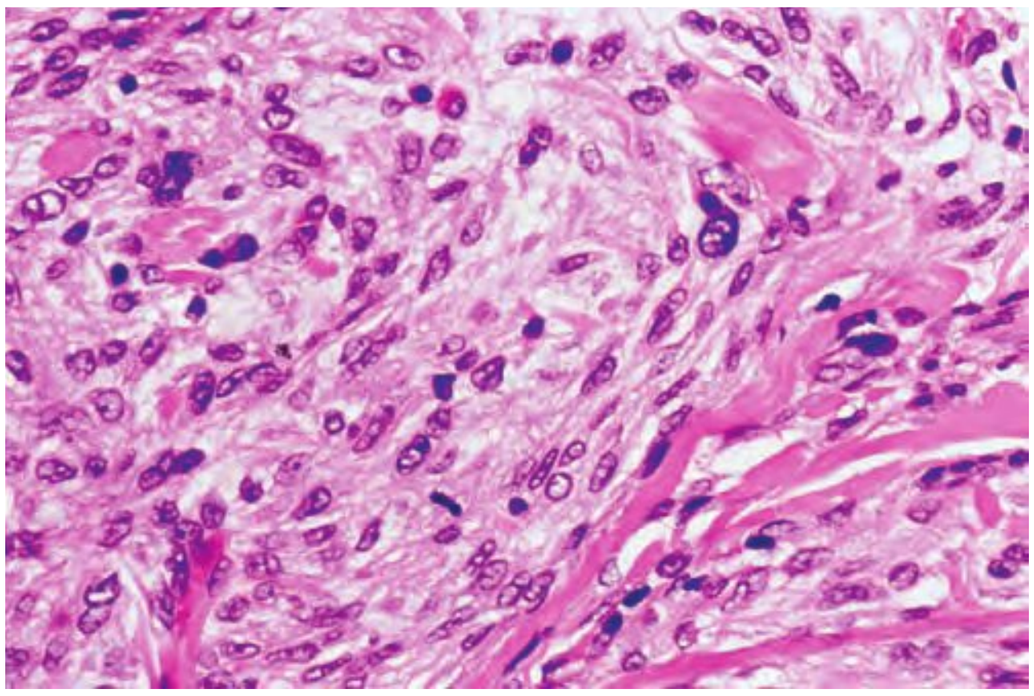


FIGURE 35-46. Atypical neurothekeoma. Tumor cells of this atypical nerve sheath myxoma vary in size and outline; some are hyperchromatic. A mitotic figure is represented to the left and below the center of the field.

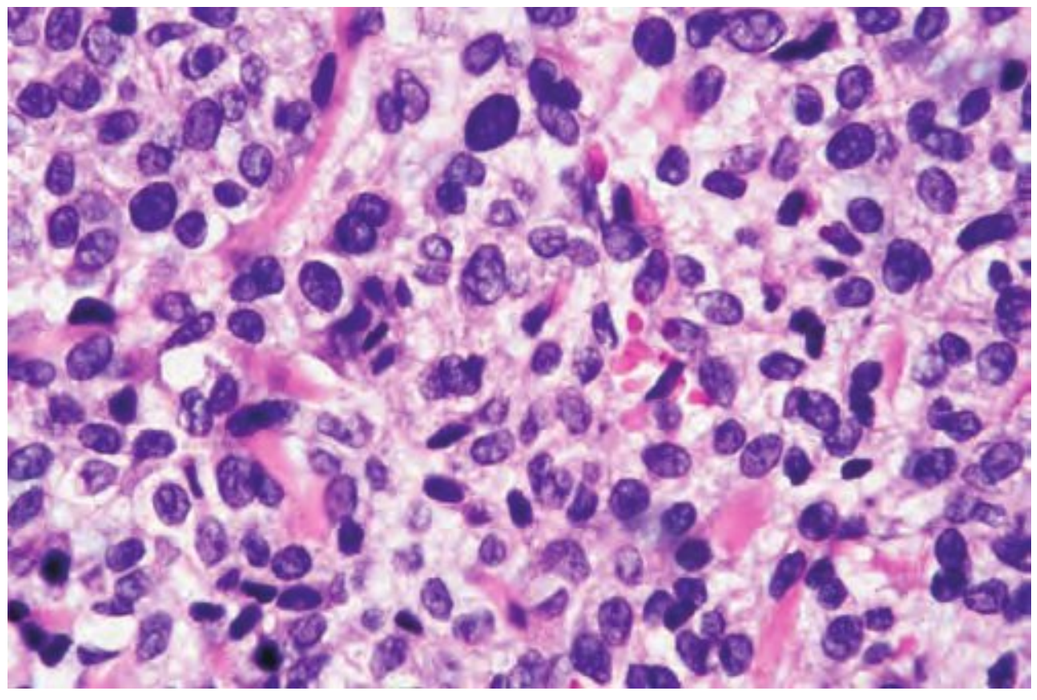


FIGURE 35-47. Atypical neurothekeoma. Cells have scanty cytoplasm. Enlarged, hyperchromatic nuclei vary in size and outline; some show prominent nucleoli.

membranes, which are suggestive of attachment plaques, and focal, poorly formed, basal lamina–like material have been described (139). Some of the cells contain phagolyosome-like structures, irregularly arranged microfilaments, and rare microfilament-attached dense bodies (140). Fibroblasts are common. In a single case, perineurial cell–like features were described (137).

Histogenesis. Immunohistochemically, the cells of NTK exhibit a variable and inconsistent phenotype. They are positive for vimentin, CD10 (140), and PGP 9.5 but do not often stain for S100 protein or epithelial membrane antigen (136,141,142). Weak and variable expressions of smooth muscle–specific actin, collagen type IV, NK1/C3, and CD57 have been reported (35,132–143).

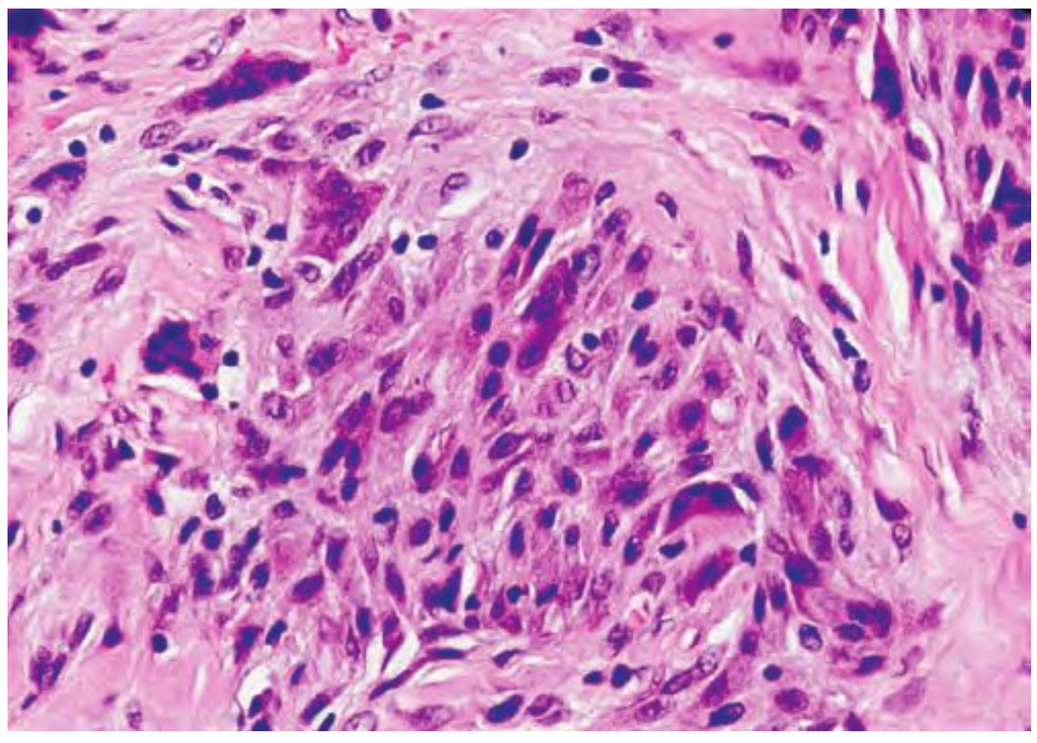


FIGURE 35-48. Neurothekeoma with multinucleated giant cells. The basic pattern of this "plexiform" lesion suggested a variant of nerve sheath myxoma. Focally, as in this field, the patterns overlap with those of plexiform fibrous histiocytoma.

PGP 9.5 recently has been found to be a rather nonspecific marker in the practice of surgical pathology (144). NK1/C3, although having been cited as a marker that distinguishes cellular neurothekeoma from other dermal tumors (145), was found to be positive in a spectrum of neoplastic tissues; it was also positive in many dermal tumors of possible histiocytic origin (146).

Differential Diagnosis. Intraneural neurofibromas are rare in the dermis and only slightly more common in the subcutis. Immunoreactive axons, a feature of intraneural neurofibroma, are not a feature of NSM.

Cellular myxomas of the skin, including *angiomyxomas* (147) and *trichogenic myxomas* (90), are rare; some are poorly documented. They are solid, uniform lesions; neither the micronodular qualities of NSM nor the fascicular and nodular qualities of NTKA and B are represented. In cellular myxomas, immunoreactions for S100 protein are negative (35). Examples of cellular myxoma appear to have been included in some reports of NSM. Zelger et al. suggested that some reported examples of NSM were perineuriomas (37).

Spindle cell nevus of the Spitz type, particularly dermal variants, might be confused with NTK. A strong and uniform reaction for S100 protein would favor a variant of Spitz nevus or some other variant of nevus, such as a cellular blue nevus with prominent fascicular components. The pigmentation of deep penetrating nevus is not a feature of NTK.

In rare examples, minimal deviation *neurotropic melanoma* would be a consideration. Most spindle cell melanomas are S100 protein positive. Not all desmoplastic and neurotropic melanomas are immunoreactive for HMB-45, but a positive reaction would exclude NTK. *Neurothekeoma A* might be mistaken for a metastatic malignant melanoma (a lesion lacking a primary configuration). A positive reaction for S100 protein and HMB-45 would strongly favor a diagnosis of malignant melanoma.

The immunohistochemical distinctions between NSM and NTK provide evidence that "cellular neurothekeoma" could well be something other than a nerve sheath tumor (136). Zelger et al. proposed that "cellular neurothekeoma" is a variant of dermatofibroma (148), but it is difficult to accommodate the fascicular patterns of NTK in the category of dermatofibroma.

The commonness of many of the histologic patterns in the groups NSM and NTK could depend on the degree of differentiation or the functional status of Schwann cells. In the latter promotion, NK1/C3 positivity could be evidence of the ability of Schwann cells to function as histiocytes. It has been argued that "cellular neurothekeoma" is a variant of dermatofibroma or fibrous histiocytoma (136); in this promotion, NK1/C3 positivity is evidence of the "histiocytic" nature of the tumor cells, and the lesion could then be assigned to the "fibrohistiocytic" category. Positivity for CD10 could be offered in support of the "histiocytic" nature of "cellular neurothekeoma," but this type of positivity has also been observed in myelin sheaths (149) and wallerian degeneration. It is too

soon to assign cellular neurothekeoma to the "fibrohistiocytic" category. The "fibrohistiocytic" category is perhaps more poorly defined than when A. P. Stout proposed the concept of the "facultative" fibroblast.

Some examples of NTKB with involvement of the subcutis and with representation of numerous giant cells would be difficult to distinguish from plexiform fibrous histiocytoma of children and young adults (Fig. 35-48) (36). In the nodular portions of plexiform fibrous histiocytoma, the cells are closely spaced and often are admixed with multinucleated giant cells. Plexiform fibrous histiocytoma has a close association with fascia. A myxoid matrix is not prominent but focally may be a feature. The fascicular ("plexiform") qualities of NTK have complicated attempts to assign this lesion to its proper category (150). It has been suggested that NTK and plexiform fibrous histiocytoma might be one and the same lesion. Such an approach would not necessarily require that priority be assigned to the fibrous histiocytoma category.

Sclerosing myofibroblastomas, as well as rare myxoid or epithelioid pilar leiomyomas, of the skin should be considered in the differential diagnosis (151). Cells of the cellular portions of myxoid leiomyomas clearly are smooth muscle in type. In some examples of NTKA, in which some of the cells are immunoreactive for smooth muscle actin, the tumor cells are consistently negative for desmin (35).

Epithelioid fibrous histiocytoma (EFH) (*epithelioid cell histiocytoma*, *adventitial cellular myxofibroblastoma*) (152,153), a lesion favoring acral sites, tends to be polypoid; it is mostly confined to a widened papillary dermis. Some examples are mostly myxoid. Large, vacuolated cells with muciparous qualities are occasionally a feature. Many of the dendritic histiocytes that are found among tumor cells of EFH are reactive for factor XIIIa, and some are reactive for S100 protein. Examples of EFH can be identified in some reports of NSM.

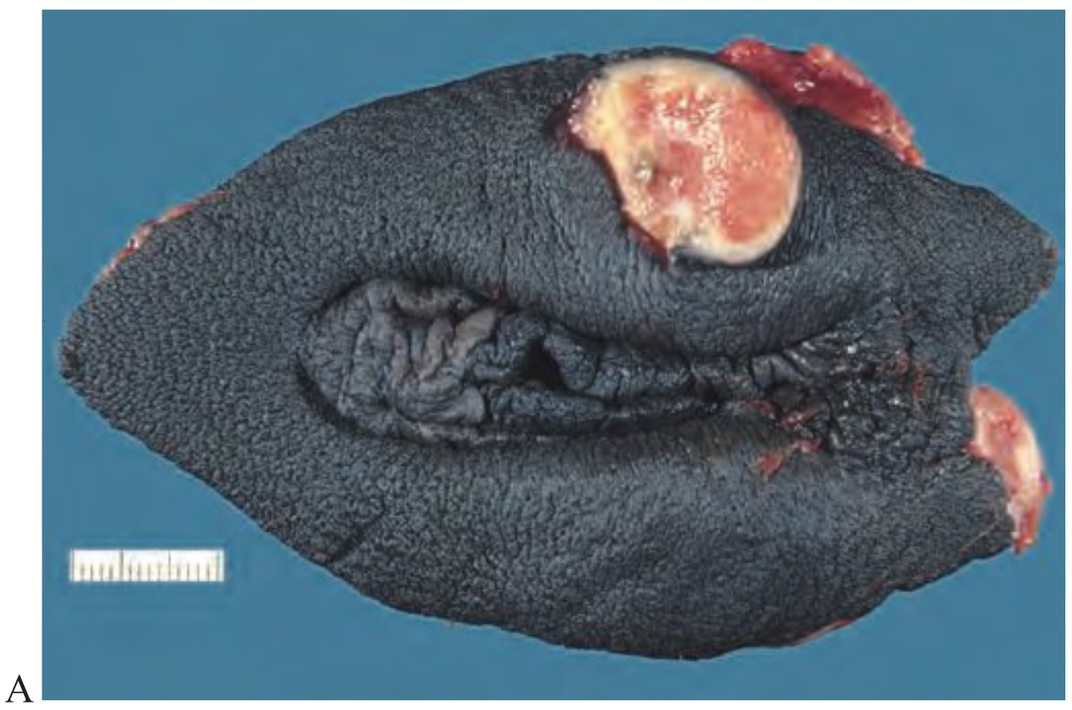
Granular Cell Tumors

Granular Cell Nerve Sheath Tumor

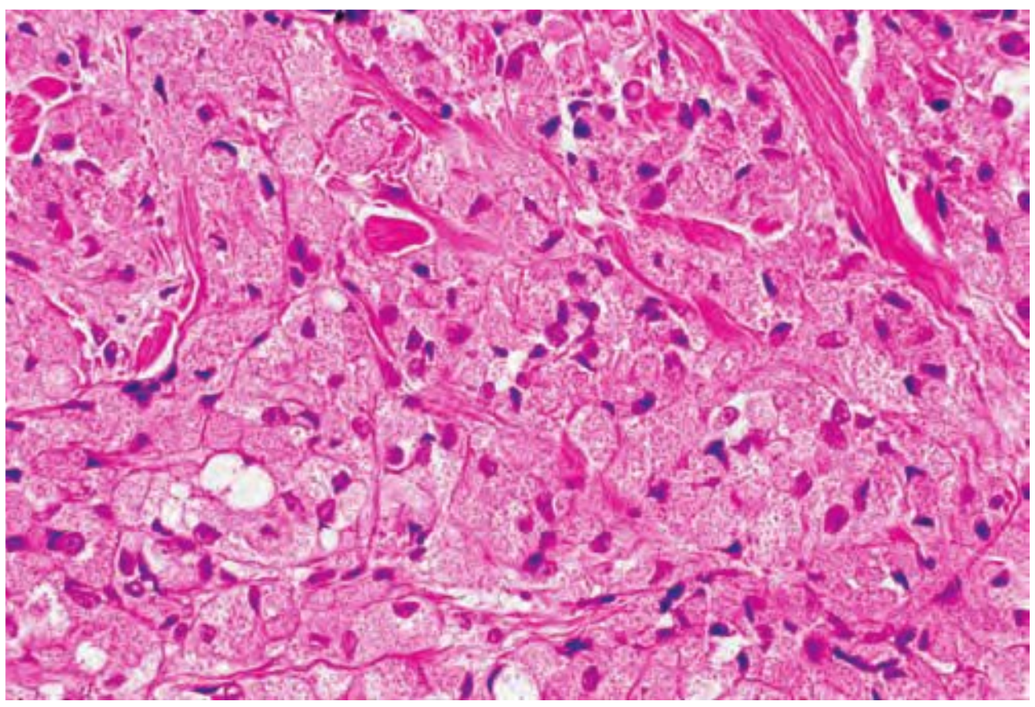
Granular cell nerve sheath tumor (GCNST) (*granular cell myoblastoma, granular cell schwannoma, granular cell tumor*) usually is solitary. In about 10% of the cases, lesions are multiple; they may be multifocal. Forty percent of the cases involve the tongue (154), but the skin and the subcutaneous tissue also are common sites (Fig. 35-49A). Other reported sites include the esophagus, stomach, appendix, larynx, bronchus, pituitary gland, uvea, and skeletal muscle (155).

GCNSTs of the skin are well circumscribed, raised, firm, and nodular. Some examples are verrucoid at the surface. Generally, lesions range from 0.5 to 3.0 cm in diameter. The cut surface often is faintly yellow and homogeneous. Tenderness or pruritus has been an occasional complaint.

Histopathology. Most GCNSTs are extraneural; rare examples have been intraneural, at least in part. Broad fascicles of tumor cells infiltrate the dermis among the collagen bundles (Fig. 35-49B). Extension of fascicles of tumor into the subcutis is common. The tumor cells are large and polygonal (Fig. 35-49B); cell membranes are distinct. Faintly eosinophilic, uniform, small granules that are periodic acid-Schiff (PAS) positive and diastase resistant fill the cytoplasms. Scattered, laminated, cytoplasmic globules with peripheral halos (residual bodies) (Fig. 35-50) are also represented. Nuclei usually are small and centrally located. They tend to be round to oval in outline but, in some examples, are plump, irregular, and hyperchromatic



A



B

FIGURE 35-49. Granular nerve sheath tumor. A: This granular cell tumor involves a labia majora of the vulva. The cut surface of the tumor is exposed; it is yellow-tan and somewhat granular. The specimen is the product of a vulvectomy. B: In this example, the cells are plump and polygonal; fine granules, uniform in size, fill the cytoplasm of each cell. In this category, nuclear characteristics are variable from case to case; in this example, there is some variability in nuclear size and outline. An occasional nucleus contains an inclusion of cytoplasm. Nucleoli are variable in size.

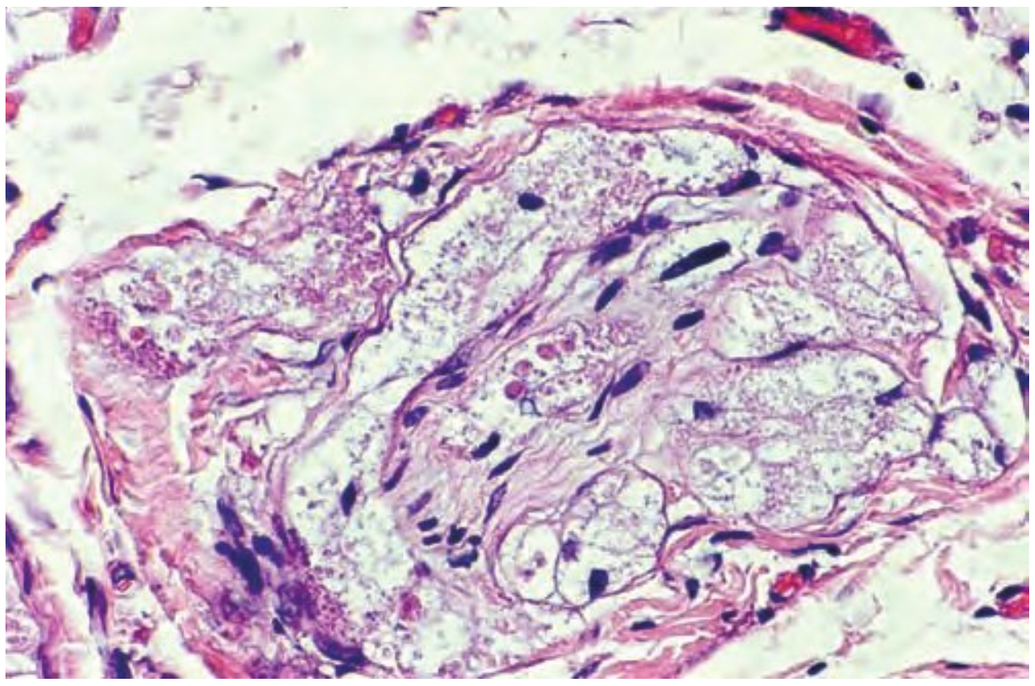


FIGURE 35-50. Granular cell nerve sheath tumor, neurotropism. Granular cells infiltrate the perineurium and the endoneurial space of this small nerve. In the cytoplasm of some of the cells, in addition to fine, uniform granules, there are larger, rounded, acidophilic bodies that are "residual body like."

with a central nucleolus. Mitoses are uncommon. Some clusters of tumor cells are surrounded by PAS-positive, diastase-resistant membranes, strands of collagen fibers, and occasional flattened, satellite cells (154). Interstitial spindle cells have fibroblast-like qualities (25). Rarely, fascicles of tumor cells are entrapped in a dense fibrous matrix (sclerosing variant).

Neurotropic spread along peripheral nerves both within and at the advancing margins of the tumor is often a feature (Fig. 35-50). Rarely, deep GCNSTs have an intraneural component that expands the involved nerve.

The histologic features of some GCNSTs are of a type that, in other neoplastic systems, might be characterized as indicative of a malignancy (156). Mitoses are an acceptable feature of GCNST; they are not a marker for malignant transformation. GCNST infiltrates locally; it should be completely excised. Recurrences are common after incomplete excision.

Infiltration of skeletal muscle is a common feature of GCNST involving the squamous mucosae; in such areas, regenerating and degenerating muscle fibers are entrapped among fascicles of tumor cells. *Plexiform GCNST* is characterized by perineural extensions of tumor along the neural plexus of the dermis in the absence of a discrete mass (157).

Ultrastructurally, tumor cells are outlined by basal lamina (158,159). The preponderant cytoplasmic granules are largely phagolysosomes. They appear as membrane-bound vacuoles measuring 200 to 900 nm in diameter. Some of the larger cytoplasmic bodies have the appearance of residual bodies or myelin figures (154,158,159). The peripheral satellite cells of the fascicles are outlined by a discontinuous basal lamina (160). Interstitial cells of the tumor contain angulate bodies (25).

Histogenesis. The granular cell category is heterogeneous. Not all examples mark as nerve sheath tumors; some of the immunohistochemically divergent lesions are also cytologically atypical (161). The classic immunohistochemical profile is positive for S100 protein, peripheral nerve myelin proteins, such as P2 protein and PO protein (162), PGP 9.5 (163), NSE, and vimentin.

Differential Diagnosis. A *xanthoma* is excluded by the identification of cytoplasmic granules (rather than vacuoles). A fascicular arrangement of cells favors GCNST.

Angulated, elongated columns of bland squamous cells occasionally extend from the epidermis into GCNST among the fascicles of tumor cells (*pseudoepitheliomatous hyperplasia*). On biopsy specimens from tumoral lesions of the tongue, genitalia, or the mucous membranes of the upper respiratory tract, esophagus, or anus, such patterns should be interpreted with caution. If one is confronted with such patterns on a superficial biopsy specimen, a careful search for a component of granular cells might avoid a mistaken diagnosis of carcinoma and, in turn, needless aggressive surgery.

Tumor cells with cytoplasmic granular-cell qualities are occasionally a feature of *granular cell lesions of diverse lineage*, such as basal cell carcinoma (164) and dermatofibroma (165). The granules of rare granular squamous cell carcinomas, in contrast to those of other benign and malignant granular cell tumors, are PAS negative, and desmosomes are seen on electron microscopy (166). In the jawbones, a granular cell variant of ameloblastoma has been described. Granular cell change has been noted in smooth muscle tumors (167).

The *primitive polypoid granular cell tumor* (*dermal non-neural granular cell tumor*) presents as a painless nodule, mainly on the extremities or face (168). Lesions are both polypoid and endophytic. The tumor cells are immunoreactive for NKI-C3 and are negative for S100 protein, smooth muscle actin, Melan-A, CD34, desmin, and cytokeratin. The reported cases have behaved in a benign fashion (168).

Granular Cell Epulis of Infancy

Granular cell epulis of infancy is a polypoid tumor of the gingiva of the newborn, with a predilection for girls (169). It shares the basic histologic features of GCNST but is immunohistochemically distinctive. The immunohistochemical profile is NSE^{+}, vimentin^{+}, S100^{-}, GFAP^{-}, CD57^{-}, MBP^{-}, lysozyme^{-}, a1-ACT^{-}, and laminin^{-}. Interstitial cells are positive for S100 protein; they do not contain angulate bodies (170).

Malignant Granular Cell Tumor

Malignant granular cell tumor (MGCT) is uncommon. Most of the reported cases have occurred on the skin or in the subcutaneous tissue (171). As in benign GCNST, a few cases have been reported from other areas, such as the sciatic nerve (172) and the viscera. A variety of malignant tumors may masquerade in granular cell patterns. In all instances, an acceptance of the diagnosis MGCT is predicated on circumspection.

In the skin and subcutaneous tissue, MGCT, a rapidly growing, poorly defined nodule or mass, may reach considerable size and undergo ulceration (172). Extensive metastases to viscera, skin, and skeletal musculature occur, with or without

regional lymph node metastases (173). Some lesions, even in the absence of demonstrable metastases, have been characterized as MGCT (174).

Histopathology. There are two types of MGCT (175). In one type, in spite of the clinically malignant course, the histologic appearance of the primary lesion, and even of the metastases, is that of a benign GCNST, except for occasional mitotic figures and mild cellular pleomorphism with nuclei that are slightly larger than those seen in most benign GCNSTs (173,175,176). In the general category of GCNST, these cytologic features are too common to provide a reliable identification of lesions with the potential for metastasis. In evaluating the malignant potential of histologically benign or indeterminant granular cell tumors, clinical data, such as large size of the tumor, rapid growth, ulceration, and invasion into adjacent tissue, are of greater diagnostic value than the histologic features (177). The average diameter of "histologically benign, clinically malignant" granular cell tumors has been found to be 9 cm, as compared with 1.85 cm for the benign variety (175,177).

In the second type of MGCT, both the primary lesion and the metastases are histologically malignant; they show transitions from typical granular cells through pleomorphic granular cells to pleomorphic, nongranular spindle and giant cells with numerous mitotic figures (178,179).

In benign GCNST, immunohistochemical tests for S100 protein, NSE, and vimentin are regularly positive. In MGCT, the same tests often are negative.

Fibrolamellar Nerve Sheath Tumor

Fibrolamellar nerve sheath tumor (FNST) is a solitary tumor of the dermis (180). In a recently reported example, a 25-year-old man had a solitary rubbery nodule of the right cheek (181).

Histopathology. FNST is nonencapsulated but sharply defined in the dermis. Coarse, rigid, eosinophilic lamellae are arranged in parallel arrays in stacks of four or more. Neighboring stacks are random in orientation, one to the other, but in some areas the patterns that result from the abutment of neighboring stacks have storiform qualities. Some examples are mostly myxoid; in them, the fibrous lamellae are more delicate and widely spaced. Tumor cells, each with a small nucleus, scanty perikaryon, and rigid, thin, polar extensions of cytoplasm, resemble perineurial cells. They are isolated in clear or mucinous matrix among the fibrous lamellae. Rarely, a few loosely clustered, pigmented dendritic melanocytes have been a feature.

FNST is histologically distinctive but may be simply an exaggeration of perineurial-like patterns that are occasionally manifested in cutaneous neurofibromas.

FNST shares features with *sclerotic fibroma*, as manifested either sporadically or in the setting of *Cowden's disease*. A demonstration of immunoreactivity for S100 protein by some of the tumor cells strongly favors the diagnosis of FNST.

TUMORS OF PERINEURIAL CELLS ("PERINEURIOMAS")

Storiform Perineurial Cell Fibroma, Soft Tissue type

Storiform perineurial cell fibroma, soft tissue type (SPCF; *storiform perineurial fibroma*; *"soft tissue perineurioma"*) is a solitary, symmetrically expansile, and well-circumscribed tumor; it most commonly affects the subcutis (3,182–184), but the deep soft tissue and even viscera may be involved. The clinical features are not well established. The lesion is a fibroma whose component cells express the phenotype of perineurial cells. In the series reported by Hornick and Fletcher (185), there was a slight preponderance of females. A painless mass in the subcutis was the most common clinical presentation; for slightly more than one fourth of Hornick and Fletcher's cases, the deep soft tissue was affected. Most of their cases were well circumscribed; 12 cases microscopically showed focal, infiltrative margins; 14 cases were classified as atypical perineuriomas; only 2 tumors recurred locally; and there were no metastases. In recognizing an atypical variant of perineurioma, the possibility that some atypical examples might be precursors of MPNST of perineurial type mostly has been dismissed. MPNST of perineurial type has been set apart from atypical perineurioma; it is grouped in the general category of MPNST. The atypical forms are being promoted as benign lesions in which atypia is dismissed as "degenerative" ("ancient") change. In the series reported by Hornick and Fletcher (185), mitotic activity ranged from 1 to more than 5 mitoses per hpf. Among the atypical perineuriomas, mitoses ranged from 0 to 7 per 30 hpf. The conceptual approach to atypical, mitotically active perineuriomas is the same as the cavalier approach to atypical, mitotically active "cellular schwannoma."

Histopathology. SPCF is circumscribed. At its periphery, the interface with soft tissue is defined by a thin capsule consisting of several loosely spaced, delicate fibrous lamellae. Beneath the capsule, thin collagen fibers form a delicate, fibrous matrix. Cells with plump, angulated nuclei and rigid, polar, cytoplasmic extensions are loosely spaced (Fig. 35-51). Fascicles in storiform patterns are variably represented. In most examples, small nerves are embedded in, or may be traced into, the tumor. The tumor cells tend to form thin, concentric layers around entrapped small nerves, blood vessels, and collagen bundles. Small stacks of hyalinized (skeinoid?) fibrous lamellae, somewhat similar to those of fibrolamellar nerve sheath tumor, occasionally are a focal variation in such lesions (Fig. 35-51).

Histogenesis. The cytologic features are perineurial cell like. In some examples, tumor cells are immunoreactive for vimentin and EMA (183). The latter reaction may be weak or patchy; it is most likely to be best developed in cells in or near the capsule. In other examples, scattered aggregates of tumor cells in more central locations are reactive for S100 protein. Claudin-1, a tight-junction–associated protein, was recently reported as a common expression in membranous,

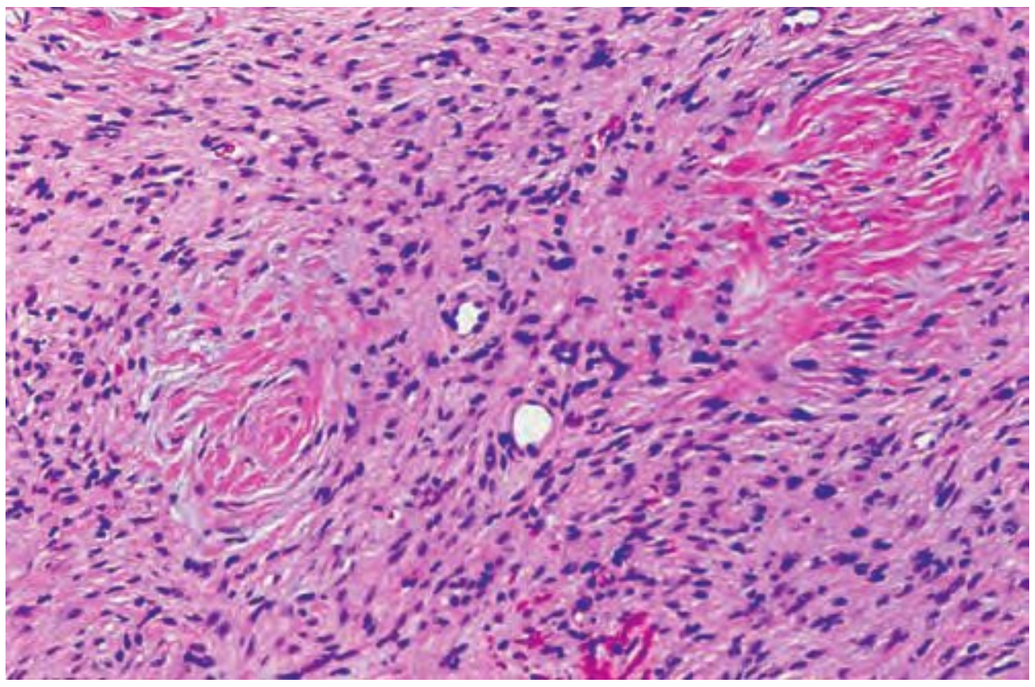


FIGURE 35-51. Storiform perineurial cell nerve sheath tumor (soft tissue "perineurioma"). Spindle cells are individually isolated in a delicate fibrous matrix. There are two collections of stacked, acidophilic fibrous lamellae.

granular patterns in perineuriomas (186). An abnormality of chromosome 22 was reported (187). One example of soft tissue perineurioma in a patient with neurofibromatosis type 2 was reported (188).

Differential Diagnosis. Storiform patterns appear to be variations that are expressed in a variety of nerve sheath tumors. Perhaps variants of both schwannomas and neurofibromas have been included in this category of "perineurioma." The evidence that SPCF is purely perineurial in character is unconvincing. For some problematic lesions, "cellular" schwannoma would be a diagnostic consideration.

Fibrous histiocytoma of the subcutaneous fat and dermatofibroma also are considerations in the differential diagnosis.

Dermatofibrosarcoma protuberans (DFSP), in its nodular, well-differentiated components, might be confused with SPCF. It has been variously classified as a fibroblastic, fibrohistiocytic, or neurocristic tumor. The pigmented variant of DFSP (*Bednar tumor*) has been characterized as pigmented storiform neurofibroma. The nature of pigmented dermatofibrosarcoma is controversial but, in one study, perineurial cell–like qualities were observed (189). The cells of DFSP, like some cells of nerve sheath tumors, are immunoreactive for CD34 (190). DFSP is described in detail elsewhere (Chapter 32).

Acral Perineuriomas

Pacinian Neurofibroma

The designation *pacinian neurofibroma* has been assigned to a variety of lesions. The nature of this lesion has not been carefully examined by immunohistochemical studies (191,192).

Intraneurial Perineurioma

Intraneurial perineurioma (*intraneural, symmetrically concentric perineurial cell tumor; hypertrophic interstitial neuritis; hypertrophic mononeuropathy; ISCPCT*) is an intraneural, solitary, segmental and cylindrical enlargement of a nerve (193–195). Sensorimotor defects are characteristic.

Histopathology. In the characterization of this lesion, distinctions are required between onion bulbs and pseudo–onion bulbs. Pseudo–onion bulbs are composed of cells that are immunoreactive for EMA. If the cells of a concentrically arranged cluster are Schwann cells ($S100^+$), the collection qualifies as an onion bulb pattern; if the concentrically arranged cells are mostly perineurial cells (EMA^+), the collection qualifies as a pseudo–onion bulb pattern. In ISCPCT, cells with both the structural qualities and the immunoreactivity of perineurial cells form concentric sheaths (pseudo–onion bulbs) around affected nerve fibers (Fig. 35-52) and even around small clusters of pseudo–onion bulbs (193). Collagen bundles and vessels may be similarly embraced. A specific and concentric orientation of cells about axons is a symmetric quality. Demyelination and degeneration of axons are associated phenomena; in the center of the clusters, axons may appear enlarged and irregular in outline.

Histogenesis. In ISCPCT, the concentrically arranged cells immunoreact with antibodies for EMA (193). They have the ultrastructural features of perineurial cells.

A defect in the integrity of the perineurial barrier has been proposed as the primary alteration. Delamination of the perineurium and migration of perineurial cells into the endoneurium have been offered as an explanation for the origin of pseudo–onion bulbs (194).

ISCPCT is intraneural; the concentric ensheathing of nerve fibers is a symmetric quality; the ensheathing cells have perineurial cell–like qualities.

In common with descriptions of the clonal chromosomal abnormalities in benign and malignant schwannomas, neurofibromas, meningiomas, and gliomas, monosomy of 22q and deletion of 22q11.2-qter have been described in PSCPCT (193); deletion of 22q11 is cited as a finding favoring neoplasia (193).

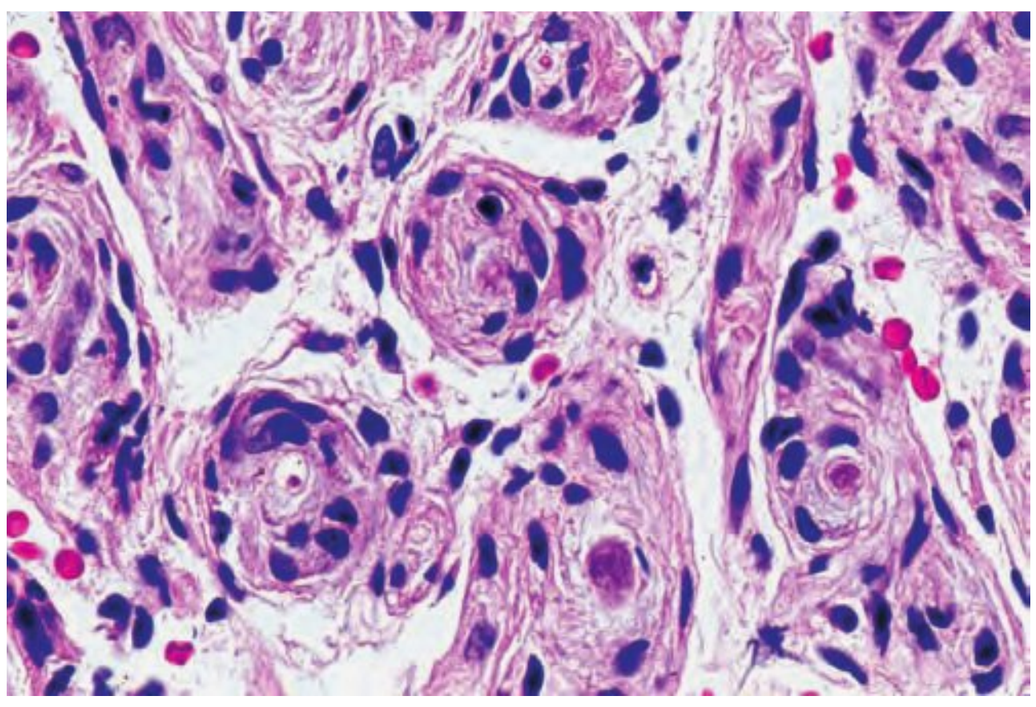


FIGURE 35-52. Perineurioma, intraneural variant. Axons are surrounded by concentric layers of spindle cells; the spindle cells are layered in onionskin patterns. The lesion is intraneural; axial symmetry is preserved.

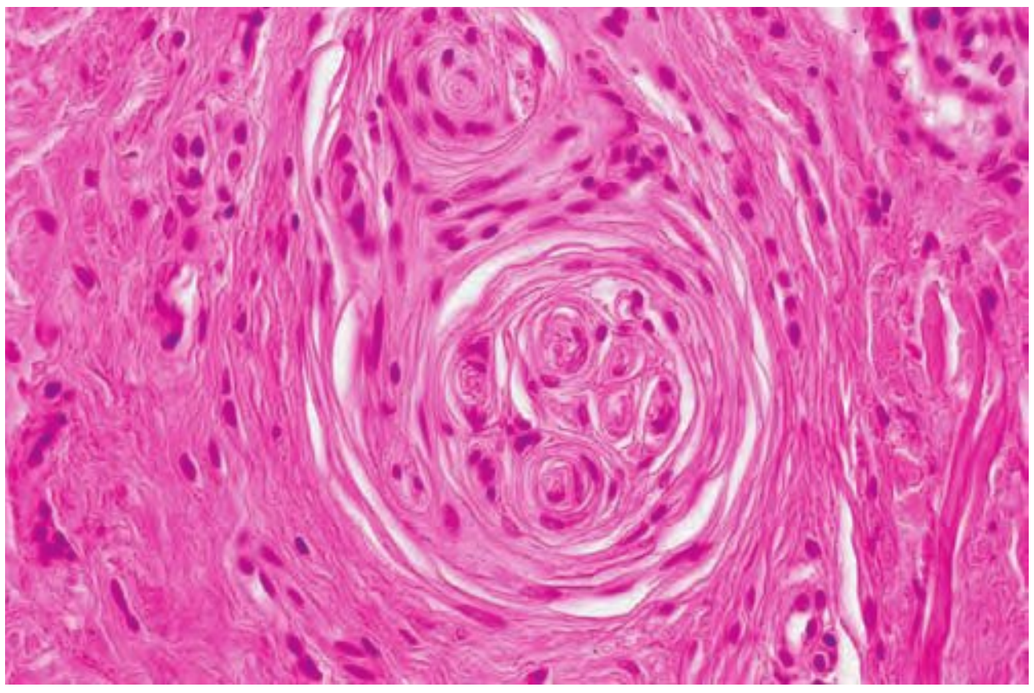


FIGURE 35-53. Hypertrophic neuropathy. In the center of the field, a small nerve is cut in cross section. The perineurium is thickened. Spindle cells are arranged concentrically about nerve fibers (onionskin pattern). Some of the spindle cells blend with the thickened perineurium.

Differential Diagnosis. The *hereditary degenerative neuropathies* are not localized and segmental (196). In addition, they are characterized by concentric hyperplasia of Schwann cells (onion bulbs) (Fig. 35-53).

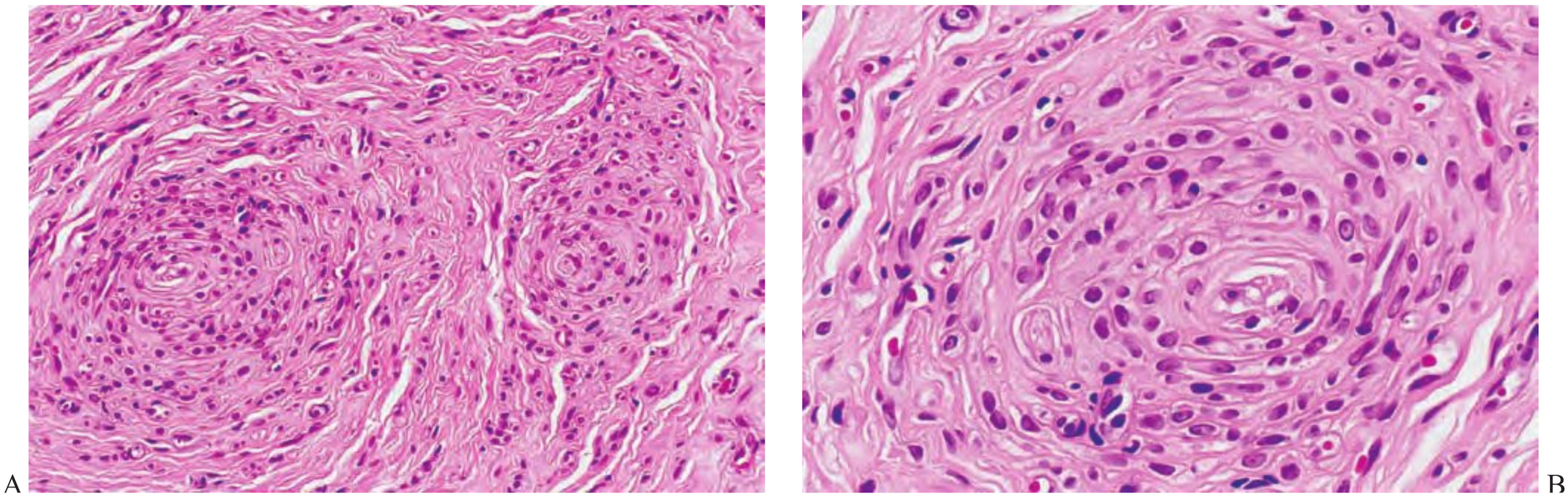
Pacinian Perineurial Cell Fibroma, Acral Type [Subcutaneous (Sclerosing) or Dermal (Fibrous) Perineurioma, PPCF]

An uncommon, small, benign tumor found mainly on the hands has been characterized as either *fibrous (dermal) perineurioma* (197) or *sclerosing (subcutaneous) perineurioma* (198,199). It should be noted that most, if not all, of the lesions in this category could, in the past, have been easily accommodated in the category of *pacinian neurofibroma*. The pacinian features should be given recognition in the designation; *pacinian perineurial cell fibroma* is a more appropriate designation. The categories of fibrous perineurioma and sclerosing perineurioma express the penchant of some observers for new designations; it additionally expresses a currently popular penchant to group dissimilar lesions in the category of perineurioma.

These small tumors are basically fibrous lesions with focal areas of increased cellularity; they are fibromas whose component cells express the phenotype of perineurial cells. They are additionally distinguished by distribution; they mostly are acral in location. They tend to be oval in outline, with the long axis perpendicular to the surface of the skin. The lesions reported by Skelton et al. had a configuration at low magnification that resembled that of a cutaneous neurofibroma (197). Some of the lesions have ill-defined margins; some are circumscribed, particularly along the deep margin, with cellularity being greatest in the area of circumscription. The cells are spindle shaped or ovoid; they have round nuclei with uniformly distributed chromatin; they have pale or clear cytoplasm. Some of the cells appear to be outlined by a delicate membrane (reticulum?). In areas, the cells form thin, interconnected ribbons (retiform patterns). In some examples, small spindle and round cells form whorls in patterns strongly suggestive of the arrangement of cells in a pacinian corpuscle (199).

An additional variant of "perineurioma," *retiform (reticular) perineurioma* (200), is a soft tissue lesion sharing some of the features of the subcutaneous or dermal variants. It should be obvious that the category of "perineurioma" has been compromised by this willingness to be extravagant in the application of the designation (Fig. 35-54A, B).

The cells are immunoreactive for EMA; claudin-1 has also been identified as a marker for perineurial cells and perineuriomas (186). Some of the tumor cells are immunoreactive for



A B

FIGURE 35-54. Sclerosing perineurial cell nerve sheath tumor (fibrous or sclerosing "perineurioma"). A: In two foci, bland, small cells with pale cytoplasm are arranged in whorls among delicate collagen fibers; the cells are round or slightly spindle shaped; some appear to be isolated by basement membranes. The bland cytologic features are reminiscent of glomus cells. The concentric whorls are reminiscent of cellular arrangements in pacinian corpuscles. In the background, the lesion is sclerotic with small spindle cells among collagen bundles. B: At higher magnification, the cells form whorls about a central nidus. The cytologic features are more epithelioid than perineurial.

muscle-specific actin and CD 99. The tumor cells show ultrastructural features of perineurial cells.

The differential diagnosis includes glomus tumor. In the past, before the era of immunohistochemistry, some lesions of this type must have been characterized as some type of pacinian neurofibroma. PPCF, in certain aspects, such as concentric symmetry about nerve fibers, shares important features with intraneural perineurioma.

NEUROMAS

Neuromas are hyperplasias of axons and associated nerve sheath cells. In most but not all cutaneous neuromas, Schwann cells and axons are arranged in interlacing (tortuous) fascicles. Axons are easily demonstrated with silver impregnation techniques. They are also easily demonstrated with monoclonal antibodies, such as those for neurofilaments, but neither silver impregnation stains nor immunoreactions in themselves distinguish between the innervated fascicles of a neuroma and those of cutaneous neurofibroma.

Neuromas can be divided into four types: extraneural (traumatic or acquired) neuromas; intraneural (isolated and spontaneous, solitary or multiple) neuromas; intraneural (multiple mucosal) neuromas, including those occurring in multiple endocrine neoplasia, type 2b; and abnormalities of sensory receptors.

Extraneural Neuromas

Acquired (Traumatic) Neuroma

Traumatic neuromas are usually solitary, firm papules or nodules at the sites of scars after local trauma (Fig. 35-55A); if they extend to the skin surface, they are skin colored or pink. In mature neuromas, a lancinating type of pain might be elicited in response to local pressure.

Histopathology. Interlacing fascicles of regenerating nerve fibers extend from the proximal end of a damaged nerve; they extend through an acquired defect in the perineurium and then into the neighboring mesenchyme. They insinuate in asymmetric patterns among collagen bundles (Fig. 35-55B). With maturation, perineuria form around each of the extraneural fascicles. Tangled fascicles in a scar form the tumor. The distal end of a severed nerve does not contribute significantly to the neuroma. In pretumorous stages, nerve fibers of both the proximal and distal segments of the disrupted nerve show wallerian degeneration (Fig. 35-2).

Rudimentary Supernumerary Digits

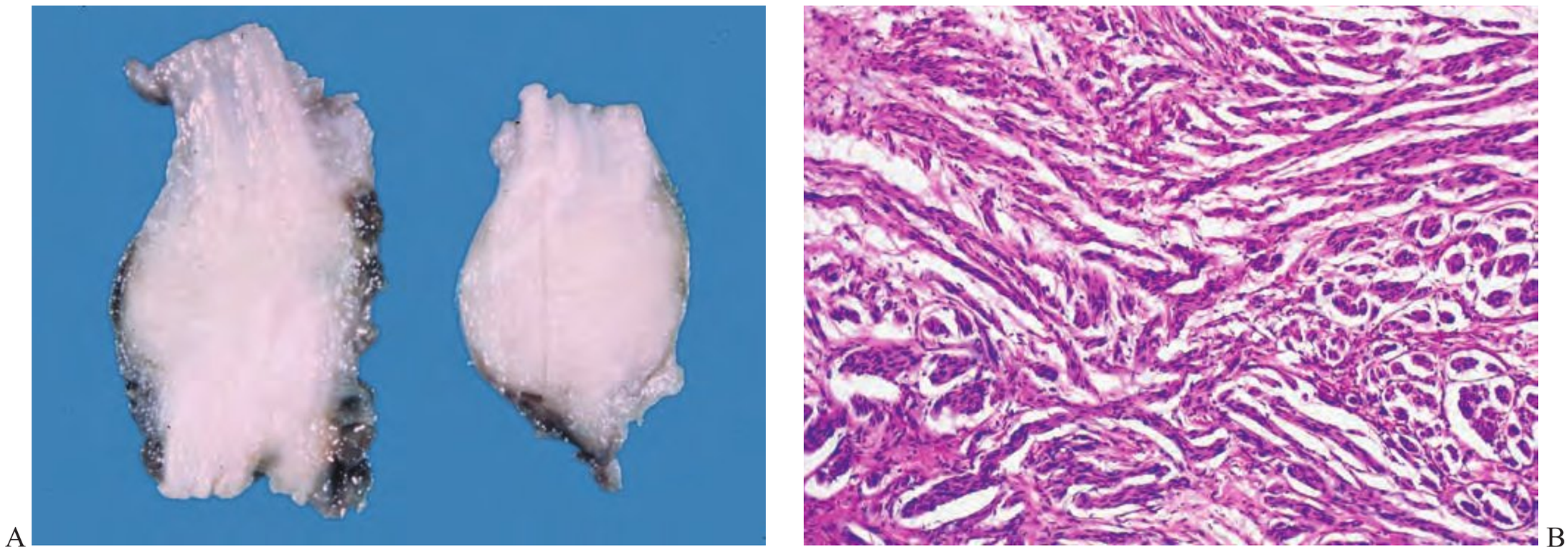
These usually are asymptomatic, smooth or verrucous papules. Like supernumerary digits, they usually occur at the base of the ulnar side of the fifth finger. They are assumed to represent the residua of either autoamputation *in utero* or postnatal destruction of a supernumerary digit (201).

Histopathology. Much of what comprises a rudimentary digit shows the histologic pattern of an acquired neuroma. Some of the nerve fibers of the neuroma, among those that are located close to the epidermis, terminate in closely spaced Meissner corpuscles (201).

Intraneural Neuromas

Palisaded and Encapsulated (Sporadic and Spontaneous) Neuroma

Palisaded and encapsulated (sporadic and spontaneous) neuroma (PEN) is a firm, rubbery, skin-colored or pink papule or nodule (202–205). It commonly affects the "butterfly area" of



A B

FIGURE 35-55. Extraneural (traumatic neuroma). A: This neuroma has been bisected along the long axis of the specimen. The neuroma is centrally placed; the cut surface in the region of the neuroma is homogeneous and white. Proximal and distal portions of the involved nerve are attached to the tumor. B: Fascicles of Schwann cells are arranged haphazardly in a fibrous matrix. A thin perineurium has formed at the periphery of some of the fascicles; the thin perineuria are separated from the respective Schwann cell fascicles by a clear space.

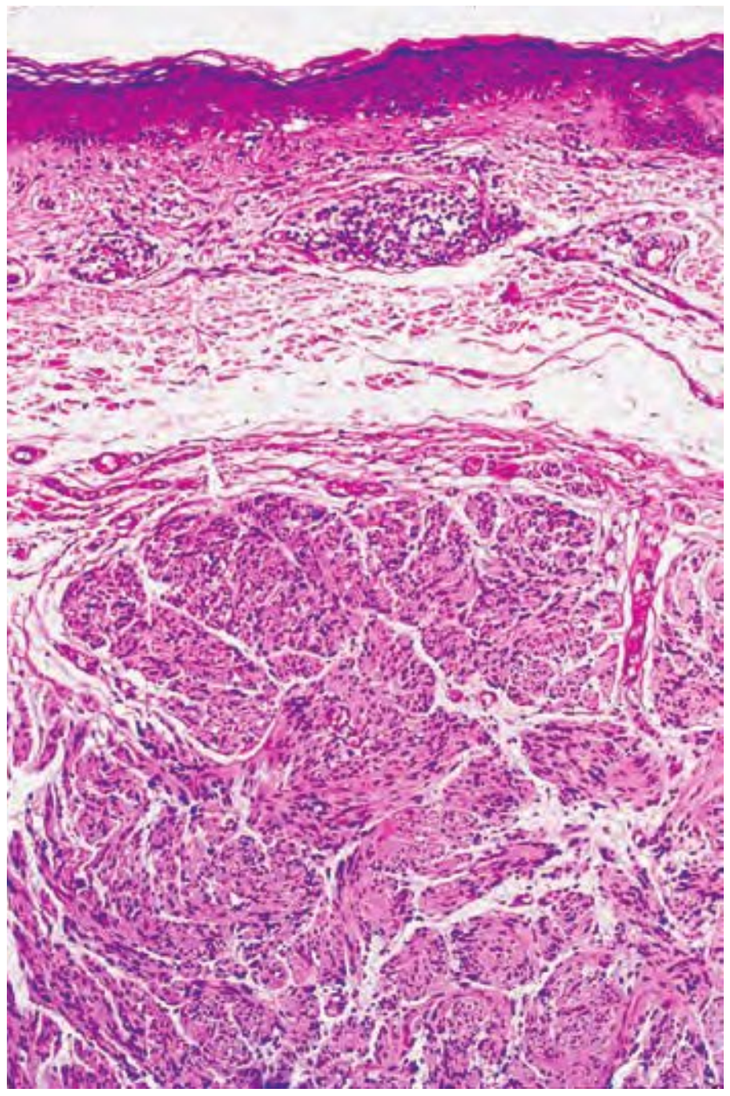


FIGURE 35-56. Palisaded and encapsulated (intraneural) neuroma. The lesion is encapsulated. Fascicles of Schwann cells are arranged in interlacing patterns; the fascicles are supported by a scanty clear or myxoid matrix. Focally, within some of the fascicles, the nuclei of the Schwann cells form ill-defined palisades.

the face. Solitary examples may arise in either early childhood or adulthood (mean age, 45.5 years). In adulthood, sporadic neuromas can be multiple. Both solitary and multiple cutaneous intraneural neuromas usually are asymptomatic. In neither presentation are the lesions associated with the stigmata of MEN. During biopsy, a lesion of PEN often is enucleated from its dermal bed and then submitted to the pathologist with little, if any, surrounding skin.

Histopathology. PEN is a bulbous expansion of a peripheral nerve, appearing as a well-circumscribed, ovoid or rounded nodule in the dermis (Fig. 35-56). Intraneurally, Schwann cells form uniform, broad (often consisting of as many as four or five cell layers), interlacing fascicles that are spaced in a clear or mucinous matrix (Fig. 35-57). Nuclear palisades are ill defined. Nuclear pleomorphism and mitoses are not features. PEN is confined by a thin, expanded perineurial sheath. In many examples, the sheath is attenuated along the surface that approximates the epidermis. This variation might be a consequence of the anatomy of a nerve; the perineurial sheath is open ended in this site. At some site along the periphery, it is usually possible to identify, as in-continuity extensions, tumor within the endoneurial space of small neighboring nerves.

The fascicles, with silver stains (Fig. 35-58) (204) and with immunoreactions for both neuron-specific enolase (Fig. 35-59) and neural filaments, are rich in axons. (205). A weak,

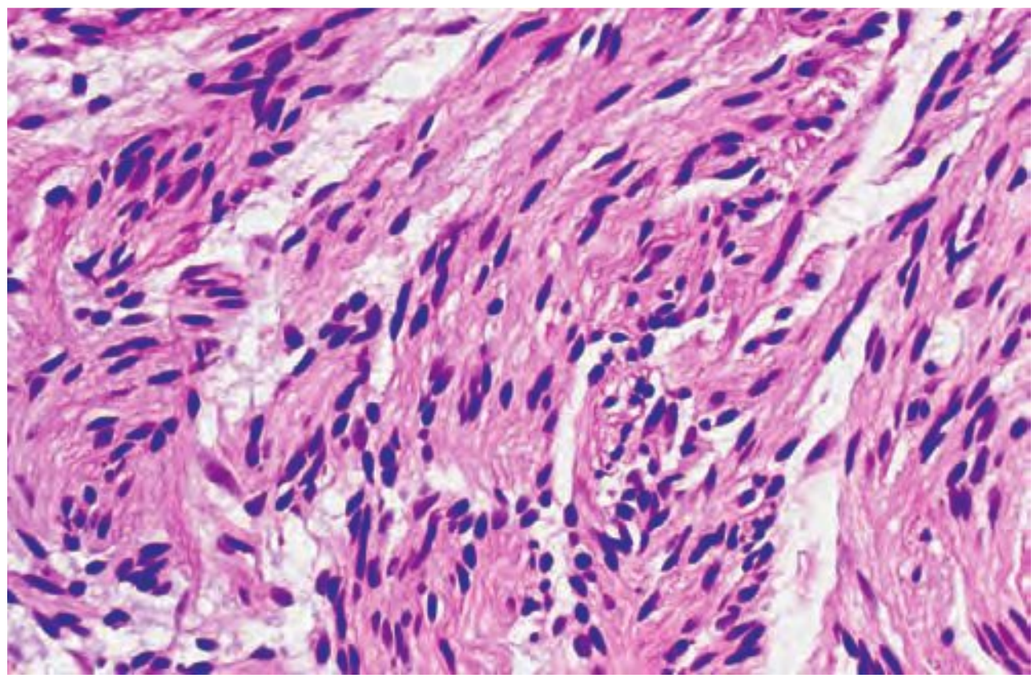


FIGURE 35-57. Palisaded and encapsulated (intraneural) neuroma. The Schwann cells form broad fascicles, which are loosely spaced in a myxoid matrix. There are scattered nuclear palisades. In cross section, the small vacuoles in the cytoplasm of some of the cells are of the type that is produced by nonmyelinated axons. Myelinated fibers also are commonly found in the fascicles.

sometimes discontinuous, reaction for EMA is a feature in the capsule of PEN (205). The presence of axons sets PEN apart from schwannoma, including all the variants. In PEN, axon representation in the fascicles is variable from lesion to lesion (204). Axon density, as evaluated by an immunoreaction to peripherin, may not be comparable to the relative density of axons with a Bodian stain (206).

Intraneural Plexiform Neuroma

Plexiform neuroma is an uncommon intraneural tumor of the dermis and subcutis. It has been characterized as a variant of PEN (33), but some examples might represent incipient plexiform schwannoma.

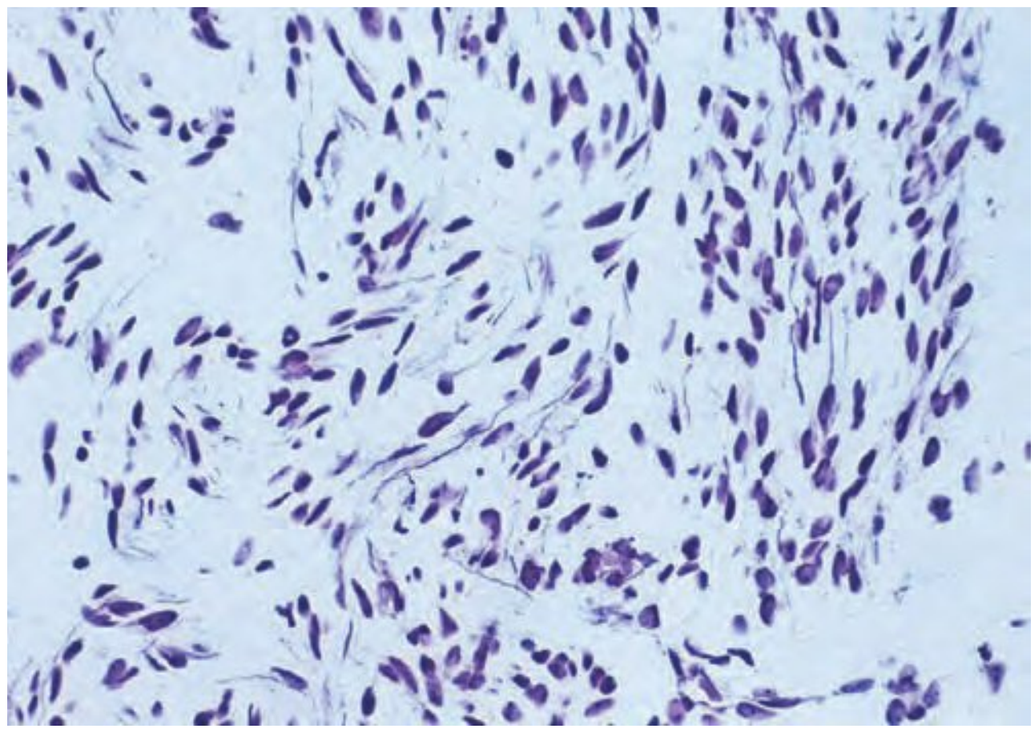


FIGURE 35-58. Palisaded and encapsulated (intraneural) neuroma (Bodian silver stain). The lesion is axon rich.

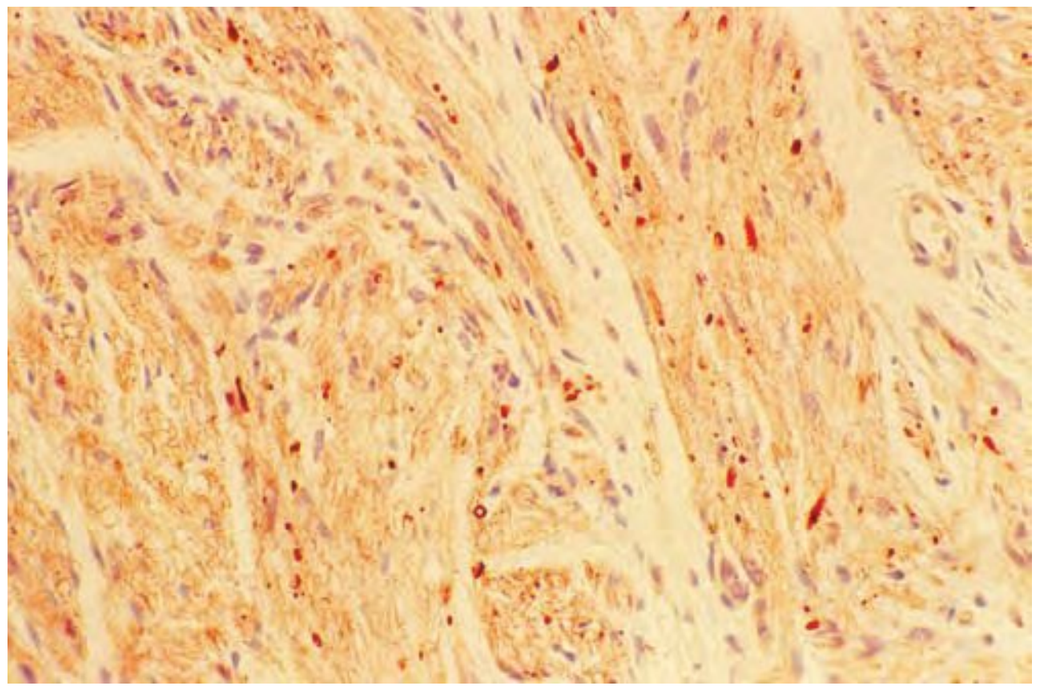


FIGURE 35-59. Palisaded and encapsulated (intraneural) neuroma (immunohistochemical reaction for neuron-specific enolase). With a reaction for neuron-specific enolase, axons are represented in large part as puncta.

Histopathology. Nodules and broad cords are circumscribed by the perineurium of the involved segment of nerve. The internal patterns of all the nodules and broad cords are basically those of PEN.

Clustered, dilated vessels with sclerotic walls and subendothelial collections of foam cells are features in common with schwannoma.

In contrast to fully developed plexiform schwannoma, plexiform neuroma, with both silver stains and immunoreactions for neural filaments, is rich in axons.

Mucosal Neuroma Syndrome

Multiple endocrine neoplasia, type 2b, first described in 1968 (34), is the only one of three types (i.e., types 1, 2, and 2b) to show mucosal and cutaneous neuromas (*mucosal neuroma syndrome* [MNS]). *Multiple* (*intraneural*) *neuromas*, many of which are periorificial, are often its earliest manifestation. First appearing in early childhood, they are seen as small nodules, often in large numbers, on the mucosa of the lips, tongue, oral cavity (207,208), the conjunctiva, and the sclera. Some patients show small, nodular neuromas, usually only in small numbers, on the skin of the face (208). Lesions occasionally are represented in large numbers on and about the nose and on the eyelids. Quite frequently, the lips are thick, fleshy, and protruding (209). Marfanoid features and skeletal abnormalities may be present (209).

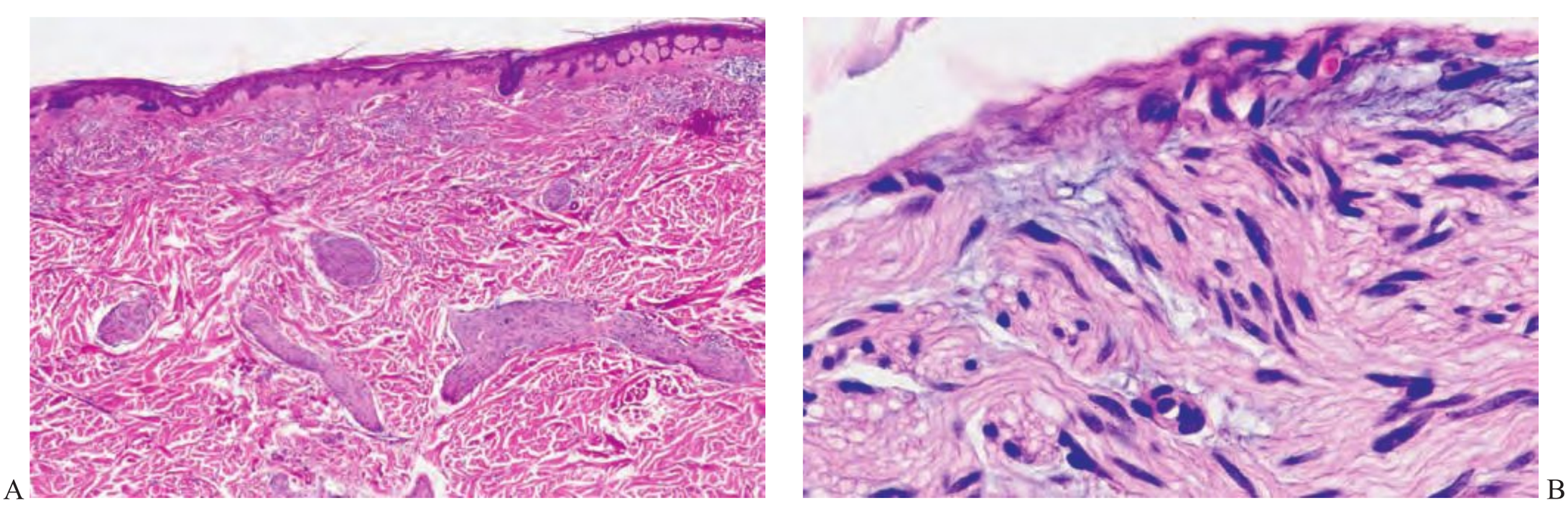
MEN, type 2b, may be inherited as an autosomal dominant trait (209). *Medullary thyroid carcinoma*, *bilateral pheochromocytoma* (208), and *diffuse alimentary tract ganglioneuromatosis* are associated disorders of variable frequency (210).

Histopathology. The neuromas of MNS are intraneural and plexiform. Characteristically, the involved nerves are slender. Many are uniform in diameter, but bulbous expansions also are a feature. Within the confines of the perineurium, fascicles that are fairly uniform in diameter and composed of two or more nerve fibers are interlaced in asymmetric patterns; they are closely spaced back to back in a clear or mucinous (endoneurial) matrix. The fascicles of nerve fibers in the mucosal and cutaneous lesions are richly innervated.

Multiple mucocutaneous neuromas may be encountered in the absence of other stigmata of MEN (211,212).

Linear cutaneous neuroma (*dermatoneurie en strie*), a sporadic variant of an intraneural neuroma, is manifested clinically as a group of raised linearities (213,214). It differs from the mucosal neuroma syndrome in clinical presentation and in the size of the altered nerves in the dermis. It has been proposed that linear cutaneous neuromas are a manifestation of MEN, type 2b (213).

Histologically, nerves of the dermis and subcutis are slightly enlarged and hypercellular (Fig. 35-60A, B). Internally, Schwann cells are increased in number, and nerve fibers are



A B

FIGURE 35-60. Linear (intraneural) neuroma (hyperneury). A: Nerves of the dermis are enlarged; they show Schwann cell hyperplasia; the cross-sectional diameter is increased. B: At higher magnification, interlacing fascicles of innervated Schwann cells form asymmetric patterns; they are confined by a perineurium.

tortuous. This combination of features results in loss of axial symmetry in the affected segments (Fig. 35-60B).

Ensheathed neuroma is a dermal microscopic lesion. Hypercellular nerves of the dermis are ensheathed by benign squamous epithelium (215). This type of reaction occasionally is encountered in the site of a recent biopsy.

Special Stains (Applicable to All Neuromas). With Luxol-fast blue stain, some of the fibers in all forms of neuroma may be myelinated.

Electron Microscopy (Applicable to All Neuromas). Ultrastructurally, fascicles that are composed of both myelinated and nonmyelinated nerve fibers are the chief feature of both extraneural (214) and intraneural neuromas. Those of a mature, extraneural neuroma are ensheathed by multiple lamina of perineurial cells (216). Generally, perineurial cells do not outline the individual, asymmetric fascicles of intraneural neuromas.

Histogenesis (Applicable to All Neuromas). The immunohistochemical profile is positive for S100 protein, collagen type IV, vimentin, and NSE and neural filaments.

In mature traumatic neuroma, the majority of the individual nerve fascicles are surrounded by cells that are immunoreactive for EMA, indicating perineurial differentiation (203). Collagens type I and III are deposited among the fascicles. The nerve fibers of the newly formed fascicles are supported by a matrix that is rich in acid mucopolysaccharides (203).

In spontaneous intraneural neuromas, such as PEN and those of the mucosal neuroma syndrome, the local proliferation of axons within the confines of the perineurium has not been adequately explained.

Pacinian Neuroma

Pacinian neuroma is an occult, painful lesion (217). It is found in the same anatomic sites as pacinian corpuscles (217).

Histopathology. Pacinian corpuscles form a localized cluster but are otherwise unremarkable. The corpuscles may vary in size.

If a cluster of corpuscles is continuous with an extraneural neuroma, it would be difficult to attribute the symptomatology to the cluster of corpuscles.

Patterns in which cells and fibers are concentrically layered are common in the setting of nerve sheath tumors. Some examples of nerve sheath tumors with such patterns have been characterized as "pacinian neurofibroma." Some of these lesions are being characterized as "fibrous" or "sclerosing" perineurioma (197,198).

SMALL BLUE ROUND CELL TUMORS

This category includes *primary, cutaneous, small-cell undifferentiated carcinoma* (*Merkel cell tumor*); *primitive neuroectodermal tumors* (PNETs), such as *Ewing's sarcoma* and *neuroepithelioma*; *neuroblastoma*; *primitive mesenchymal tumors*, such as *small-cell osteosarcoma* and *embryonal* and *alveolar rhabdomyosarcoma*; rare *melanomas of infancy* that arise in the setting of *giant congenital nevus* (*melanoblastoma of infancy*) (218); and *melanotic neuroectodermal tumor of infancy* (219). On hematoxylin-eosin–stained sections, the tumor cells of all these lesions have few distinguishing characteristics, other than scanty cytoplasm and closely spaced, "dark" nuclei. The primitive patterns provide a challenge in differential diagnosis; lesions with these characteristics have been grouped as "primitive neuroectodermal tumors." In this category, some of the lesions share certain basic features, but mostly they are distinguished by patterns of divergent differentiation as manifested morphologically or as demonstrated immunohistochemically (220). Small blue round cell tumors are more common in soft tissue or bone (221,222). In the skin, cutaneous small (Merkel) cell undifferentiated carcinoma is most frequent.

Cutaneous Small (Merkel) Cell Undifferentiated Carcinoma

Cutaneous small-cell undifferentiated carcinoma (*CSCUC*; *Merkel cell*, *neuroendocrine*, or *trabecular carcinoma*) (223–231) is an uncommon tumor. It mostly occurs as a solitary nodule, usually on the head or on the extremities (229). Multiple lesions have been observed, either localized to one area or widely distributed. The tumors are usually few in number but occasionally are multitudinous. CSCUCs have a high rate of recurrence and metastasis (230).

The lesions of CSCUC are firm and red-pink. They usually are nonulcerated and range in size from 0.8 to 4.0 cm in diameter.

Histopathology. Tumor cells with scanty cytoplasm and round or irregular nuclei are closely spaced in trabecular patterns and sheets (Figs. 35-61 and 35-62) (231,232); less commonly, they are arranged in ribbons and festoons. Pseudorosettes are an

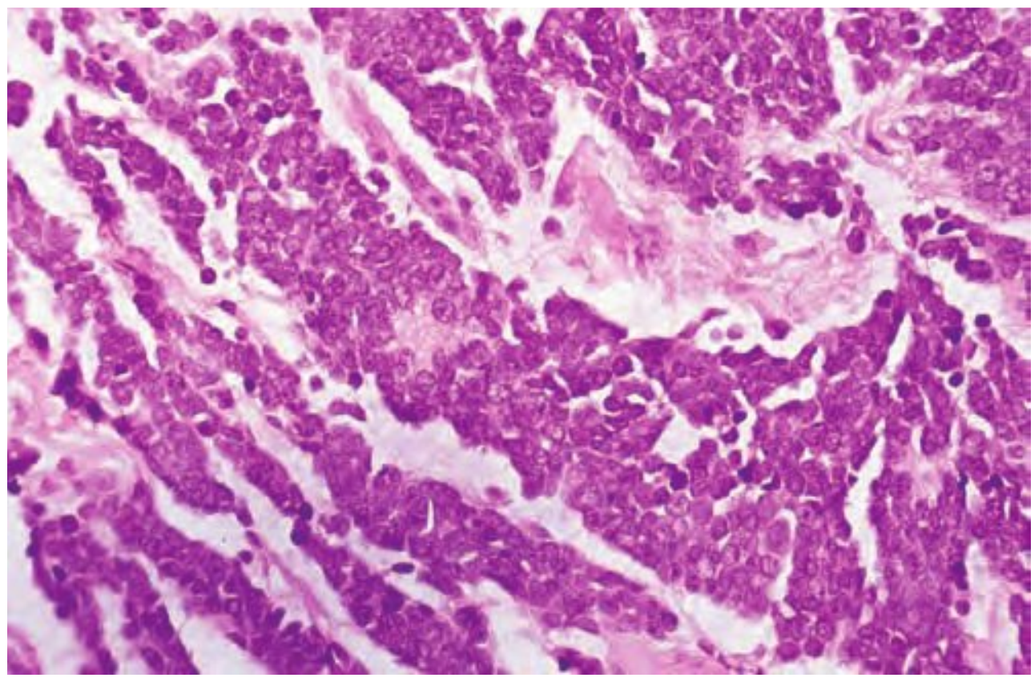


FIGURE 35-61. Merkel cell tumor. Atypical but uniform small blue cells form fascicles that vary in size. The cells have scanty cytoplasm; nuclei are crowded. Chromatin is delicate but uniformly distributed. Nucleoli are inconspicuous. There are scattered pyknotic nuclei. Each fascicle is outlined by a mucinous sheath that abuts on a fibrous matrix.

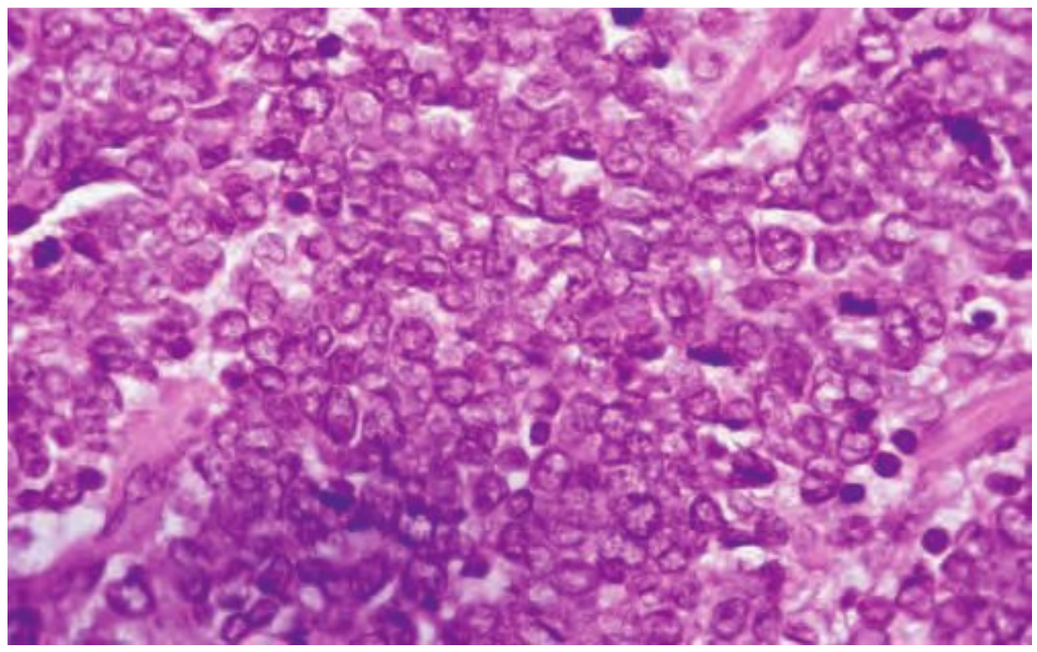


FIGURE 35-62. Merkel cell tumor. In this field, there is some central clearing of nuclear chromatin. The nuclei contain one or several nucleoli. There are scattered mitotic figures.

occasional feature (233). Nuclear chromatin often is dense and uniformly distributed. In some examples, nuclei, focally or uniformly, show margination of chromatin. Nucleoli generally are inconspicuous. Nuclear molding may be a feature. Mitoses and nuclear fragments are regular features (223). For some CSCUC, the nests of cells are supported by scant, delicate, and paucicellular stroma. Lymphoid infiltrates are common at the margin and focally in the stroma. Contact with the epidermis is rare, but if a lesion invades the epidermis, the patterns may include intraepidermal collections of tumor cells (234,235). Patterns of keratinocytic dysplasia in the overlying epidermis and even islands of squamous cell differentiation in the dermal nests are uncommon features (226,229,236). At the interface between the tumor and the epidermis and at the margins of the tumor, dilated, thin-walled vessels commonly contain tumor cells.

The immunohistochemical profile is positive for NSE (238), protein gene product, chromogranins, Ber-EP4 (237), and CD57 (239). A single punctate zone of cytoplasmic immunoreactivity for cytokeratins, especially CK20, or neurofilaments is most characteristic (240). EMA is expressed in 75% to 80% of CSCUC (241). A reaction for CK20 has been offered as a finding against the diagnosis of metastatic small-cell carcinoma of the lung (241). Thyroid transcription factor-1 (TTF-1) is specific for pulmonary small-cell undifferentiated carcinoma of the lung (PSCUC) in situations in which the differential diagnosis includes PSCUC and CSCUC (242).

Ultrastructurally, cytoplasmic, membrane-bound, round, dense-core granules of neuroendocrine type measure 100 to 200 nm in diameter (225,233). Perinuclear bundles or whorls of intermediate filaments that are 7 to 10 nm wide (243) and small desmosomes are regularly present. Tonofilaments attached to the desmosomes have been only found in a few cases (244).

Histogenesis. The origin of the CSCUC is controversial. Divergent differentiation is expressed in neuroendocrine, squamous, adnexal (241,245), and melanocytic phenotypes (246).

CSCUC shares genetic changes with tumors of neural crest origin, such as melanoma, pheochromocytoma, and neuroblastoma (247).

Differential Diagnosis. Cutaneous metastases from atypical carcinoids or small-cell undifferentiated carcinoma (oat cell carcinoma) of the lung may be confused with primary CSCUC (248).

The nuclear characteristics of the cells of CSCUC differ from those of the cells of most lymphomas. Immunohistochemical studies are an aid in the differential diagnosis. If lymphoma remains a problem, even in the face of a negative reaction for leukocyte common antigen, reactions for the antigens L-26 and CD3 may provide more definitive information (249).

Primary small-cell undifferentiated carcinomas have been observed in most organ systems. They are not peculiar to the skin, but those in the skin often have distinguishing characteristics. Small-cell undifferentiated carcinomas of both the skin and lung are neuroendocrine carcinomas, but the former designation (i.e., small-cell undifferentiated carcinoma) has a greater degree of specificity; it gives recognition to basic patterns that are expressed in distinctive primary neoplasms in a variety of organ systems. The nuclei of PSCUC are irregular; they often have a pointed extremity. Patterns of squamous cell and glandular differentiation are variable features of PSCUC. Clinicopathologic correlations are an aid in the differential diagnosis.

The primary basaloid carcinomas and undifferentiated carcinomas of the skin appendages, including lymphoepithelial variants, also must be considered in the differential diagnosis (250).

Tumors that are histologically similar to CSCUC have been observed as isolated lesions in lymph nodes (251).

Peripheral Neuroblastoma

Neuroblastoma, as a primary soft tissue tumor, is a diagnosis of exclusion. The skin is a most unlikely site. In infancy, the differential diagnosis of undifferentiated, small-cell malignancies of the skin and soft tissue includes metastatic neuroblastoma. A thorough workup to rule out a metastasis from an occult site, such as the adrenal gland or paravertebral ganglia, is required. The clinical features of metastatic neuroblastoma in infancy include the patterns of blueberry muffin baby (252) and blanching subcutaneous nodules (253). Adult neuroblastomas have been documented (254,255).

Histopathology. Neuroblastomas are undifferentiated, small-cell malignancies. Solid sheets of undifferentiated cells often are the preponderant patterns, but septation, neuropil, differentiation as manifested by variation in cytologic features, and Homer Wright rosettes (often characterized as pseudorosettes), if identified, are an aid in diagnosis. Neuroblasts are distinguished by the formation of cell processes. The designation *neuropil* gives recognition to a matrix of cytoplasmic processes, including those of neurons, Schwann cells, and glial cells. It

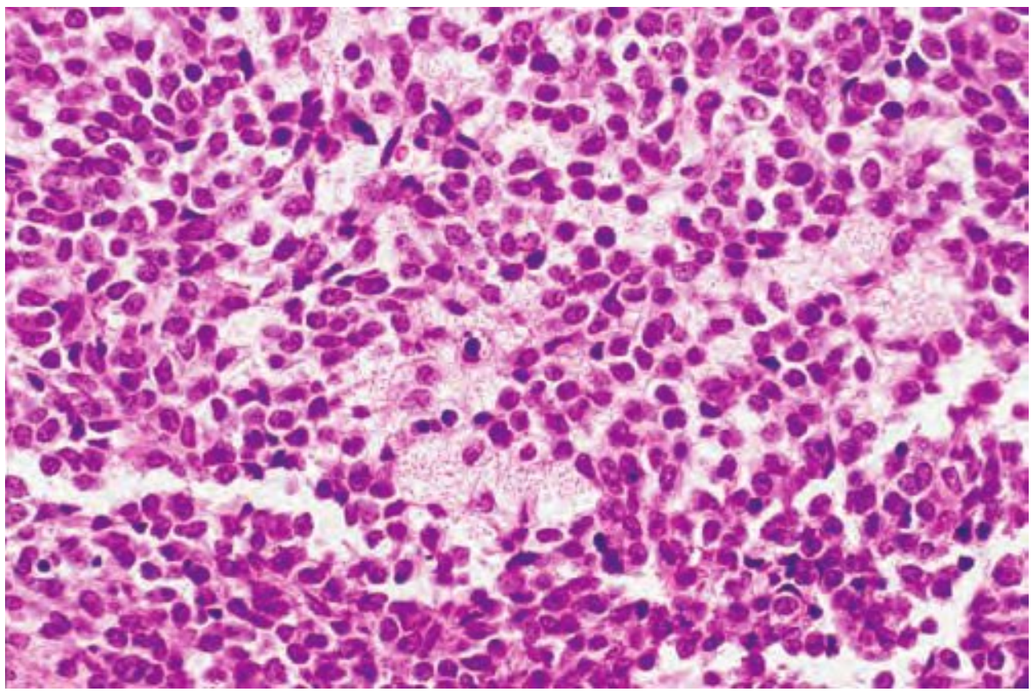


FIGURE 35-63. Differentiating neuroblastoma. Uniform, atypical small blue cells form sheets. In areas, the diffuse patterns are interrupted by pale, rounded collections of delicate fibrils (neuropil).

gives recognition to patterns of "matrical" differentiation in neuroectodermal tumors (Fig. 35-63). Larger cells with slightly eccentric, round nuclei, prominent central nucleoli, and marginated chromatin provide evidence of neuronal differentiation (Fig. 35-64); such cells, when identified, usually are sprinkled about among the more primitive cells.

Depending on the degree of differentiation, the immunohistochemical profile is positive for neural filaments, NSE, S100 protein, and synaptophysin. Other neuroendocrine markers may be positive (256).

Metastatic neuroblastoma possesses an innate tendency for maturation (differentiation). As a consequence, metastases from a neuroblastoma may present as immature or mature ganglioneuroma (257). Problems are complicated by the rare case in which a primary neuroblastoma of the adrenal gland, with distant metastases, undergoes complete regression in the primary site.

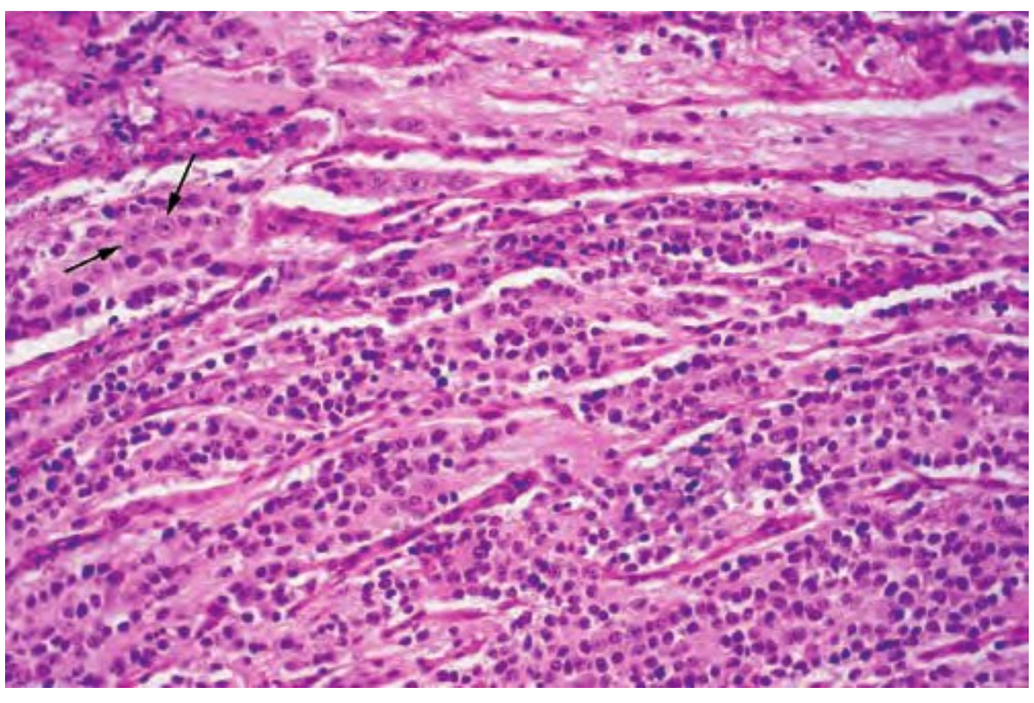


FIGURE 35-64. Differentiating neuroblastoma. The lesion is partitioned by delicate fibrous septa. Tumor cells are clustered among the septa; the hypocellular, fibrillated matrix among the cells is neuropil. Scattered cells have plump, round nuclei with a central nucleolus (arrow); these distinctive cells are differentiating ganglion cells.

Ganglioneuroma

Ganglioneuroma is exceedingly uncommon in the skin (258–260). Rare examples appear to be in the nature of heterotopias (260). Other examples may represent divergent differentiation of phenotypically pluripotent neurocristic cells. Still others may represent metastatic neuroblastoma that has matured into a ganglioneuroma.

Histopathology. The basic pattern of a ganglioneuroma is that of a neuroma in which characteristic ganglion cells are either clustered or individually isolated (260). Small, primary ganglioneuromas of the skin may be characterized by numerous, mature ganglion cells and an inconspicuous background of neurosustentacular cells (261). A desmoplastic variant has been reported (262).

Histogenesis. Schwann cells are reactive with immunoperoxidase stain for S100 protein (263). Schwann cell fascicles of a ganglioneuroma, like those of all neuromas, are innervated. Ganglion cells are reactive for NSE and chromogranins. Immaturity, as manifested by foci of small, dark cells, spongy neuropil, and lymphoid infiltrates, signals the need for additional studies to rule out a differentiating metastatic neuroblastoma. In immature ganglioneuroma, the neurons may not be associated with satellite cells.

PRIMITIVE NEUROECTODERMAL TUMORS

Ewing's Sarcoma and Peripheral Neuroepithelioma

Originally, the designation, *primitive neuroectodermal tumor* served as a taxonomic convenience when confronted with the histologic pattern of a poorly differentiated, small, round cell neoplasm showing some evidence of neuroectodermal differentiation. The designation has been attributed to A. P. Stout, but there is no mention of this designation in the commonly cited reference. The designation has supplanted that of neuroepithelioma, acquiring some degree of specificity.

Ewing's sarcoma (EWS) and *peripheral neuroepithelioma* are PNETs; they are members of the category of small, round cell tumors. EWS, including an atypical variant (264), is a rare malignant neoplasm of bone and soft tissue. *Peripheral neuroepithelioma* (PNE) (the "primitive neuroectodermal tumor") generally is a tumor of the deep soft tissue, with rare examples in bone. It has been reported in internal viscera. *Askin's tumor* of the chest wall is also cited as an example of PNET. Some examples of PNETs have had their origin in a peripheral nerve (265) or have been a component of MPNST (malignant schwannoma) (114).

Histopathology. Primitive neuroectodermal tumors are tumors composed of small blue cells (266). In Ewing's category, the cells tend to be glycogen rich. Nuclear characteristics are uniform;

chromatin patterns tend to be open (266). In the neuroepithelioma category, the cells focally form pseudorosettes.

Histogenesis. Useful but variably positive reactions include NSE, CD57, and synaptophysin. In EWS and peripheral neuroepithelioma, tumor cells are immunoreactive for CD-99 (MIC2) (267–270); the reaction is sensitive but not specific; a positive reaction provides a distinction between PNET (positive) and neuroblastoma (negative).

Both EWS and PNE are characterized by the presence of chromosomal translocation t(11;22) (q24;q12), and the EWS gene has recently been identified at the breakpoint on chromosome 22 (271).

Differential Diagnosis. Neuroepithelioma-like patterns may be encountered as a regional variation in MPNST (114) and in the setting of cutaneous small-cell undifferentiated carcinoma (233).

Melanotic Neuroectodermal Tumor of Infancy

Melanotic neuroectodermal tumor of infancy affects the tissues of the oral cavity but also may be found in other sites (272–275). Expressions of neural and epithelial markers, melanogenesis, and occasional glial and rhabdomyoblastic differentiation are variably represented. The patterns of melanotic neuroectodermal tumor of infancy have been compared to those of the retina at 5 weeks' gestation (275).

HETEROTOPIAS

Cephalic brain–like heterotopias (CBHs) (nasal gliomas) are found most commonly in the skin near the root of the nose (276–282), but they may be intranasal (40%) or extranasal (60%). Extranasal CBHs, ranging in size from 1 to 5 cm, are smooth, firm, noncompressible, and skin colored. They do not pulsate or transilluminate. On the external surface of the nose, they usually are not midline. Intranasally, CBHs present as a firm, smooth, red-to-purple protrusion and usually measure 2 to 3 cm in diameter. They may resemble a hemangioma. Some examples are both intranasal and extranasal, with the two components being connected through a defect in the nasal bone (277). Other common bony defects that are associated with CBH involve the fonticulus frontalis, the cribriform plate, and the space between nasal bone and cartilage (277). Some examples are connected by a fibrous cord to the dura. Other sites of involvement include the scalp, oropharynx, nasopharynx, tongue, and subcutaneous tissue overlying T-12 (278).

Histopathology. CBHs are not encapsulated. They are disorganized and commonly show admixtures of glial tissue (Fig. 35-65), randomly distributed, mature neurons, increased vascularity, focal calcification, and fibrous tissue (281). Strands of neural tissue and fibrous tissue are interwoven (280). Fibrillary and gemistocytic astrocytes, activated oligodendrocytes, and giant astrocytes are variably represented. Astrocytes are the most conspicuous cellular component. In some examples, the astrocytic component may resemble a low-grade astrocytoma. Neurons usually are small; for some examples, they are absent, but, for others, they are focally prominent (281). Ependymal and retinal epithelium and even choroid plexus–like components have been observed (282). Focal areas of oligodendroglial differentiation may be prominent; in such areas, the neuropil may be immunoreactive for both NSE and synaptophysin. The degree of differentiation in these heterotopias may reflect the age of the patient at the time of excision. Some examples are remarkable for the diversity of cell types, all of which are representative of neuroectodermal differentiation. An oligodendroglioma arising in ectopic brain tissue of the nasopharynx was reported (283).

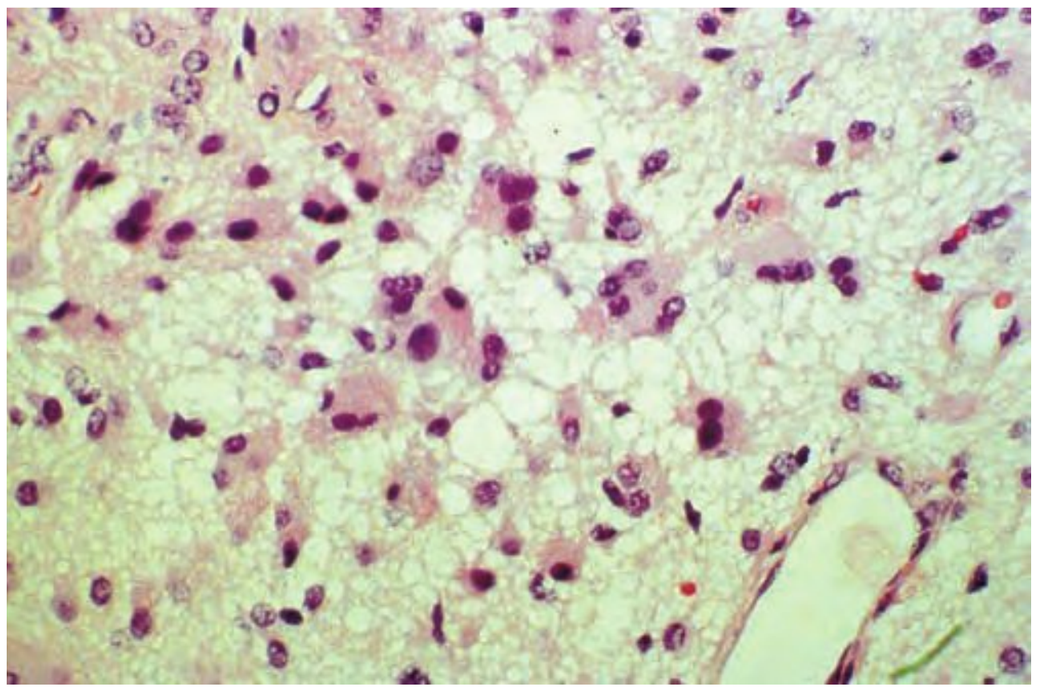


FIGURE 35-65. Parapharyngeal cephalic brain–like heterotopia. Astrocytes are supported by neuropil.

Immunohistochemically, neurons react for NSE and neural filaments. Astrocytes and ependymal cells are, and oligodendroglial cells are not, immunoreactive for GFAP. Oligodendroglial cells share some immunoreactions with Schwann cells.

Differential Diagnosis. *Encephaloceles* (extracranial protrusions of brainlike tissue that are in continuity with the subarachnoid space) may show a high degree of organization (284). CBH and encephaloceles of the same anatomic sites have similar clinical features. A distinction between CBH and encephalocele is not always possible, but encephaloceles are connected to the subarachnoid space by a sinus tract, thus making an ordinary biopsy inadvisable. A rhinorrhea with leakage of spinal fluid and even septic encephalitis may ensue following a biopsy. Computerized tomography (284) and neurosurgical consultation should precede any operative intervention of either CBH or encephalocele (280).

CUTANEOUS MENINGIOMAS AND MENINGOTHELIAL HETEROTOPIAS

Beyond the confines of the central nervous system, cells with the features of meningothelial cells may be encountered in skin

and soft tissue (285). They may be represented in patterns of a neoplasm (and properly characterized as *ectopic* meningioma). They may be represented in patterns similar to those manifested in the coverings of *meningoceles*, *meningomyeloceles*, and *meningoencephaloceles* (and properly characterized as heterotopia or dysplasia).

Definitions of various pathways and an understanding of developmental phenomena provide an explanation for the presence of meningothelial cells in the skin and soft tissue:

1. Precursors of meningothelial cells may be displaced into the dermis and subcutis during embryogenesis. Such remnants, located mainly in subcutaneous tissue of the scalp, forehead, and paravertebral regions of children and young adults (285–288), may develop into congenital meningeal heterotopias. They are relatively restricted in distribution along the lines of closure of the developing neural tube. Some of these lesions qualify as acelic meningeal heterotopias (rudimentary meningoceles) (287). For such examples, occult connections with the central nervous system may become apparent only at the time of surgery; a leakage of spinal fluid into the surgical defect will provide the evidence. Histologic patterns include features of those of both the dura and the leptomeninges.

2. True ectopic meningiomas, distributed along the course of cranial nerves of the sensory organs of the face and head, tend to occur in adults; they arise from extensions of arachnoidal lining cells along peripheral nerves (288). Some ectopic meningiomas arise in sites that are far from the axial skeleton. The histologic patterns of benign ectopic meningiomas recapitulate those of the meningiomas of the central nervous system.

3. Large, intracranial meningiomas may extend in direct continuity through foramina or old operative defects into the neighboring soft tissue; they qualify as *perforating* meningiomas. Their histology corresponds to that of the primary intracranial lesion and, once defined, is predictive of their behavior.

4. *Anaplastic* (*malignant*) *meningiomas* (including sarcomatous variants) and *papillary and hemangiopericytomatous variants* may aggressively invade bone, soft tissue, and scalp. They also may be associated with intracranial seeding and extracranial, mostly pulmonary metastases. Histologically benign meningiomas rarely have seeded the brain surface or metastasized (289).

Histopathology. Heterotopias are not well circumscribed (289). Cells of such lesions are cytologically bland and loosely attached to their neighbors. They commonly outline thin, angulated clefts, a feature that may be mistaken as evidence of vascular differentiation (Fig. 35-66) (288,290). Whorls of cells and psammoma bodies, if identified, are an aid in diagnosis. The supporting fibrous matrix is loosely fissured.

The complexities of the classification of true meningiomas (whether intracranial, ectopic, or metastatic) and the details of the corresponding histopathology preclude a presentation in this section. The basic features include sheets and nests of polygonal or spindle cells, whorls of cells, psammoma bodies (Fig. 35-67), intranuclear inclusions of cytoplasm, immunoreactivity for EMA, and scanty, condensed stroma or thin clefts at the interface between nests.

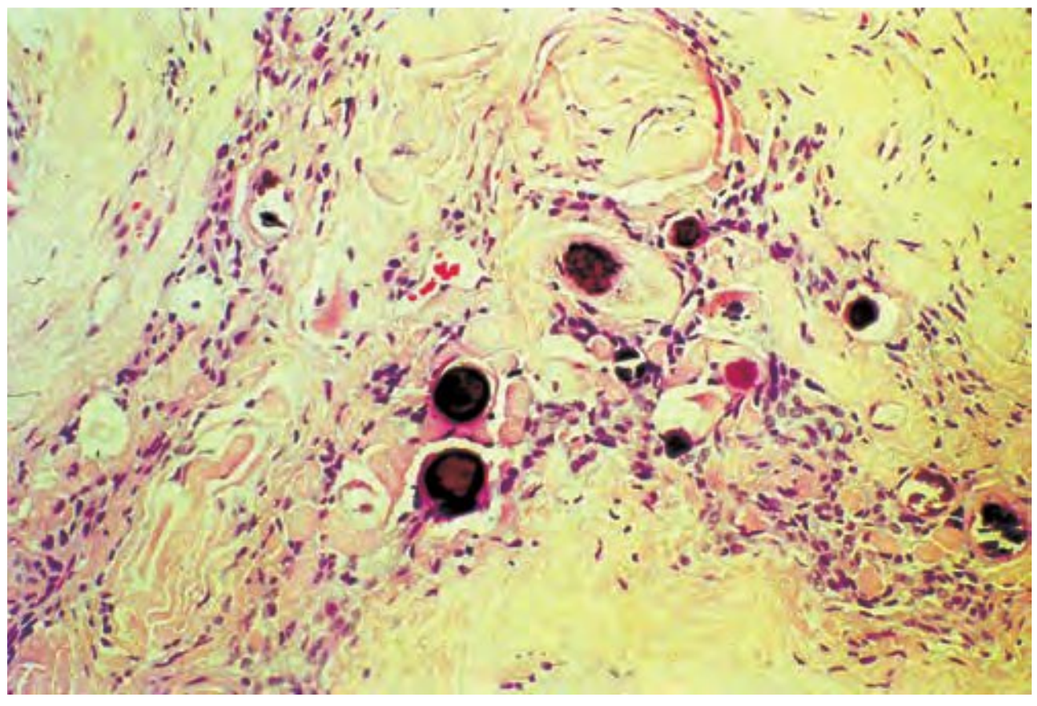


FIGURE 35-66. Meningeal heterotopia. Spindle cells with angulated, uniform nuclei form traceries among collagen bundles. There are clefts in some of the thin nests of spindle cells. The rounded, basophilic structures are psammoma bodies.

Anaplastic (malignant) meningiomas are characterized by dense cellularity, nuclear atypia, mitoses, necrosis, and invasion of the brain and even soft tissue. The basic patterns of common meningiomas usually are preserved, but some examples are frankly sarcomatous.

Ultrastructurally, poorly formed basal lamina, rare desmosomes, abundant mitochondria, and elaborate interdigitating, cytoplasmic processes are all features of meningothelial cells.

Histogenesis. Like intracranial meningiomas, the cells of ectopic meningiomas and meningeal heterotopias react immunohistochemically for vimentin and EMA (291–294).

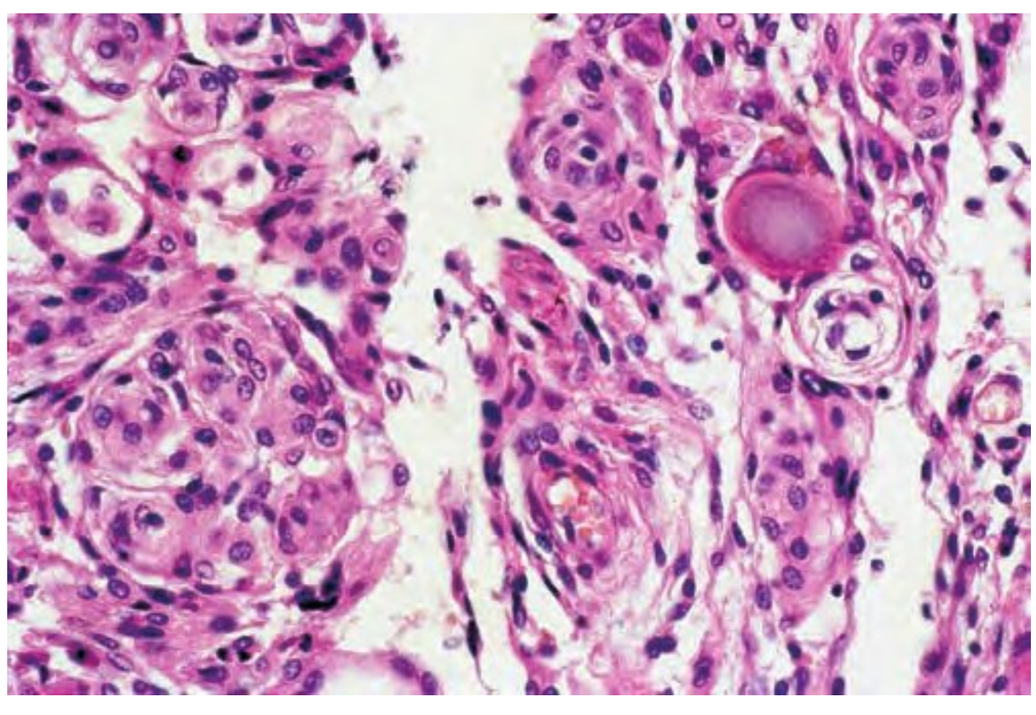


FIGURE 35-67. Cutaneous meningioma. Small, uniform spindle and epithelioid cells are arranged in nests and whorls; there are clefts among the nests. A psammoma body is represented.

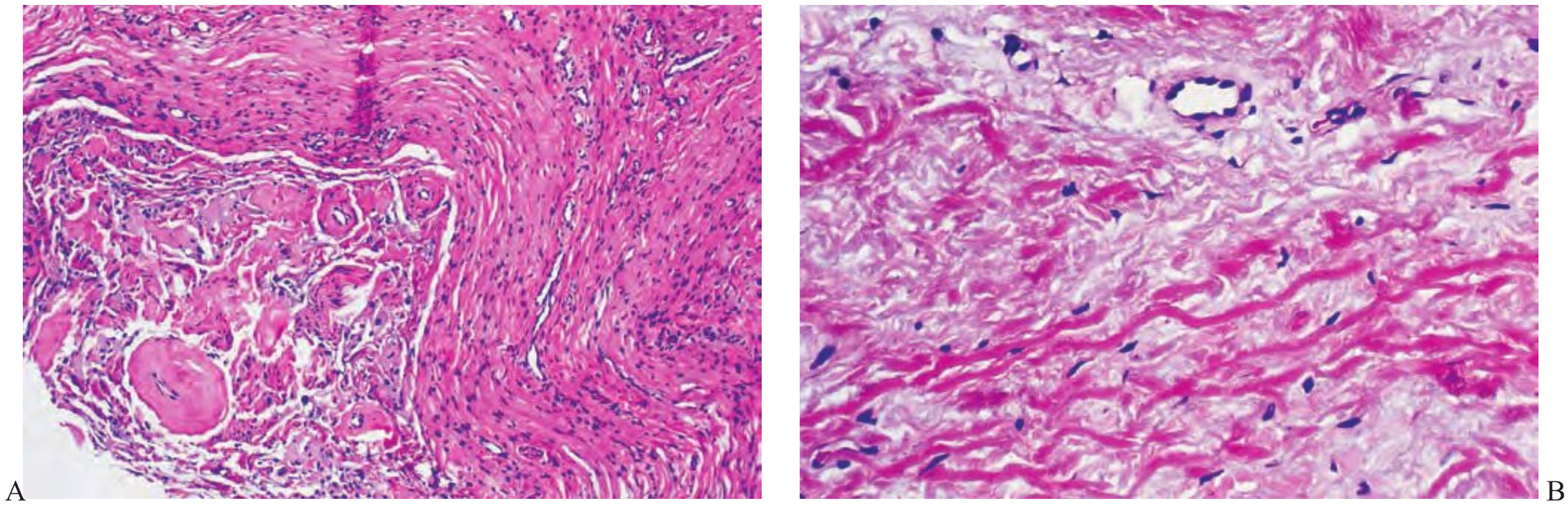


FIGURE 35-68. Impingement neuropathy (Morton's neuroma). A: To the left and extending to the bottom of the field, a nerve is cut in cross section; the perineurium is thickened and fibrotic. Individual nerve fibers and small clusters of nerve fibers are loosely spaced in a myxoid matrix. There are scattered hyaline deposits in the endoneurial space. Vessels of the endoneurium are cut in cross section; they have thickened, hyalinized walls. B: The connective tissue adjacent to an affected nerve shows hyperelastosis; the elastic fibers are increased in diameter. Often in Morton's neuroma, the changes in the adjacent connective tissue are similar to those of elastofibroma dorsi.

Depending on the histologic subtype, the expression of certain antigens, especially cytokeratins and S100 protein, is variable (288–294).

Differential Diagnosis. Meningoceles, meningomyeloceles, and meningoencephaloceles, like meningeal heterotopias, present along the lines of closure of the neural tube. Arachnoidal components are associated with both dense and loosely laminated, vascularized fibrous tissue. If there is an associated encephalocele (or myelocele), then tissue of the central nervous system, other than its coverings, will also be represented.

Ependymal rests also may be found in the sacrococcygeal region. Some are organized in patterns that resemble microscopic myxopapillary ependymomas (295). Such rests may provide an explanation for the origin of rare *ectopic ependymomas* in the sacrococcygeal region (296).

NEURAL TUMORS OF A DEGENERATIVE NATURE

In *impingement neurofasciitis* (*Morton or interdigital "neuroma"*), the compression of nerves and soft tissue between bony or other hard surfaces may induce degenerative changes. The responses include demyelination and endoneurial fibrosis, mucinous and fibrinous degeneration of soft tissue (fascia), deposition of preelastin over the surfaces of elastic fibers (in patterns resembling those seen in lesions of elastofibroma dorsi), and fibrinous bursitis (Fig. 35-68A, B) (297). In the excised specimen, nerve, related vessels, soft tissue, and a portion of synovium often are represented (Fig. 35-69). All of these phenomena, manifested in the interdigital area of so-called Morton neuroma, have nothing in common with the neuromas. In the altered nerves, localized, oval zones of mucinous or fibrous matrix may focally displace the nerve fibers. In them, spindle and stellate cells are loosely arranged in whorls. Similar epiphenomena, which were characterized by Renaut as an "intravaginal hyaline system," are often encountered as an incidental finding in normal nerves (4).

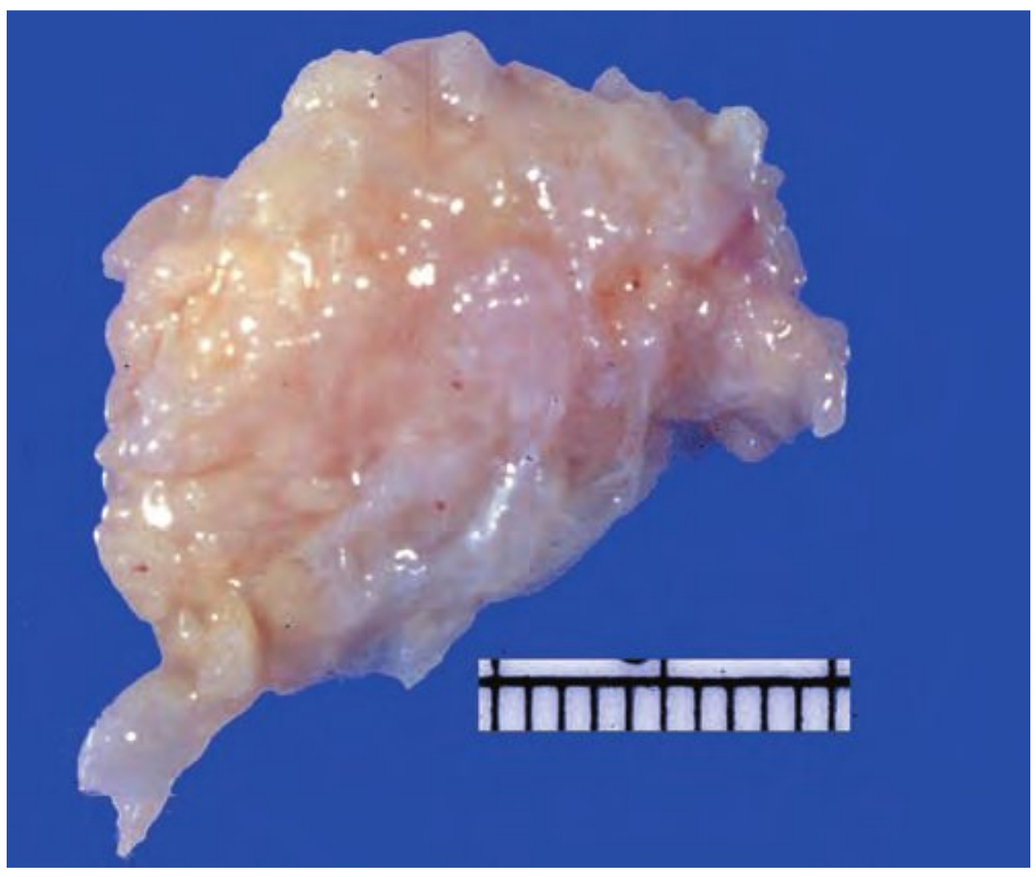


FIGURE 35-69. Morton's neuroma. A portion of a small nerve enters and exits a tumor. The tumor is not a neoplasm; it is an inflammatory process. The inflammatory process involves the interdigital nerve, soft tissue, and associated vessels. A portion of inflamed synovium often is included as part of the excised specimen.

Ganglion cyst of nerve is an uncommon tumor of a degenerative nature. In preferential sites, a superficial nerve impinges on a bony protuberance.

Initially, the perineurium and endoneurium are mucinous, expanded, and paucicellular. In one or more sites, cystic changes ensue. The end result is a mucinous cyst that expands the endoneurial space, compresses the axial bundle, and distends the perineurial sheath. A condensation of fibrous tissue forms the wall of the cyst.

Ganglion cyst of nerve is distinguished from periarticular ganglion cyst by location.

NEUROTROPIC GROWTH: GENERAL COMMENTS

Neurotropic growth of tumor is common in the skin. Generally, the identification of this phenomenon is sufficient to characterize any related primary neoplasm of the skin as aggressive [e.g., neurotropic melanoma (121), epidermoid carcinoma (298), and keratoacanthoma]. Rarely, benign invasion of nerve sheaths by squamous epithelium has been noted in reexcision specimens after a biopsy (299), and the cells of benign blue nevi and related lesions, and of congenital nevi, may occasionally be seen within nerves. Ensheathed neuroma is characterized by hyperplastic nerves that are ensheathed by benign squamous epithelium in the absence of a history of local trauma (300).

Primary malignant lymphoma, as a solitary tumor of peripheral nerve, is rare. Misdraji et al. reported a series of four cases (301). The lesions were all diffuse, large B-cell lymphomas. The involved sites included sciatic nerve (two cases), radial nerve (one case), and sympathetic chain and T2 spinal nerve (one case). At the time of the report, two of the patients had died of their disease. One patient at autopsy had evidence of neurolymphomatosis. The second patient had evidence of disseminated disease, including lymphomatous meningitis.

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CHAPTER 36

Waine C. Johnson

Metastatic Carcinoma of the Skin

INCIDENCE AND DISSEMINATION

Cutaneous metastases are of diagnostic importance because they may be the first manifestation of an undiscovered internal malignancy or the first indication of metastasis of a supposedly adequately treated malignancy. The site of the primary tumor, if unknown, may be suspected by the histopathology and appropriate immunoperoxidase studies. Cutaneous metastases are generally uncommon but have been reported more frequently in recent years. In a study of 7,316 patients with internal cancer, Lookingbill and colleagues (1) found 367 (5%) to have skin involvement. Of 4,020 patients with metastatic disease, Lookingbill and associates (2) reported that 420 (10%) had cutaneous metastases. Nine percent of 7,518 patients with internal cancer who were autopsied at Roswell Park Memorial Institute had skin metastases (3). The incidence of various tumors that are metastatic to the skin correlates well with the frequency of occurrence of the primary malignant tumor in each gender.

A review of 724 patients with cutaneous metastases in 1972 by Brownstein and Helwig (4) showed that in women, commensurate with the greater frequency of carcinoma of the breast, 69% of all cutaneous metastases originated in the breast. Carcinoma of the large intestine accounted for 9% of cutaneous metastases, and carcinoma of the lungs and ovaries accounted for 4%. In recent years, the incidence of cutaneous metastasis from carcinoma of the lungs in women has significantly increased, and carcinoma of the lungs has become the most frequent cause of cancer deaths in women (as it is in men) (5,6). The study by Brownstein and Helwig (4) of cutaneous metastases in men revealed the following incidences of primary carcinoma: lungs, 24%; large intestine, 19%; oral cavity, 12%; and kidney and stomach, each 6%. Metastatic melanoma was found in 13% (4) (see Chapter 28).

Due to the relative rarity of carcinomas of the thyroid gland (7,8), pancreas (9), liver, gallbladder, urinary bladder (10), endometrium, prostate (11,12), testes, and neuroendocrine system, cutaneous metastases of these tumors are also relatively rare. A review by Schwartz (13) reported cutaneous metastatic disease as the first sign of internal cancer most commonly seen with cancer of the lung, kidney, and ovary.

Dissemination may take place through the lymphatics or the bloodstream. In carcinomas of the breast and oral cavity, metastases reach the skin largely through lymphatic channels and are often located in the overlying skin. In contrast, cutaneous metastatic lesions in other carcinomas are often the result of hematogenous dissemination and may appear in any area of the skin (14). Cutaneous metastases are more likely to be found in older individuals. Rare metastases found in the young are usually derived from a neuroblastoma or, less commonly, a rhabdomyosarcoma (15).

Cutaneous metastases usually appear as multiple, discrete, painless, and freely movable papules or nodules of sudden onset (Fig 36-1). Cutaneous metastases occur in about 10% of cases of metastases (2). The nodules are usually 1 to 3 cm in diameter, but much larger lesions have been reported (16). Metastases tend to occur on cutaneous surfaces near the site of the primary tumor, but exceptions to this include the scalp, which may be as frequent as 5% of all cutaneous metastases. Metastasis to the umbilicus is relatively common, and the underlying primary tumor is usually an adenocarcinoma of the stomach, ovaries, endometrium, or breast (11,17). A zosteriform pattern of skin metastasis has been reported to occur on the chest wall and abdominal wall, and the most frequent site of the primary was the breast, ovary, lung, prostate, bladder, or stomach (18,19).

Distinction of a primary carcinoma of the skin from a metastatic lesion can be a problem when dealing with a solitary lesion (Fig. 36-2). Some examples include primary mucinous adenocarcinoma of skin (20–22), adenocarcinoma of the mammary-like glands of the vulva (23), cutaneous signet-ring carcinoma (24), primary carcinoids (25,26), and adnexal carcinomas (27).

To establish a diagnosis of a primary mucinous carcinoma of the skin, the presence of a peripheral myoepithelial layer, if present, is helpful (21). Immunoperoxidase positivity with CD15, CK5/6, and 34BE12 (22) favor a primary lesion. A number of studies have shown that p63 staining of a tumor favors a primary tumor over a metastatic lesion (27). Except for sebaceous tumors, there is rare reactivity for primary adnexal carcinoma of the skin with CD10 in comparison with metastatic carcinoma, especially metastatic renal cell carcinoma (28).

Although metastatic lesions can occur at any site, the scalp, head, and umbilicus are more frequent. Finding of the primary tumor or the presence of serum chromogranin (25) would indicate a metastatic carcinoid.



FIGURE 36-1. Metastatic carcinoma of stomach origin to the face. Multiple dermal and subcutaneous nodules are seen on the face and neck.



FIGURE 36-2. Metastatic ovarian carcinoma to the inguinal area. A single nodule of recent onset.

Some immunoperoxidase studies that are helpful in distinguishing primary tumors from metastatic lesions are shown in Table 36-1.

CARCINOMA OF THE BREAST

Cutaneous metastases that occur predominantly by lymphatic dissemination include inflammatory carcinoma, carcinoma en cuirasse, telangiectatic and nodular carcinoma, and carcinoma of the inframammary crease. Alopecia neoplastica and mammary carcinoma of the eyelid are probably caused by hematogenous spread (13).

Inflammatory breast carcinoma is characterized by an erythematous patch or plaque with an active spreading border that resembles erysipelas and usually affects the breast and nearby skin (13). Rarely, inflammatory metastatic carcinoma may arise from primary involvement of other organs. The inflammatory appearance and warmth are attributed to capillary congestion.

En cuirasse metastatic carcinoma is characterized by a diffuse morphea-like induration of the skin and rarely involves skin from other primary carcinomas. It usually begins as scattered papular lesions coalescing into a sclerodermoid plaque without inflammatory changes.

Telangiectatic metastatic breast carcinoma is characterized by violaceous papulovesicles resembling lymphangioma

TABLE 36-1 Immunoperoxidase Studies

Type of Carcinoma	CK7	CK20	TTF-1	Antithyroid	P63	PSA/PSAP	RCC-MA
Breast carcinoma	+	−	−	−	−/+	−	−
Lung, small cell carcinoma	+	−	+	−	−/+	−	−
Gastrointestinal carcinoma	−	+	−	−	−	−	−
Renal cell carcinoma	−/+	−	−	−	−	−	+
Thyroid carcinoma	−	−	+	+	−	−	−
Ovary carcinoma	+	−/+	−	−	−	−	−
Prostate carcinoma	−/+	−/+	−	−	−	+	−
Primary mucinous carcinoma of the skin	+	−	−	−	+/−	−	−
Merkel cell carcinoma	−	+	−	−	+/−	−	−
Adenocarcinoma of mammary-like glands of the vulva	+	−	−	−	−	−	−
Adnexal carcinoma	+/−	−/+	−	−	+/−	−	−

+, almost all are positive; −, almost all are negative; −/+, most are negative; +/−, most are positive.

circumscriptum (13). A violaceous hue, which is often present, is caused by blood in dilated vascular channels.

The nodular form appears as multiple firm nodules that may show ulceration. An exophytic nodule may occur in the inframammary crease resembling a primary squamous cell or basal cell carcinoma and occurs more frequently in women with large breasts.

Alopecia neoplastica occurs as oval plaques or patches of the scalp and may be confused clinically with alopecia areata or a scarring alopecia. Metastatic mammary carcinoma in the eyelid clinically presents as a painless swelling with induration or as a discrete nodule (13).

Histopathology. In inflammatory carcinoma, histologic examination of the skin reveals extensive invasion of the dermal and often the subcutaneous lymphatics by groups and cords of tumor cells. The tumor cells are similar to those in the primary growth and atypical in character with large, pleomorphic, hyperchromatic nuclei. There is marked capillary congestion, which is the reason for the clinical appearance of erythema and warmth (13). Often, there is interstitial edema and a slight perivascular lymphoid infiltrate. The extensive lymphatic dissemination is caused by retrograde lymphatic spread into the skin secondary to blockage of the deep lymphatics and lymph nodes. Fibrosis is not a significant feature. Some studies indicate that only 1% to 4% of patients with metastatic breast carcinoma present with the inflammatory or erysipeloid type and that most of these patients have intraductal breast carcinoma (29).

In carcinoma en cuirasse, also referred to as *scirrhous carcinoma*, the indurated areas show fibrosis and may contain only a few tumor cells. The tumor cells may be confused with fibroblasts. The tumor cells have elongated nuclei similar to fibroblasts, but the nuclei are larger, more angular, and more deeply basophilic. The tumor cells often lie singly; however, in some areas, they may form small groups or single rows between fibrotic and thickened collagen bundles (Fig. 36-3). This latter feature of "Indian filing" is of particular diagnostic importance and may be seen in any histologic variety.

In telangiectatic carcinoma, the tumor cells tend to be located more superficially in the dermis within dilated lymphatic vessels than those in inflammatory carcinoma. The blood vessels are congested with red blood cells, as in inflammatory carcinoma, but usually also contain aggregates of neoplastic cells. The presence of many dilated blood vessels immediately beneath the epidermis gives rise to the clinical appearance of hemorrhagic vesicles.

In nodular carcinoma, there are variably sized groups of tumor cells in the dermis, and these nodular areas are surrounded by fibrosis. Depending on the tumor type, some cells may show a glandular arrangement, which may be quite ill-defined (Fig. 36-4). Sometimes, a nodule may be pigmented and clinically suggestive of a melanoma or pigmented basal cell carcinoma. The pigment results from melanin accumulation within the cytoplasm of neoplastic cells and in the stroma (30).

Carcinoma of the inframammary crease has been described as islands of epithelial cells with hyperchromatic nuclei extending contiguously with the epidermis from the dermis (31).

In hematogenous metastases, the histologic picture varies with clinical presentation. In alopecia neoplastica, the features resemble those of the en cuirasse type, with single files of tumor cells between thickened collagen bundles. Metastatic mammary carcinoma involving the eyelid has been described in 13 patients, and in 8 of them, the microscopic features had a prominent histiocytoid appearance (32).

Epidermotropic involvement from metastatic breast carcinoma may mimic malignant melanoma and/or Paget's disease (33).

The signet-ring cell histologic pattern of breast carcinoma (Fig. 36-5) may also be seen in carcinoma of the gastrointestinal tract and urinary bladder (34). This may be confused with a primary cutaneous signet-ring cell carcinoma that occurs most frequently in middle-aged men on the eyelid and less frequently in the axilla (34). A primary mucinous carcinoma of

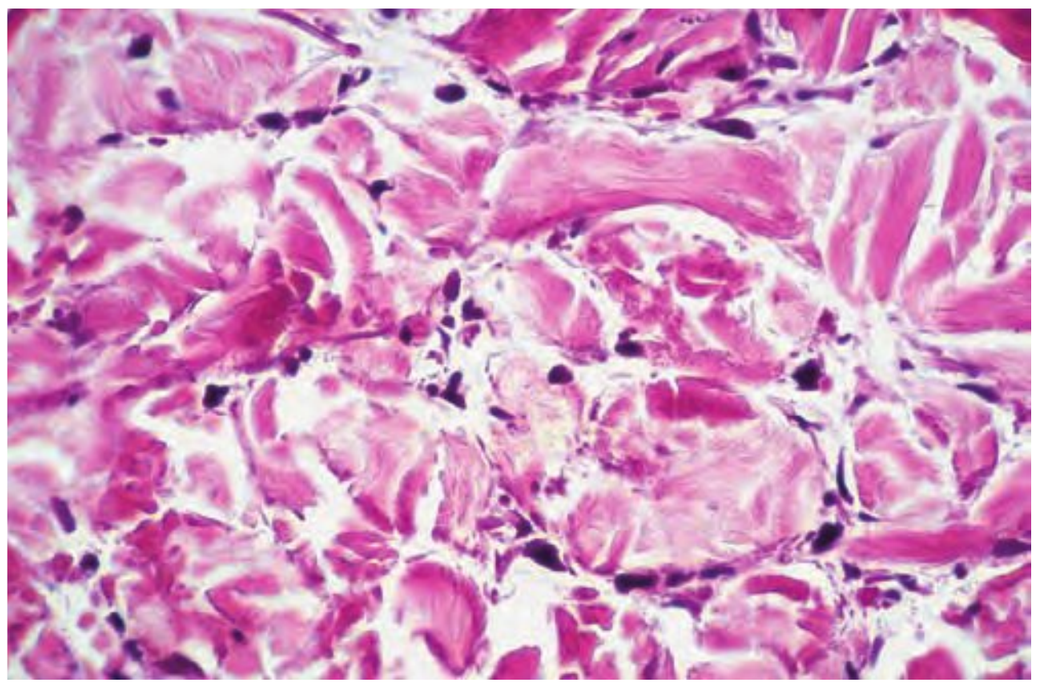


FIGURE 36-3. Metastatic breast carcinoma. Individual atypical tumor cells are seen between fibrotic collagen bundles.

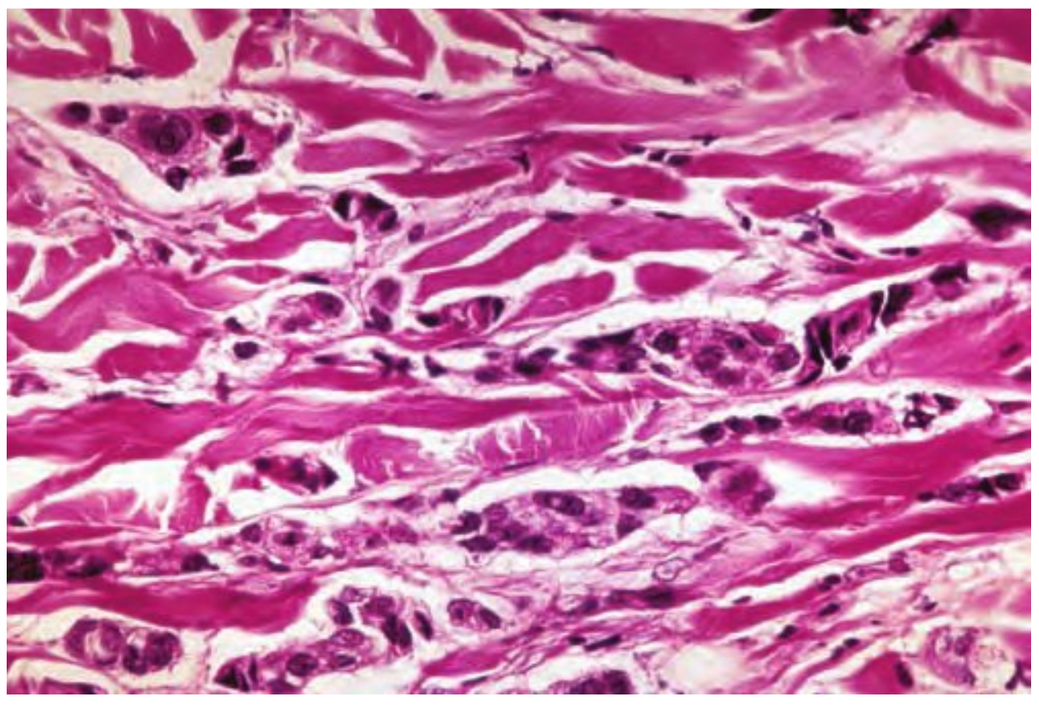


FIGURE 36-4. Metastatic breast carcinoma. Cords of atypical cells with ill-defined attempts at acinus formation infiltrating between collagen bundles.

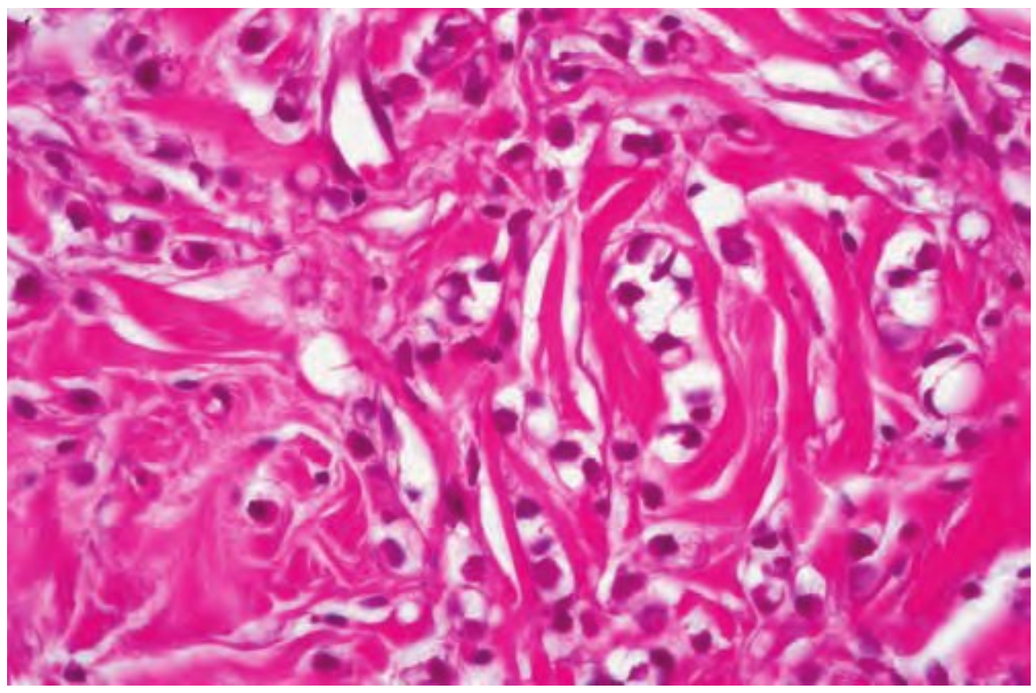


FIGURE 36-5. Metastatic breast carcinoma. This tumor demonstrates a signet-ring cell pattern.

the skin also may require distinction from metastatic lesions from the breast or colon (15). Rarely, a granular cell histologic pattern is seen.

Immunoperoxidase Studies. Cutaneous metastases are positive with most cytokeratins, except for CK20 (15), and often are positive with epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA). Reactivity with S-100 protein has been reported in as many as 84% of cases of primary and metastatic breast carcinoma (35). The presence of melanin granules and melanosomes within tumor cells that give a positive HMB-45 is rare and probably occurs secondarily to phagocytosis or melanocyte colonization of the tumor cells (30). In lesions in which there are cells positive with S-100 or HMB-45, strong reactivity with keratins or reactivity with EMA and/or CEA would rule out melanoma. A positive androgen receptor marker might be helpful in supporting metastatic breast cancer when estrogen receptors and progesterone receptors are negative (36). Primary signet-ring carcinoma of the skin has been reported to be positive with CK7 and CK20, and this would aid in distinction from the breast, which is usually negative with CK20 (34).

Mucinous carcinoma of the skin, which is generally thought to derive from the sweat glands, is positive with numerous cytokeratins but is negative with CK20. This would allow distinction from a metastatic mucinous adenocarcinoma of the colon, which would be positive with CK20 (37).

Expression of CK7 was found in the majority of cases of carcinoma, with the exception of those arising from the colon, prostate, kidney, thymus, carcinoid tumors of the lung and gastrointestinal tract, and Merkel cell tumors of the skin.

CARCINOMA OF THE LUNG

Metastasis to the skin is more common in men, but the incidence of lung carcinoma in women is increasing (5,6). In 56 patients reported with skin metastasis from lung carcinoma, 7% had a skin nodule before the diagnosis of the primary tumor, and 16% had a nodule at the same time (38). In 11 of 21 patients with cutaneous metastasis, the skin was the first extranodal site (1). Metastases may occur on any cutaneous surface, but the most common sites are the chest wall and posterior abdomen (13). Oat cell carcinoma shows predilection for the skin of the back (2). Most lesions present as a localized cluster of cutaneous papules or nodules or as a solitary nodule.

Histopathology. Cutaneous metastases were undifferentiated in approximately 40% and adenocarcinoma and squamous cell carcinoma in approximately 30% each (4). The undifferentiated tumors were often of the small cell type with hyperchromatic nuclei and scant cytoplasm, also known as *oat cell carcinomas* (4). Carcinoid tumors of the lung are derived from the bronchus and consist of solid islands and nests of uniform cells (Fig. 36-6). Other sources of carcinoid tumors include the stomach, small and large intestine, and primarily the skin (39,40). The closely packed tumor cells may suggest a malignant lymphoma. Immunoperoxidase studies are extremely helpful in making this distinction. Larger cells require consideration of metastatic amelanotic melanoma and, again, immunoperoxidase studies may be required for distinction.

Squamous cell carcinomas that are metastatic to skin are usually poorly or moderately differentiated (4). They can usually be distinguished from primary squamous cell carcinoma by the absence of proliferation from the surface epidermis and seldom show an orderly pattern of differentiation from basaloid to prickle cells with centers of keratinization. They may show occasional whorls of squamoid cells with imperfect keratinization and individually keratinized cells and sometimes have large, bizarre forms with frequent mitotic figures (4). In larger tumors, areas of central necrosis are often present. Most cutaneous metastatic squamous cell carcinomas arise in the

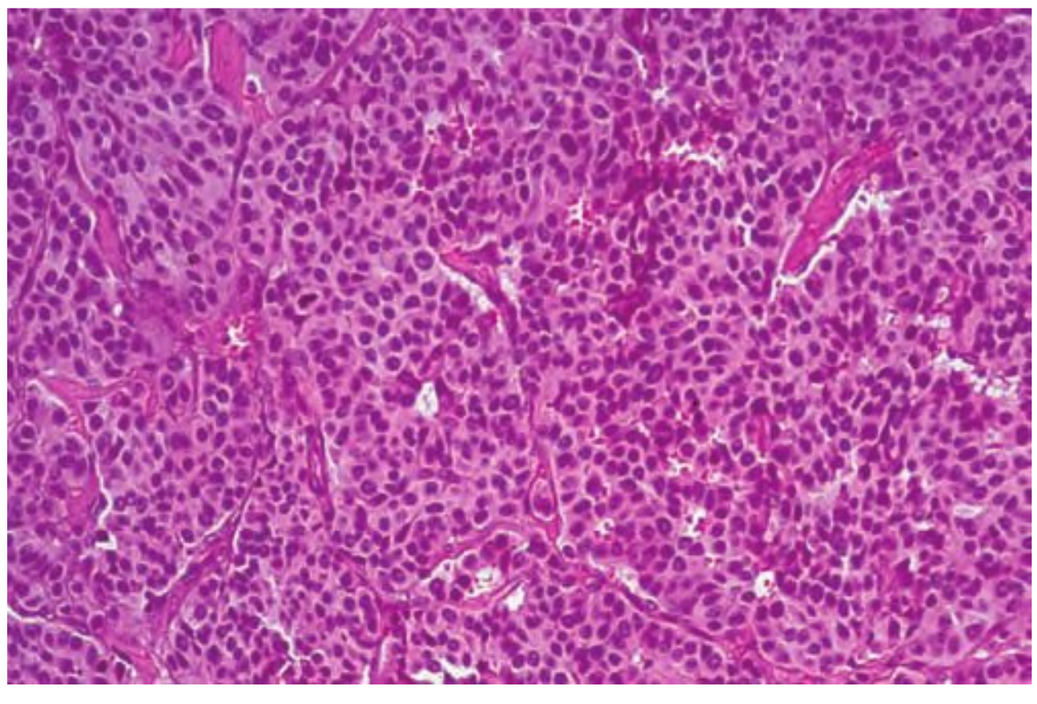


FIGURE 36-6. Metastatic carcinoid tumor from the lung. Uniform small cells without high-grade atypia, forming nests in a typical pattern of a carcinoid tumor.

lung, oral cavity, or esophagus. Tumors from the oral cavity tend to be more differentiated and nearly always appear on the head or neck. Squamous carcinoma metastatic from the esophagus shows essentially similar features to that from the lung (4).

Adenocarcinomas metastatic to the skin from the lung are often moderately differentiated, but some show well-formed, mucin-secreting, glandular structures. Individual tumor cells sometimes contain abundant cytoplasmic mucin but usually lack large pools of mucin, which is more characteristically seen from gastrointestinal metastatic adenocarcinomas (4).

Immunoperoxidase Studies. In addition to keratins that are positive in most metastatic carcinomas, most metastatic adenocarcinomas are positive with EMA and CEA. It has been stated that a positive reaction with CEA (seen in 50% of secondary neuroendocrine carcinomas) may be most helpful in differentiating between primary and secondary lesions (41). A rare exception to this consideration is the presence of ductlike structures in two instances of Merkel cell carcinoma, and these were CEA positive. This was assumed to be eccrine differentiation. Merkel cell carcinomas usually show a CK20, perinuclear dot, and/or diffuse activity, and this is rarely seen in metastatic neuroendocrine carcinomas (42). They may show reactivity to one or more of the following: protein gene product, chromogranin-A, CD56 antigen (Leu-7), and synaptophysin (41). Negative reactions with lymphocyte common antigen (LCA) and other lymphoid markers are most helpful in ruling out malignant lymphomas (43). Thyroid transcription factor 1 (TTF-1) is positive in thyroid carcinoma and small cell lung carcinoma and is negative in most cases of Merkel cell carcinoma (42,44).

GASTROINTESTINAL CARCINOMA

Carcinoma of the colon and rectum is the second most common type of primary cancer in men (13). Cutaneous lesions usually appear after the primary tumor has been recognized and occur more commonly on the abdomen or perineal areas, although the head and neck areas are sometimes involved. Metastases from gastric carcinoma may occur at any distant site, but the umbilical region is perhaps most common.

Histopathology. Most cutaneous metastases from the large intestine and all from the stomach as reported by Brownstein and Helwig (45) were adenocarcinomas (Fig. 36-7). A mucinous carcinoma pattern with small groups of tumor cells that lie in large pools of mucin is common in lesions from the large intestine. Signet-ring cell differentiation is not usually seen in lesions from the large intestine but may be present in lesions from the stomach (4). The stomach metastases are usually anaplastic, infiltrating carcinomas with variable cellularity, a loose stroma, and varying proportions of signet-ring cells. The mucin present in metastatic carcinoma from the gastrointestinal tract as well as in mucinous carcinomas from the breast and lung is a nonsulfated, hyaluronidase-resistant, sialic acid–type of mucosubstance (46–48). Histochemical

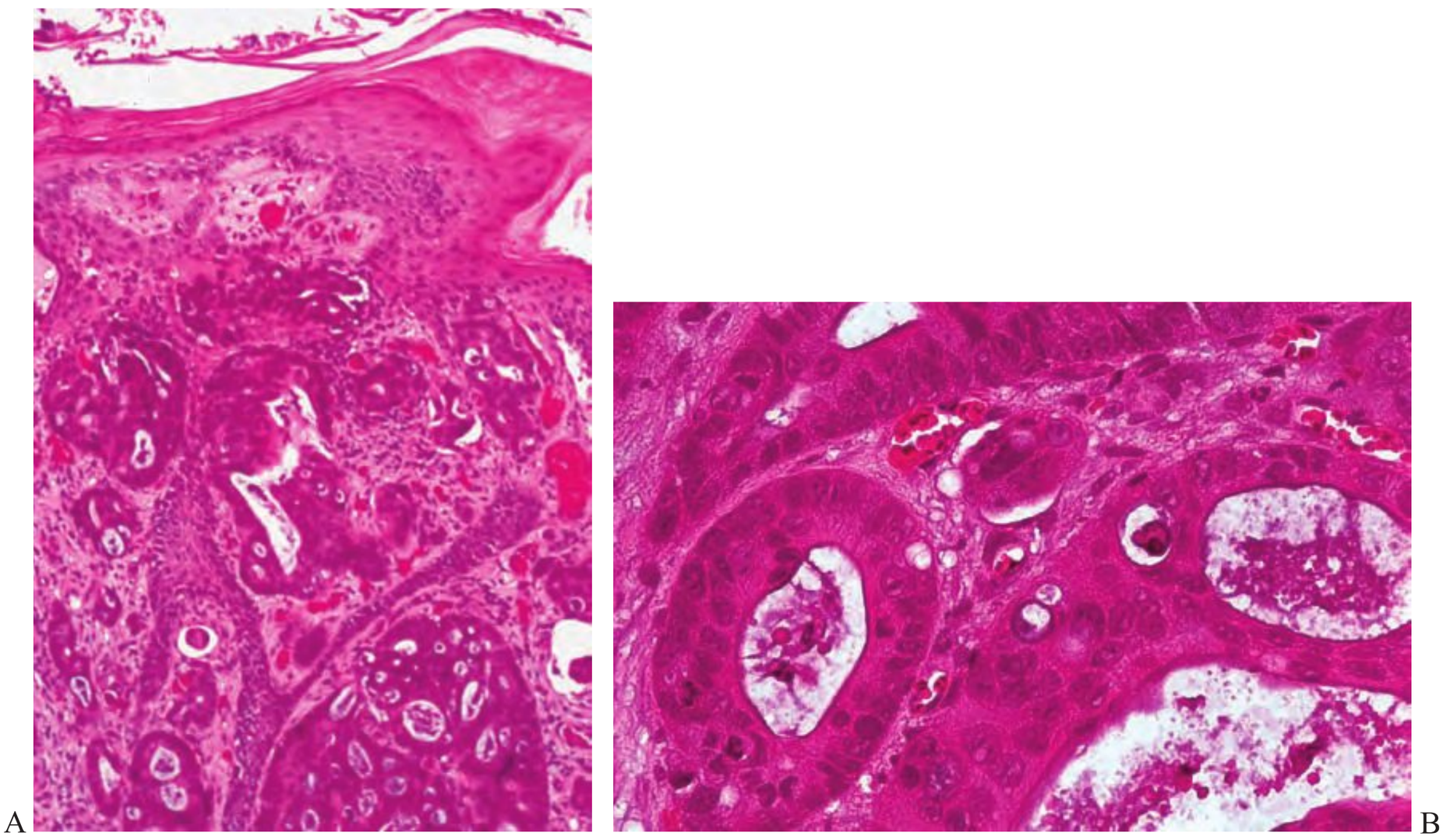


FIGURE 36-7. Metastatic carcinoma from the colon. This tumor shows secondary epidermal involvement (A) and is comprised of somewhat irregular but relatively well-formed glands (A,B).

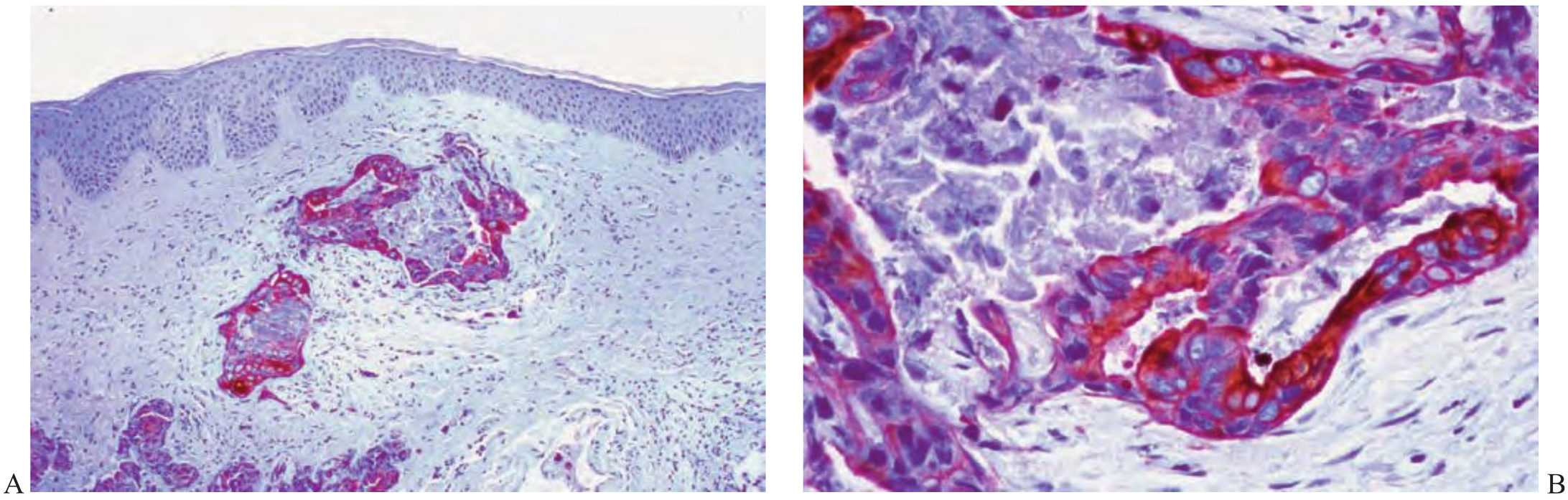


FIGURE 36-8. Metastatic carcinoma from colon, cytokeratin-20. A, B: CK20 reactivity, usually studied in coordination with that of CK7, helps to distinguish this lesion from a nongastrointestinal tract adenocarcinoma. Bladder and mucinous ovarian carcinomas may also be positive.

procedures show this mucin to be positive with colloidal iron, hyaluronidase resistant, Alcian blue positive at pH 2.5 and negative at pH 0.4, and aldehyde-fuchsin positive at pH 1.7 and negative at pH 1.0. It shows metachromasia with toluidine blue at pH 3.0, and is negative at pH 2.0, is PAS positive and diastase resistant, and is mucicarmine positive (49). In contrast, histochemical studies of adenoid squamous cell carcinoma show the mucin to be predominantly hyaluronic acid. Also, distinction from adenoid basal cell carcinoma and adenocystic carcinoma from lacrimal and salivary glands can be made based on the fact that these latter tumors contain a predominance of sulfated acid mucosaccharides (49). The differential diagnosis for metastatic carcinoma includes carcinomas of cutaneous adnexae such as sweat gland carcinomas.

Immunoperoxidase Studies. A study by Chu and associates (50) showed CK20 positivity in almost all colorectal carcinomas (Fig. 36-8) and Merkel cell tumors, pancreatic carcinomas (62%), gastric carcinomas (50%), cholangiocarcinomas (43%), transitional cell carcinomas (29%) and was nearly absent in carcinomas from other organ systems and in malignant mesotheliomas.

ORAL CAVITY CARCINOMA

Most lesions metastasizing from carcinomas of the oral cavity are spread by lymphatic invasion and are located on the face or neck (4). They usually appear as multiple or solitary nodules and sometimes are ulcerated.

Histopathology. The lesions are almost always squamous cell in type and are usually moderately or well differentiated (4). They are located usually in the deeper dermis and subcutaneous tissue with sparing of the superficial cutis. In examples with ulceration and involvement of the upper corium, distinction from primary squamous cell carcinoma of skin may not be possible (4).

RENAL CELL CARCINOMA

In renal cell carcinoma, tumors are most commonly located in the head and neck area, although any site may be involved (13,51). They often present as solitary or a few nodules and may be skin colored, reddish, or violaceous. They may occur as the first sign of internal cancer or as late as 10 years after diagnosis of the primary. They occur almost always in men.

Histopathology. The histologic features are usually those of a clear cell adenocarcinoma. They are often localized intradermal nodules and may stretch the overlying epidermis (4) (Fig. 36-9A). The tumor cells show oval nuclei with abundant, clear cytoplasm and often are in a glandular configuration (Fig. 36-9B). The stroma is vascular, and extravasated red blood cells are frequent. Intracytoplasmic glycogen is uniformly present, as demonstrated by staining with PAS and diastase-labile intracytoplasmic material. Frozen sections stained with oil red O show the presence of lipid droplets in many tumor cells (51). The histologic differential diagnosis includes adnexal tumors and especially eccrine acrospiroma (nodular hidradenoma). In contrast to the usual unilobular and hemorrhagic renal cell carcinoma, the eccrine acrospiroma tends to be multilobular and nonhemorrhagic, and often distinct ductal structures are present. Sebaceous cell tumors also may be confused, but the markedly vascular stroma and hemorrhagic nature of the renal cell cancer is fairly distinctive.

Immunoperoxidase Studies. In most cases, the tumor cells are reactive with pankeratin, AE1/AE3, CAM5.2, EMA, and CD10 (28). They are usually negative with CK7 and CK20, and about 60% in one study were positive with vimentin

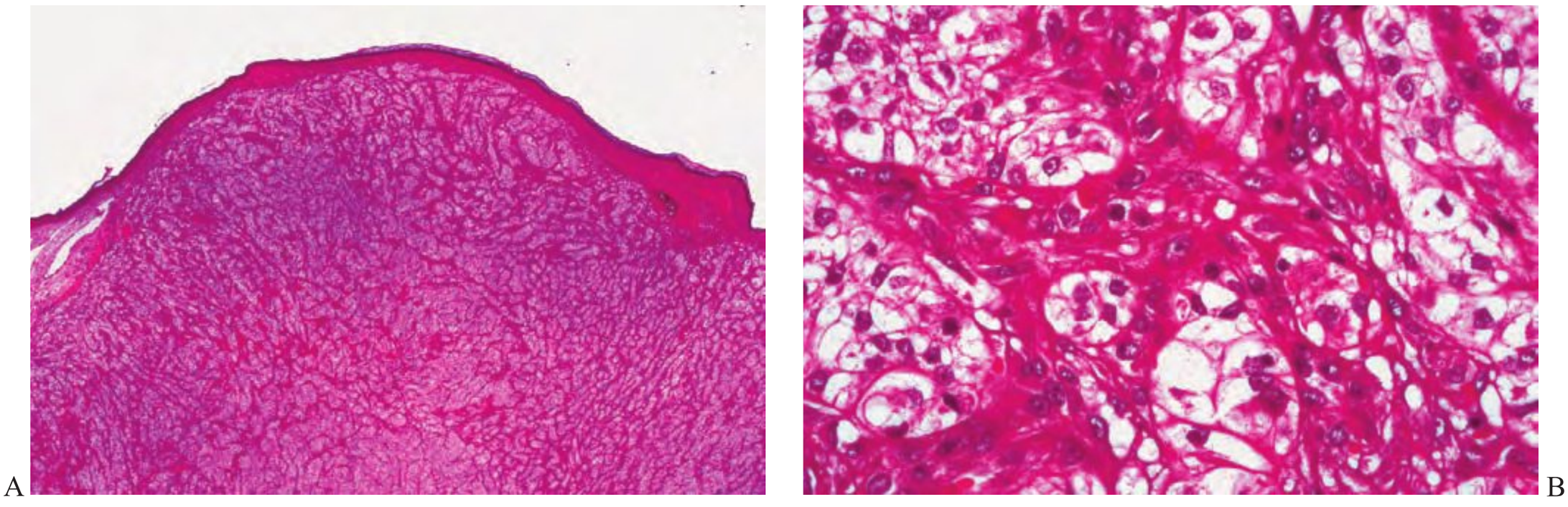


FIGURE 36-9. Metastatic carcinoma from kidney. A dermal tumor pressing on and elevating the overlying epidermis (A) and comprised of clear cells with prominent capillaries in the stroma (B).

(52,53). Renal cell carcinoma marker (RCC-Ma) is positive (54).

CARCINOMA OF THE OVARY

In carcinoma of the ovary, the most frequent sites involved are the abdomen, including the umbilicus, vulva, or back (13). Lesions of the abdomen may be in the scar sites from surgery or diagnostic procedures (2).

Histopathology. The features are usually of a moderately or well-differentiated adenocarcinoma, often having a papillary configuration and containing psammoma bodies (4). In 724 patients studied by Brownstein and Helwig (4), psammoma bodies in cutaneous masses were found only in metastases from the ovary (but might also be seen in papillary carcinomas from other sites including, for example, the thyroid).

Immunoperoxidase Studies. Papillary ovarian tumors were all CK7 positive and CK20 negative. Mucinous ovarian carcinomas (Fig. 36-10) were CK7 positive, and a few were CK20 negative (55).

CARCINOID AND NEUROENDOCRINE CARCINOMAS

Tumors in carcinoid and neuroendocrine carcinomas are assumed to be derived from the neural crest tissues and have been classified as amine precursor uptake and decarboxylase system tumors. Lesions appear as solitary or multiple cutaneous papules or nodules and may occur at any site. Primary carcinoids giving rise to cutaneous metastases (Fig. 36-6) occur most frequently in the bronchi but have been reported in various sites including the small intestines, sigmoid, colon, pancreas, stomach, thymus, and thyroid (40). In addition to carcinoid tumors, cutaneous metastases from neuroendocrine carcinomas of a variety of sites including the uterus, vulva, gallbladder, and fallopian tubes have been reported (13,56). Neuroblastoma, which is the most common cancer identified at birth, has been reported to metastasize to the subcutaneous tissue in 32% of patients with congenital neuroblastoma (13). Clinically, they have a fairly specific appearance, which has been described as like a "blueberry muffin." This term has also been used to describe some cases of congenital leukemia. Cutaneous neuroblastoma is very rare in adults, and it is impossible to distinguish between primary and metastatic lesions except for finding an internal primary tumor (57).

Histopathology. Carcinoid metastases in the skin and subcutaneous tissue consist of solid islands, nests, and cords of tumor cells (Fig. 36-6). As a rule, the cells appear quite uniform in size and shape; have small, rounded nuclei; and abundant, clear, or eosinophilic cytoplasm occasionally containing numerous eosinophilic granules (40). However, in some

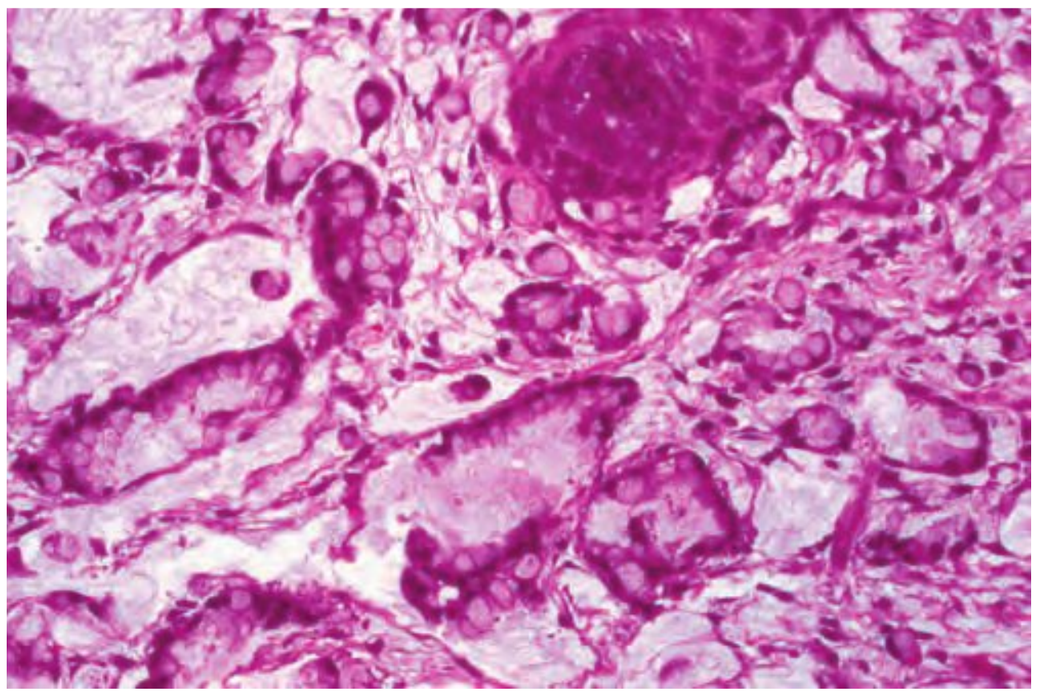


FIGURE 36-10. Metastatic mucinous ovarian carcinoma. Infiltrating acinar structures with scattered signet cells.

instances, the nuclei are hyperchromatic, and there may be areas in which the nuclei show anaplasia by being irregularly shaped, large, and hyperchromatic. Carcinoids of the bronchus usually contain argyrophil granules in contrast to those of the small intestine, which usually contain argentaffin granules, which can be demonstrated by the Fontana-Masson stain (58). Cutaneous metastases of bronchial carcinoids may have either argyrophil or argentaffin granules (59). Yet, diagnosis today is usually made with the support of immunohistochemical studies, as discussed in the next section (60). The histologic differential diagnosis may include sweat gland carcinoma or glomus tumor because of their arrangement in well-defined islands, as well as metastases from noncarcinoid neuroendocrine tumors, and primary Merkel cell carcinoma. The latter usually show more immature cells or greater cellular atypism, a greater number of mitotic figures, and a "trabecular" pattern. The presence of an intraepidermal component would also favor a primary Merkel cell carcinoma. Involvement of the deep dermis and multiple skin sites favor a metastatic lesion (56). Primary or metastatic neuroblastomas (peripheral neuroectodermal tumor) show identical features of undifferentiated, small, hyperchromatic cells with frequent rosettes of the Homer-Wright type and numerous mitoses (57). Some examples of undifferentiated lesions may not show rosettes. The histologic differential diagnosis includes other small cell carcinomas that sometimes show rosette-like structures, extraskeletal Ewing's sarcoma, lymphoma, and leukemia. Merkel cell carcinoma tends to display a trabecular arrangement, but this is not always specific.

Immunoperoxidase and Electron Microscopy Studies. Immunoperoxidase studies are of great value in distinguishing a primary Merkel cell carcinoma of the skin from a metastatic neuroendocrine carcinoma. Merkel cell carcinomas are usually positive with CK20 (60) and are negative with TTF-1 and CK7 (42,44). If the lesion is positive for CEA in nonductal or nonglandular sites, this would strongly favor a metastatic lesion (41). The presence of a positive reaction with nonspecific esterase (NSE) and EMA is not necessarily helpful, since these can be reactive in primary or secondary neuroendocrine carcinomas as well as sweat gland carcinomas. Reactivity with CK20 favors a Merkel cell tumor. If the tumor is positive with S-100, this favors an eccrine sweat gland carcinoma, metastatic breast carcinoma, or malignant melanoma. If the tumor is positive with LCA, this identifies the lesion as a malignant lymphoma. A rare exception to this rule was published by Nandedkar and colleagues (61). Calcitonin has been demonstrated in cutaneous metastasis of medullary carcinoma of the thyroid (62). Electron microscopic studies of carcinoid, neuroendocrine, and primary Merkel cell carcinomas show "neurosecretory" membrane-bound, dense-core granules measuring 100 to 250 nm in diameter (34,55,59,63). These granules do not distinguish among members of this group. Immunoelectron microscopic studies confirm the presence of cytokeratin (AE1/AE3) arranged in paranuclear areas, while cytoplasmic synaptophysin and chromogranin positivity over dense-core granules tend to confirm light microscopic immunohistochemical studies (63). Neuroblastoma has been reported to be positive with NSE but often is negative with other commonly reactive antigens of neuroendocrine tumors such as EMA, chromogranin-A, and synaptophysin (57). Electron microscopy shows membrane-bound, dense-core granules concentrated in the cytoplasmic processes. Desmosomes and microtubules are usually seen in more differentiated tumors.

MISCELLANEOUS CARCINOMAS

In metastatic carcinoma from the liver, the arrangement of malignant hepatocytes in irregular columns is fairly distinctive, and if there are acinar structures containing bile, the diagnosis is definite (64).

In choriocarcinoma, the cutaneous metastases show the two types of cells that arise from the fetal trophoblast: cytotrophoblasts and syncytiotrophoblasts. The cytotrophoblasts usually grow in clusters, and the cells appear cuboidal with large, vesicular nuclei and a pale cytoplasm. The syncytiotrophoblasts, which have large and irregular nuclei and a basophilic cytoplasm, grow around the clusters of cytotrophoblasts in a plexiform pattern resembling chorionic villi (65). The syncytiotrophoblasts have been reported to be strongly positive for human chorionic gonadotropin (HCG) antigen (66).

Metastatic carcinoma of the prostate to the skin is rare and usually occurs in the inguinal area, lower abdomen, or thighs, but distant sites of the scalp and face have been reported (13). Reactivity with prostate-specific antigen establishes the diagnosis (67).

Pancreatic cancer metastatic to the skin is rare, and the most common site is the umbilical area (13,68). Histologically, it usually represents an adenocarcinoma. Immunoperoxidase with a carbohydrate antigen (CA19-9) may be positive (68).

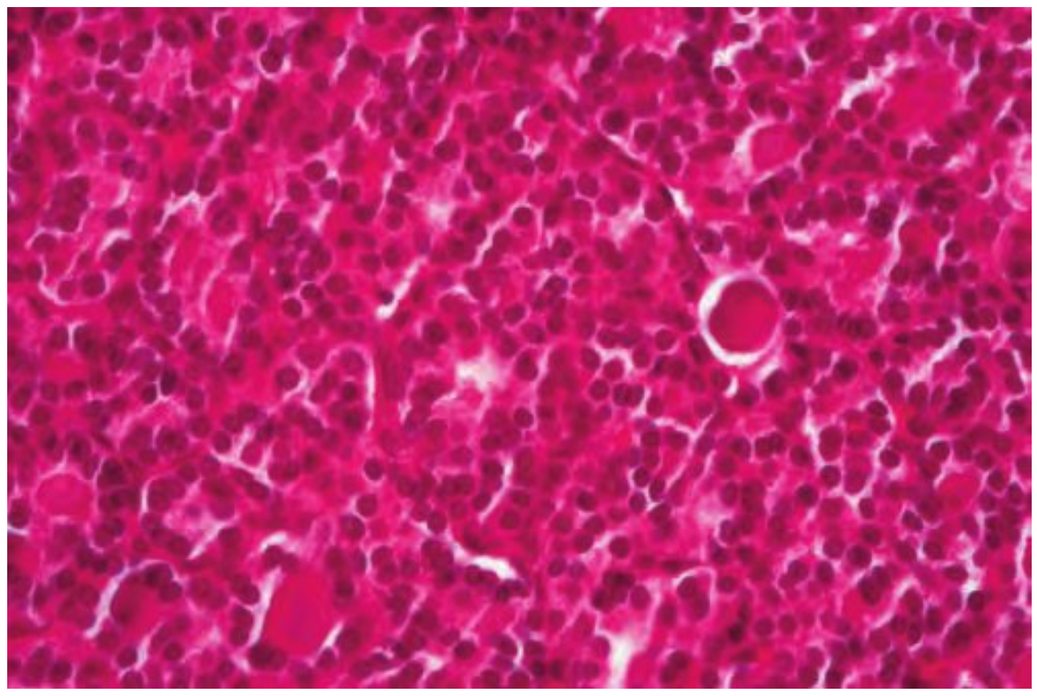


FIGURE 36-11. Metastatic carcinoma from thyroid. In this example of a metastatic follicular carcinoma, comprised of small epithelial cells forming ill-defined follicles containing pink colloid, there is little atypia, and the lesion could not be distinguished from a follicular adenoma except for its metastatic location.

This antigen is commonly present in adenocarcinoma of the pancreas but is not specific. It is usually negative in adenocarcinomas of the breast.

Cutaneous metastases from thyroid carcinoma tend to involve the abdominal skin or the head area (13). Medullary, follicular, and papillary thyroid carcinomas may retain their histologic patterns in the cutaneous metastases (Fig. 36-11). Immunoperoxidase studies often show a positive reaction to antithyroglobulin antibody (69) and TFF-1 (42).

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Electron Micrographs

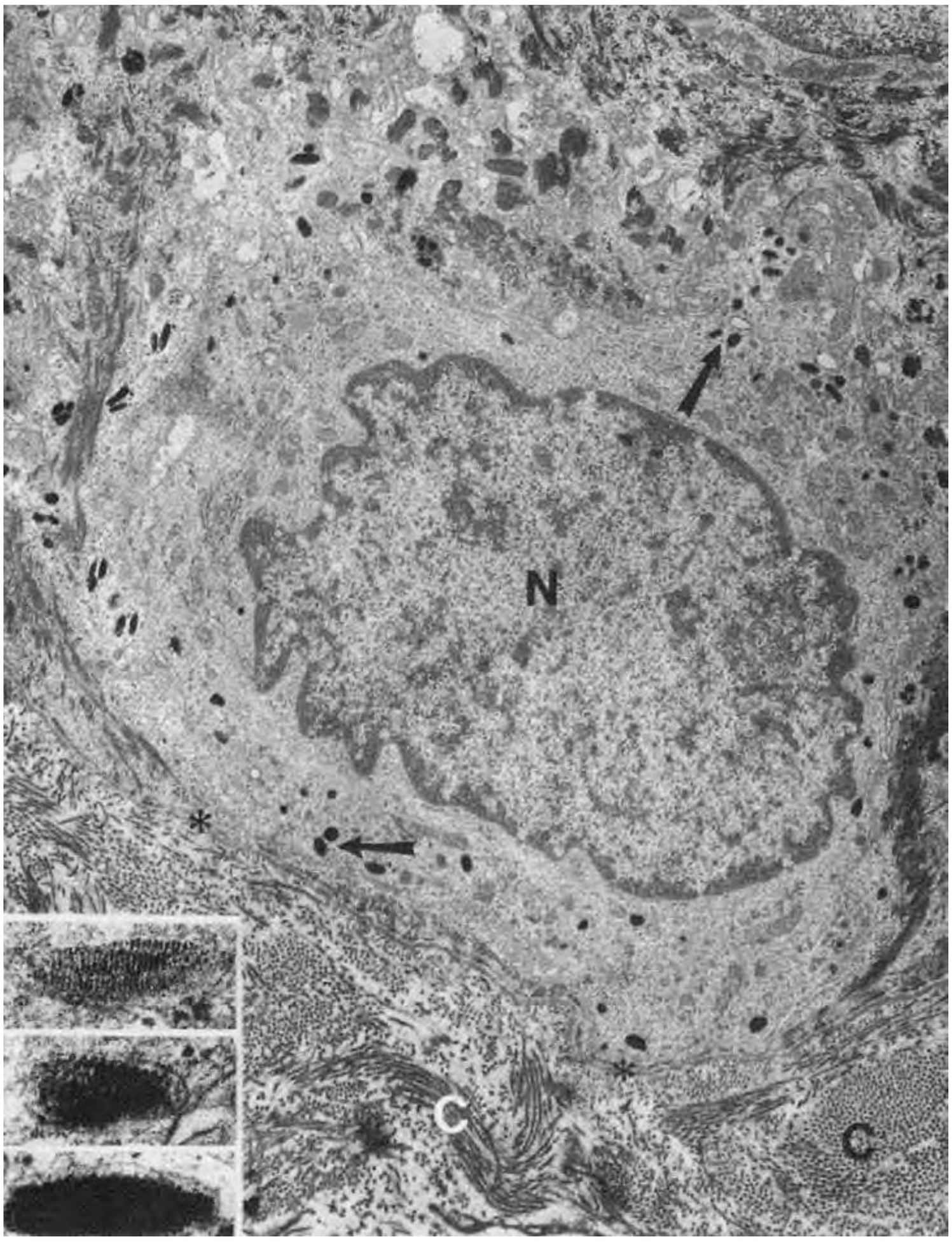


FIGURE EM-1. Melanocyte. Inset: Melanosomes. N, nucleus of melanocyte; arrows, melanosomes; C, collagen in the dermis; asterisk, basal lamina. Insets: Melanosomes in different stages of development: stage II (upper), stage III (middle), and stage IV (lower).

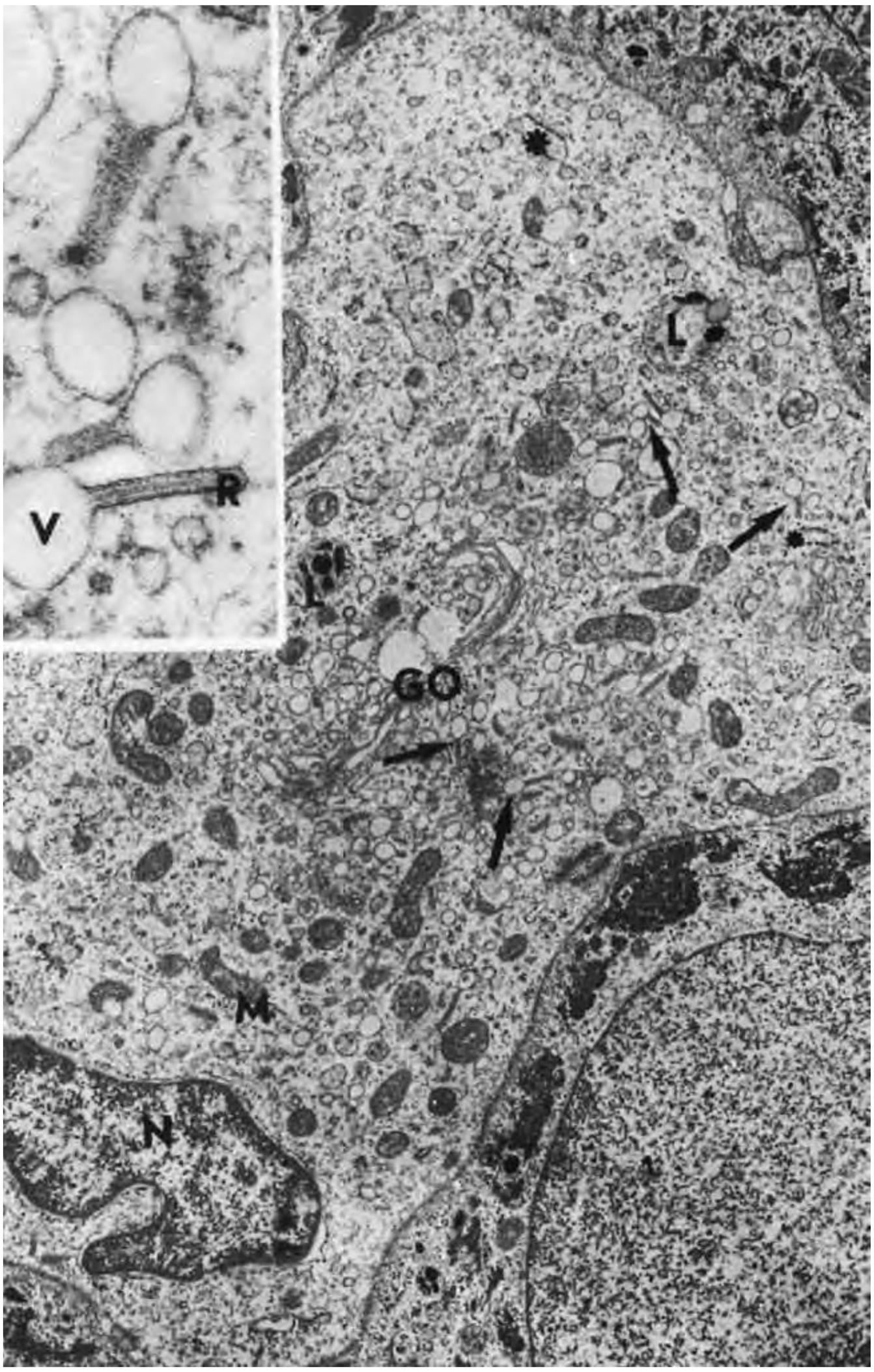


FIGURE EM-2. Langerhans cell. Inset: Langerhans granules. N, nucleus of Langerhans cell; L, lysosomes containing melanosomes; GO, Golgi complex; M, mitochondrium; asterisk, rough endoplasmic reticulum; arrows, Langerhans granules. Inset: Langerhans granules at higher magnification consisting of a vesicle (V) and a rod (R), both giving the appearance of a tennis racquet.

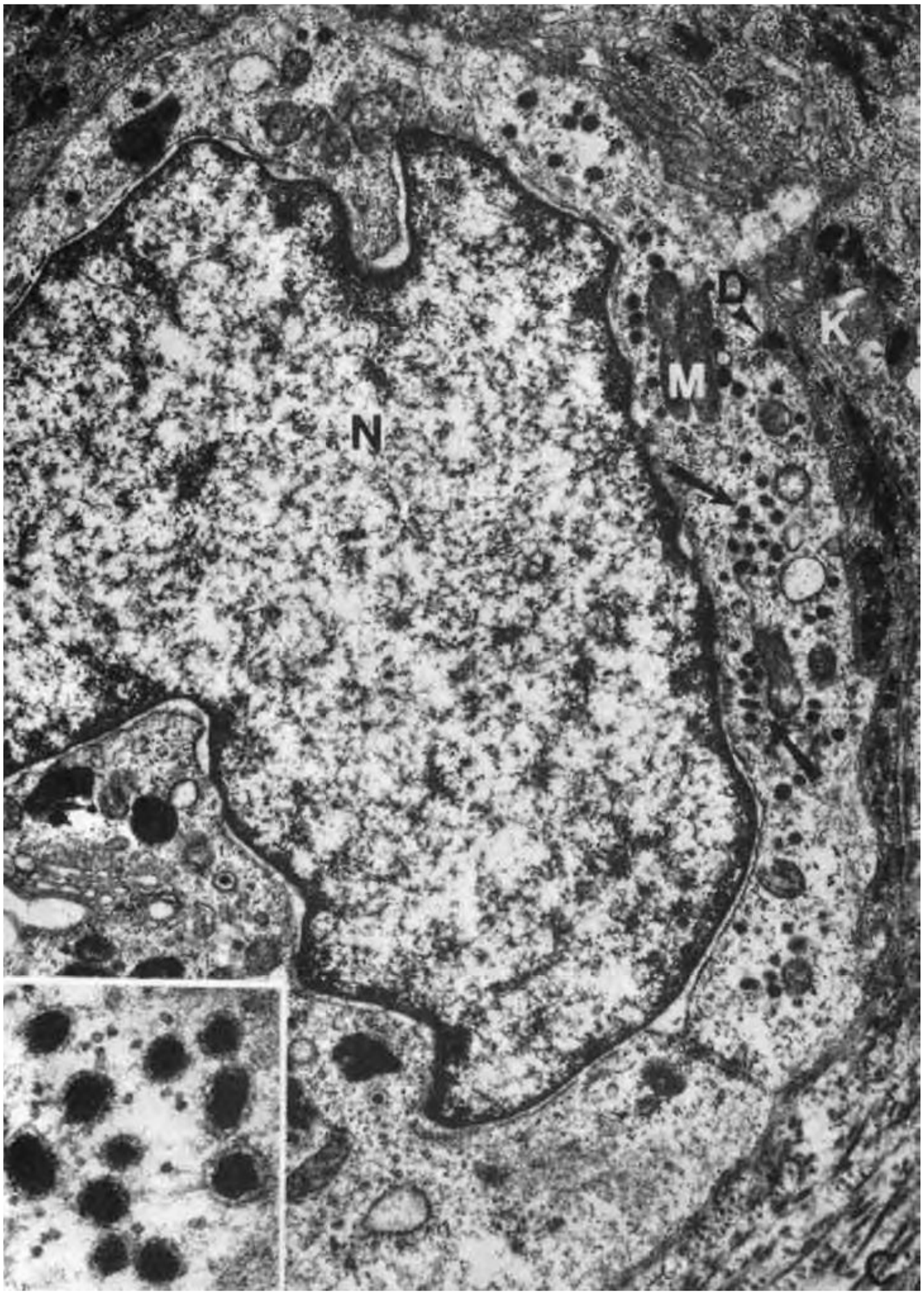


FIGURE EM-3. Merkel cell. Inset: Merkel granules. N. nucleus of Merkel cell; asterisk, on basal lamina; M, mitochondria; arrows, specific granules of the Merkel cell; D with pointer, desmosome between Merkel cell and keratinocyte (K); C, collagen with cross striation. Inset: Specific membrane-bound granules at higher magnification.

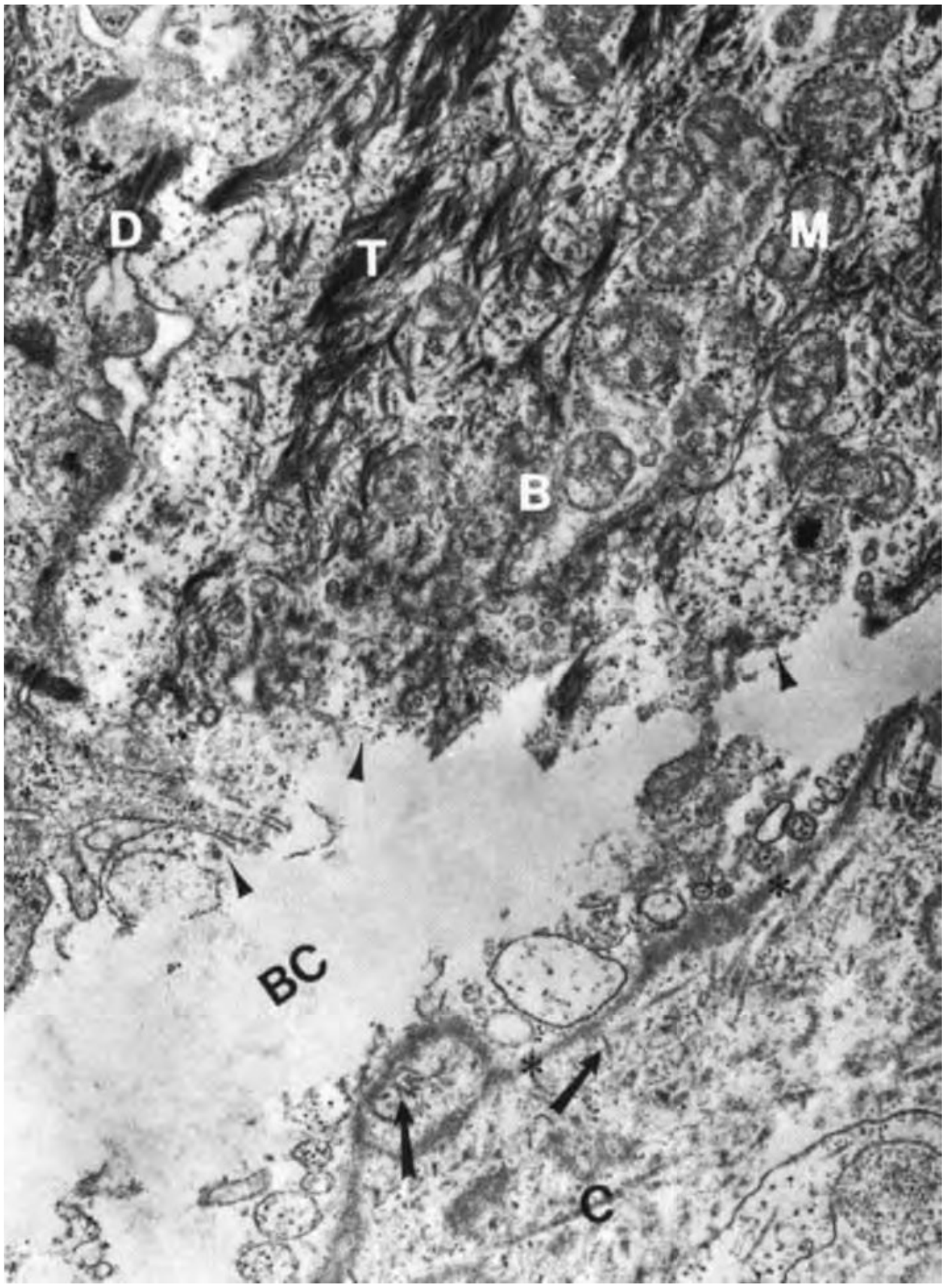


FIGURE EM-4. Epidermolysis bullosa simplex. The blister formed as the result of degenerative, cytolytic changes in the basal cells (B). The bulla cavity (BC) is situated above the basement membrane (asterisk). The basal cells are severely damaged, lacking a plasma membrane (pointers). T, tonofilaments; M, mitochondria; D, desmosome.

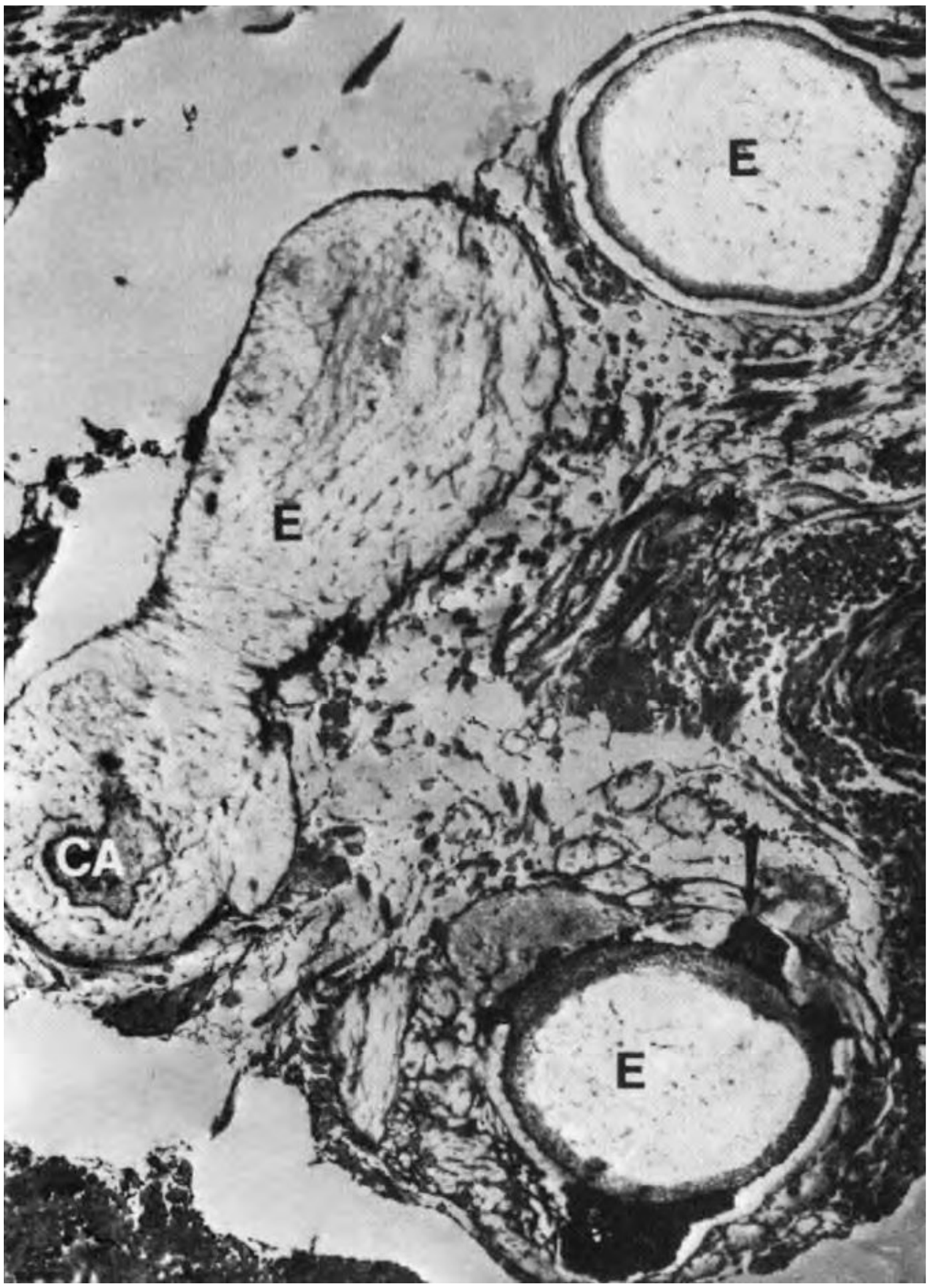


FIGURE EM-5. Pseudoxanthoma elasticum. The elastic fibers (E) are bizarrely shaped. Calcium (CA, arrows) is deposited on or around elastic fibers.

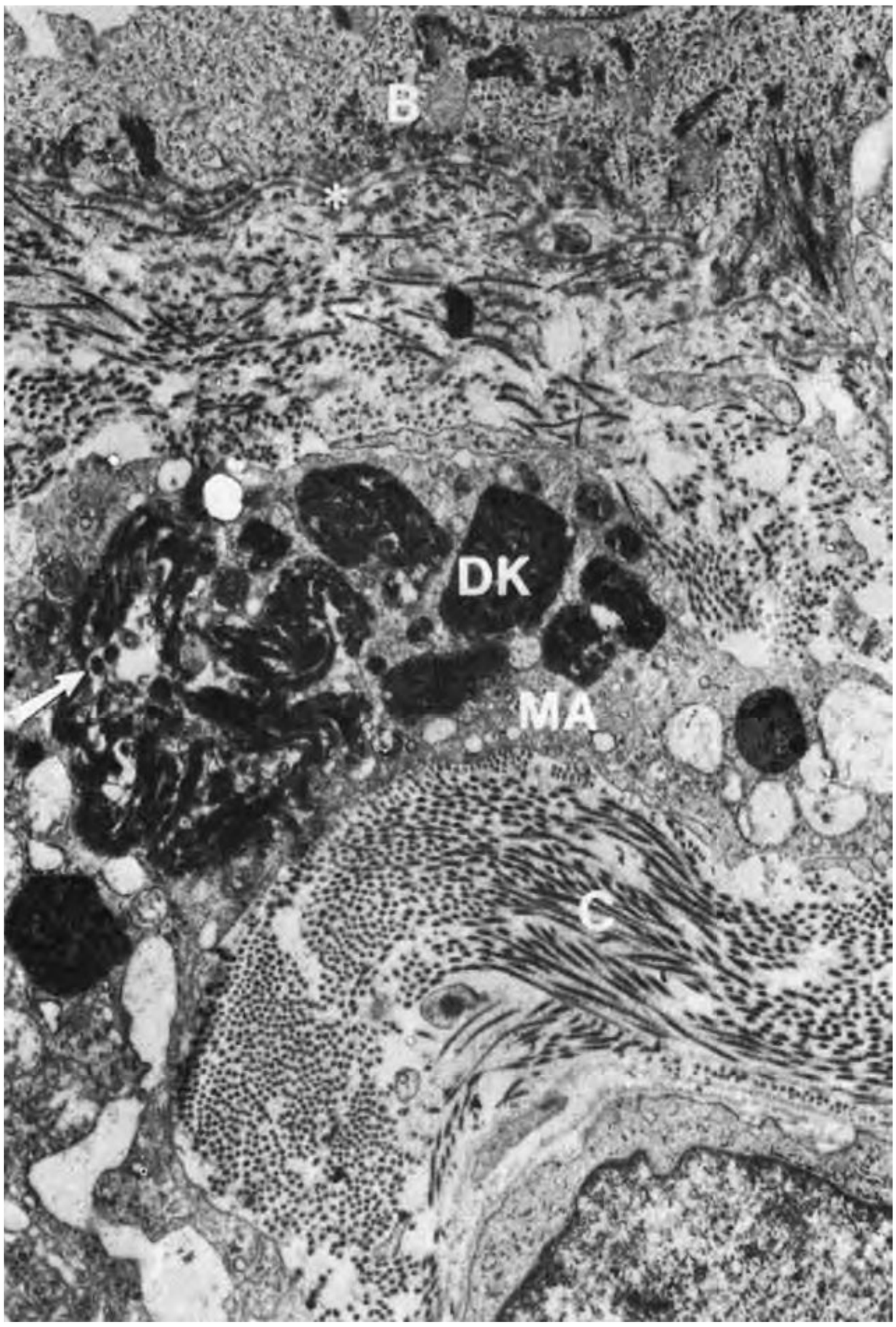


FIGURE EM-6. Incontinentia pigmenti. In this disease, dyskeratotic cells are found in the epidermis. Macrophages migrate into the epidermis, phagocytize these dyskeratotic cells as well as melanosomes, and subsequently return to the dermis. MA, macrophage containing dyskeratotic material (DK) and melanosomes (arrow); B, basal cell; asterisk, basal lamina; C, collagen.

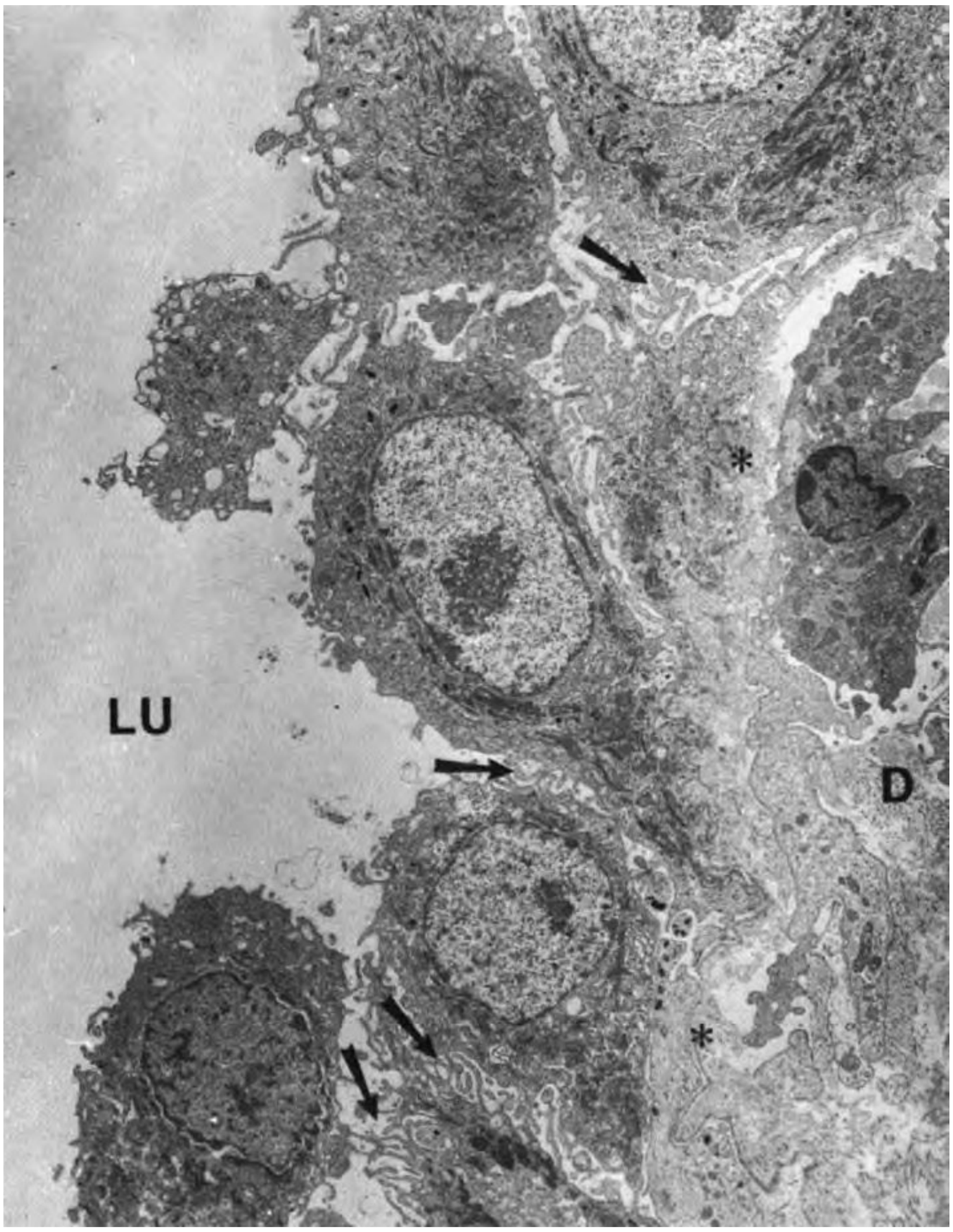


FIGURE EM-7. Pemphigus vulgaris, tombstone row. The dissolution of the intercellular cement led to the formation of a blister. At the base of the blister, one or two rows of keratinocytes are left. The cohesion of the basal cells with the dermis is well preserved. LU, blister lumen; asterisks, basement membrane; arrows, microvilli of keratinocytes; D, dermis.

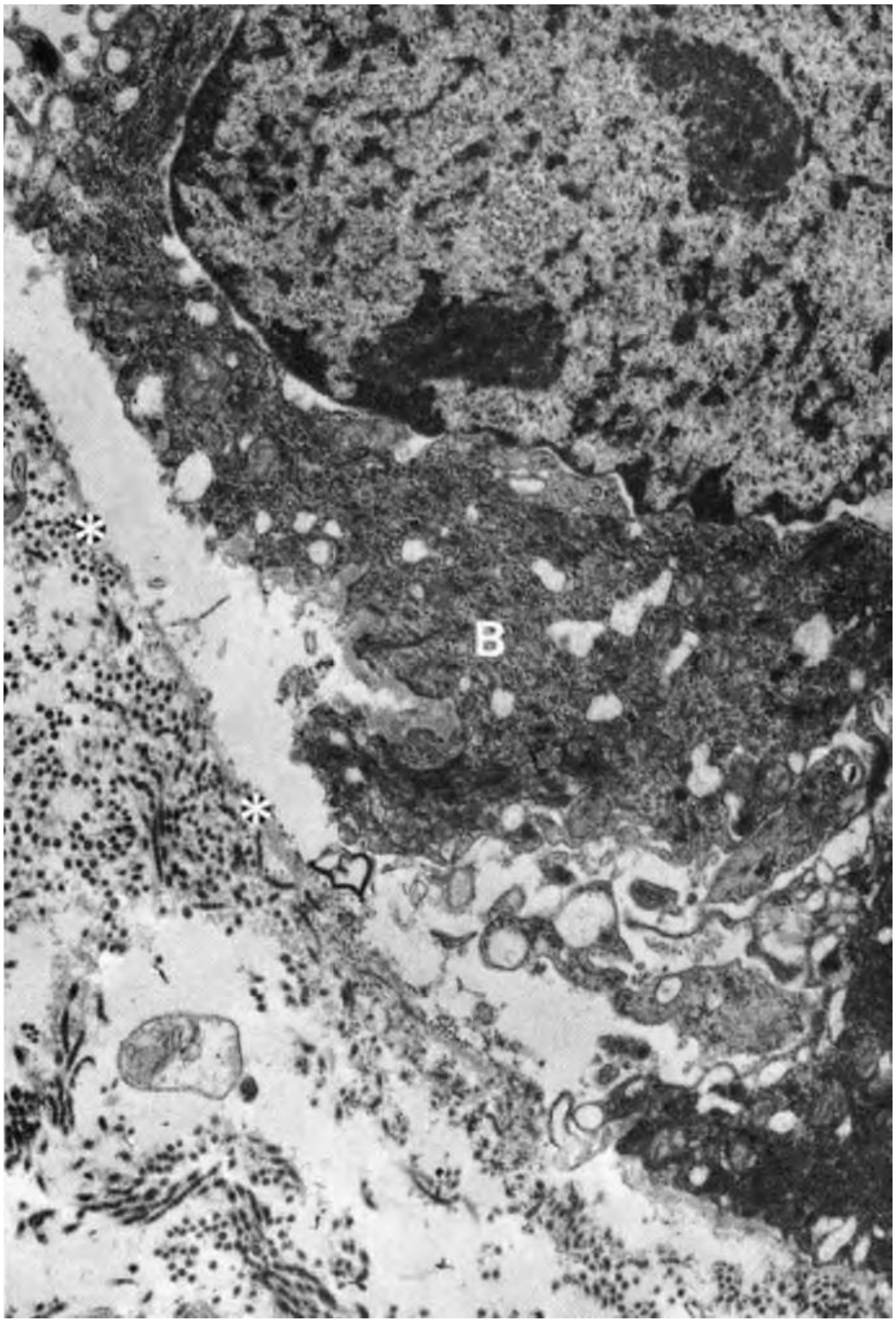


FIGURE EM-8. Bullous pemphigoid, noninflamed type. In this type of bullous pemphigoid, the blister forms between the basal cell (B) and the basement membrane (asterisks).

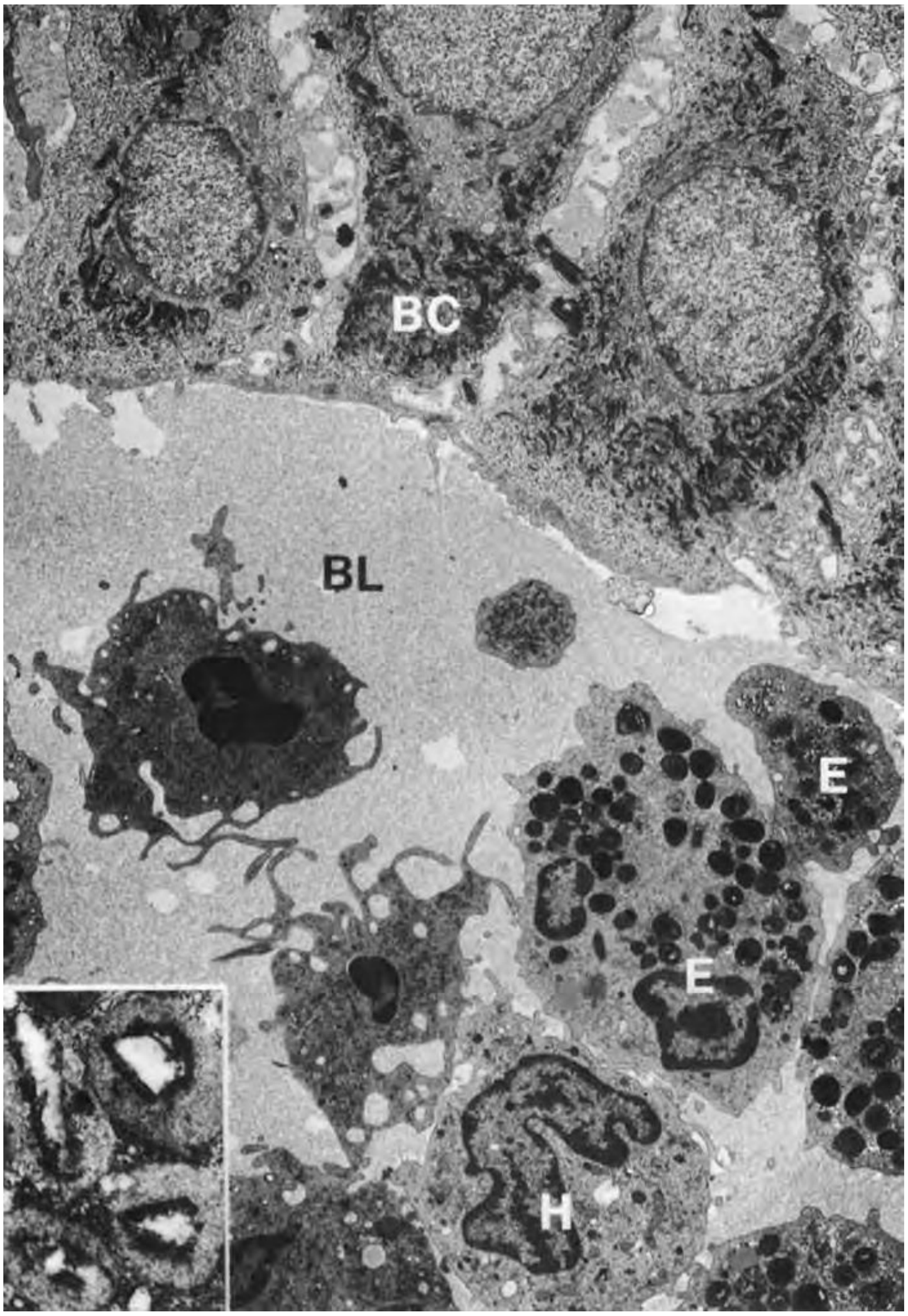


FIGURE EM-9. Bullous pemphigoid inflamed type. Inset: Granules of eosinophils. The blister (BL) contains several histiocytes (H) and eosinophils (E). The basement membrane has disappeared. The basal cells (BC) at the top of the blister are well preserved. Inset: Eosinophilic granules at higher magnification show a "crystal" at their center.

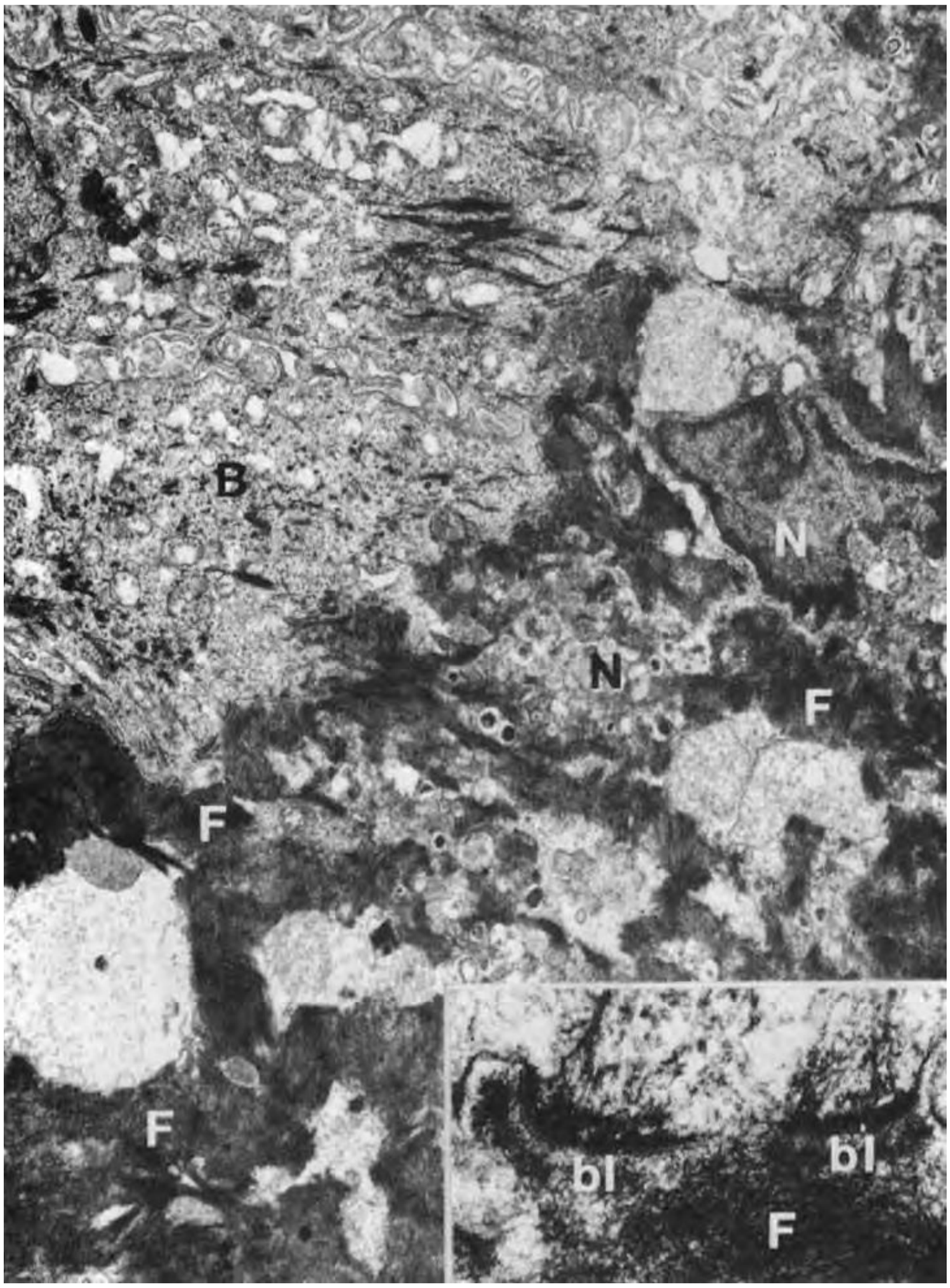


FIGURE EM-10. Dermatitis herpetiformis. Inset: Fibrin. The dermal papillae contain abundant amounts of fibrin (F). Between the meshes of fibrin, fragments of neutrophilic leukocytes (N) can be seen. B, basal cell. Inset: The fibrin (F) is attached to the dermal side of the basement membrane or basal lamina (bl). The basement membrane shows discontinuities.

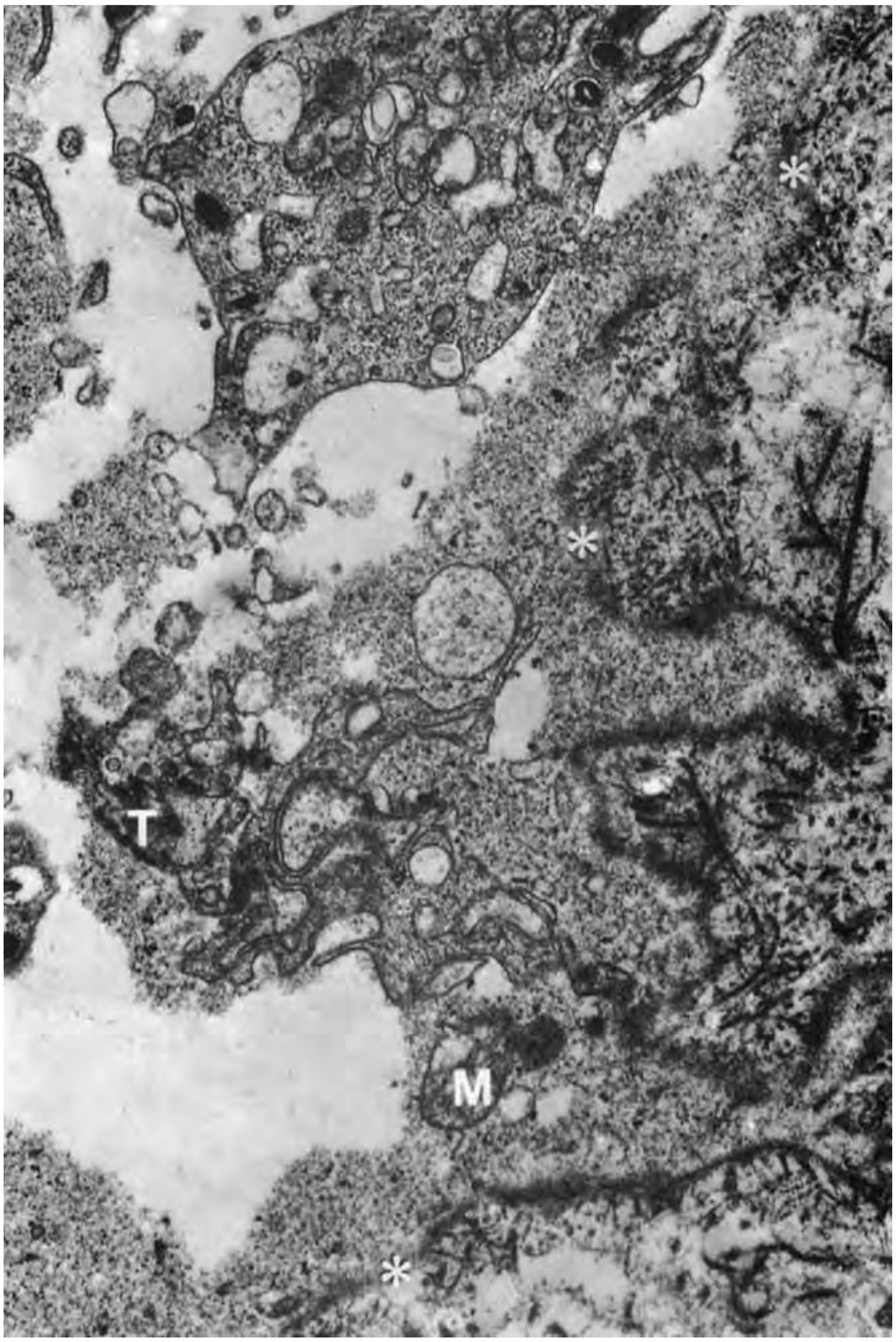


FIGURE EM-11. Herpes gestationis. In this disease, the blister forms either between basal cells and the basement membrane or, subsequent to dissolution of basal cells, between squamous cells and the basement membrane. A disintegrated basal cell containing tonofilaments (T) and mitochondria (M) and the basement membrane (asterisks) form the floor of the blister.

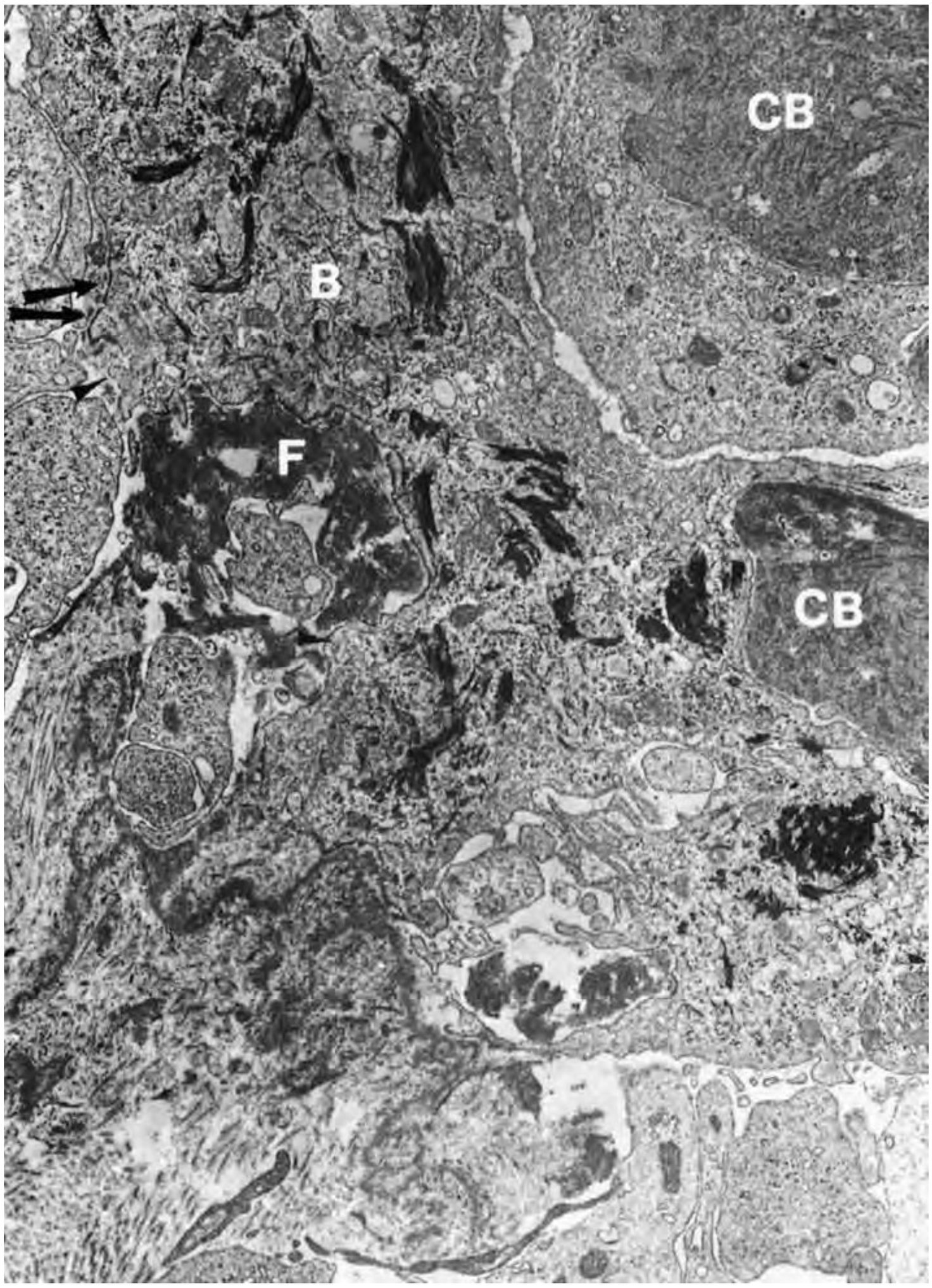


FIGURE EM-12. Lichen planus. The basement membrane is split up in some areas (arrows) and has disappeared in others (pointers). The lower epidermis contains colloid bodies (CB) consisting of numerous filaments and remnants of organelles. F, fibrin beneath the basal cell (B).



FIGURE EM-13. Solar degeneration. The elastic fiber contains in its amorphous matrix (asterisk) numerous electron-dense inclusions (/). Extensive amorphous material (A) can be seen around the elastotic fiber and among the collagen fibrils (C).

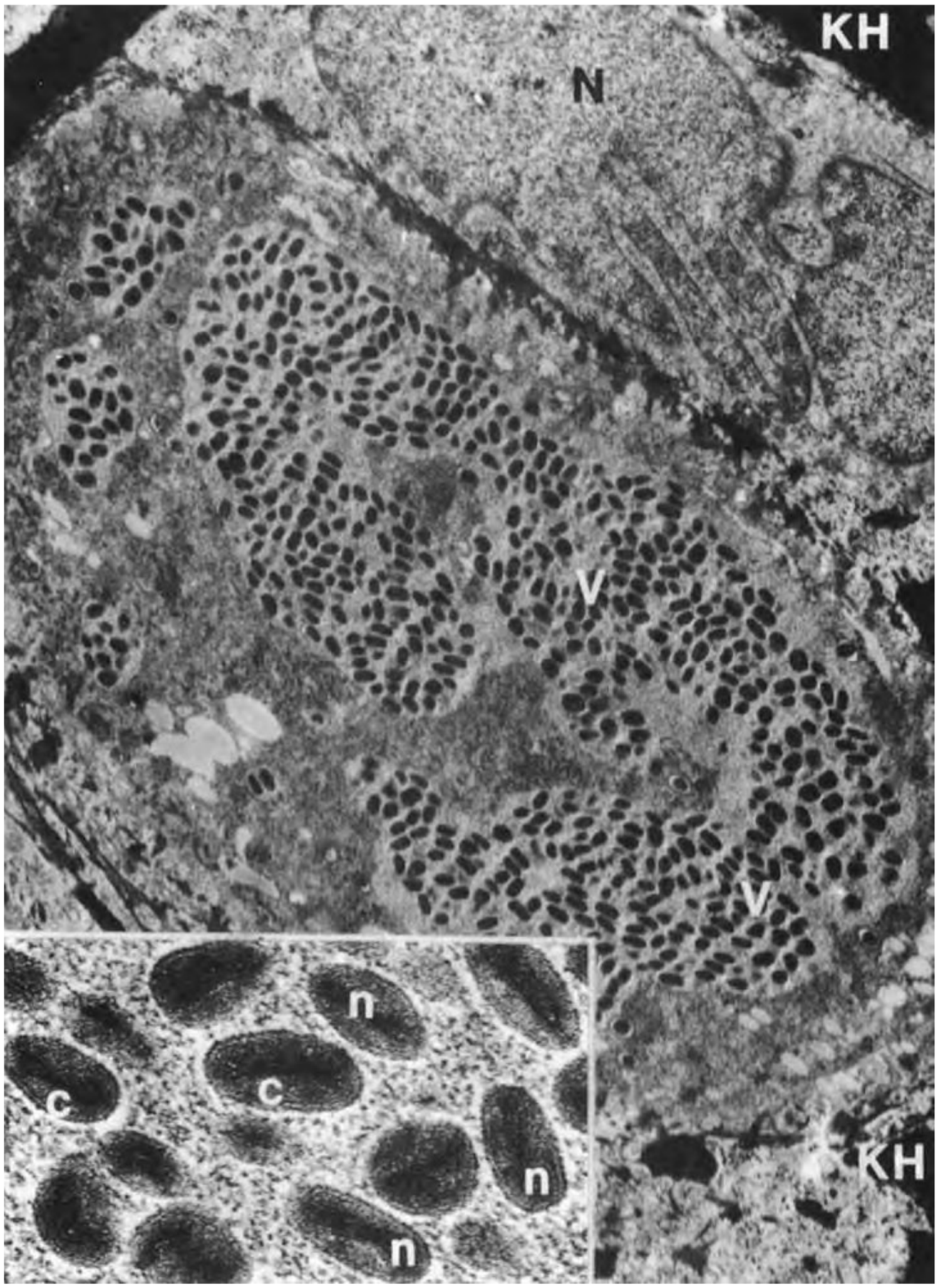


FIGURE EM-14. Molluscum contagiosum. Inset: High magnification of viruses. The granular cell contains an inclusion body consisting of numerous molluscum contagiosum viruses (V). The nucleus (N) of the cell has been displaced to the periphery of the cell. KH, keratohyaline granules. Inset: The virus consists of the dumbbell-shaped nucleoid (n) surrounded by the capsid (c).

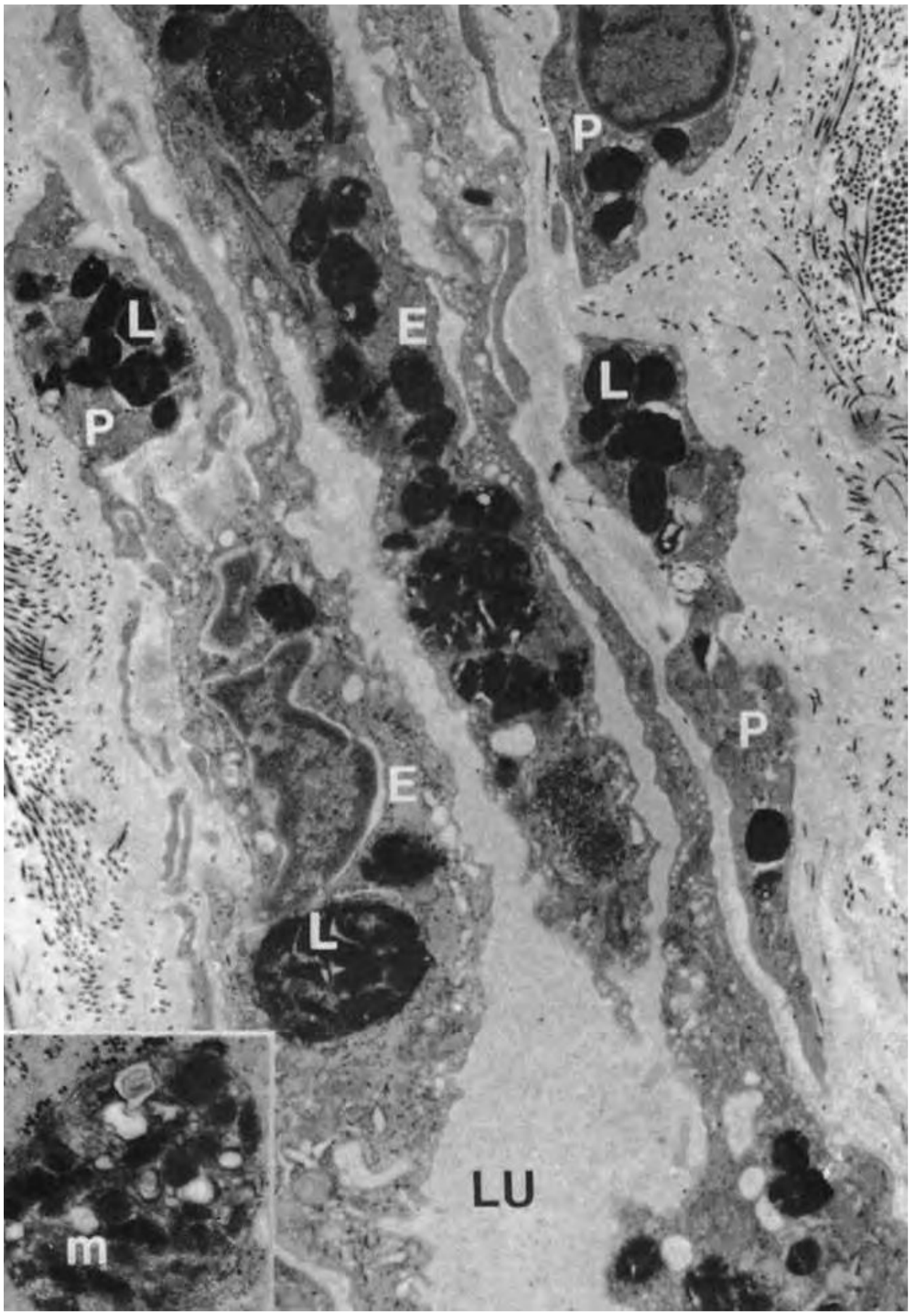


FIGURE EM-15. Angiokeratoma corporis diffusum (Fabry's disease). Inset: Lysosomal residual body. Endothelial cells (E) and pericytes (P) contain lipid deposits (L) within greatly enlarged lysosomes. LU, lumen of capillary. Inset: A large matured lysosome as a residual body shows laminated myelin figures (m).

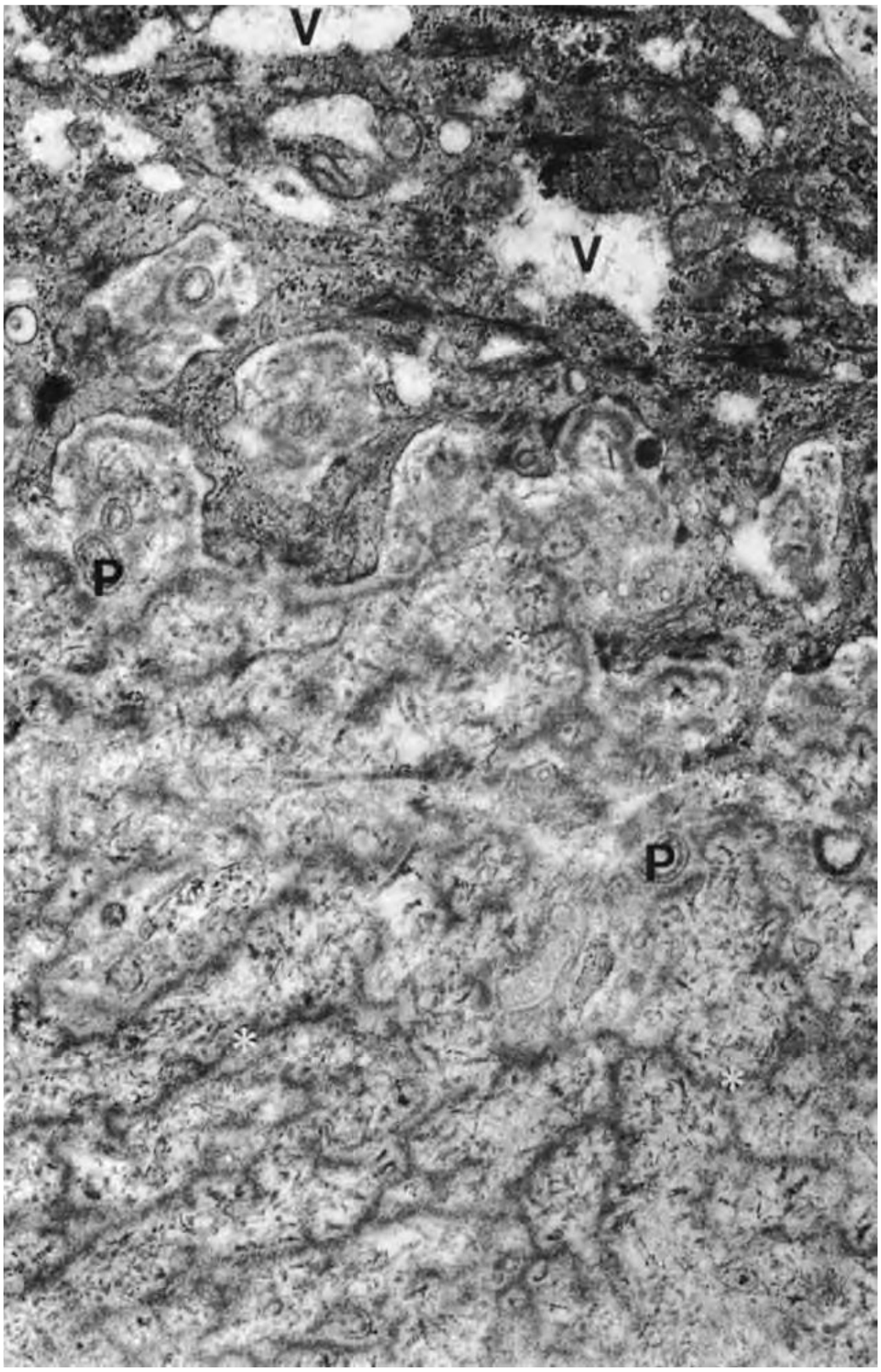


FIGURE EM-16. Discoid lupus erythematosus. The basal cell contains several vacuoles (V), which ultimately may cause disintegration of the cell. Many cross-sectioned projections (P) of the basal cell into the dermis can be seen, as can a greatly increased amount of basal lamina material (asterisks).

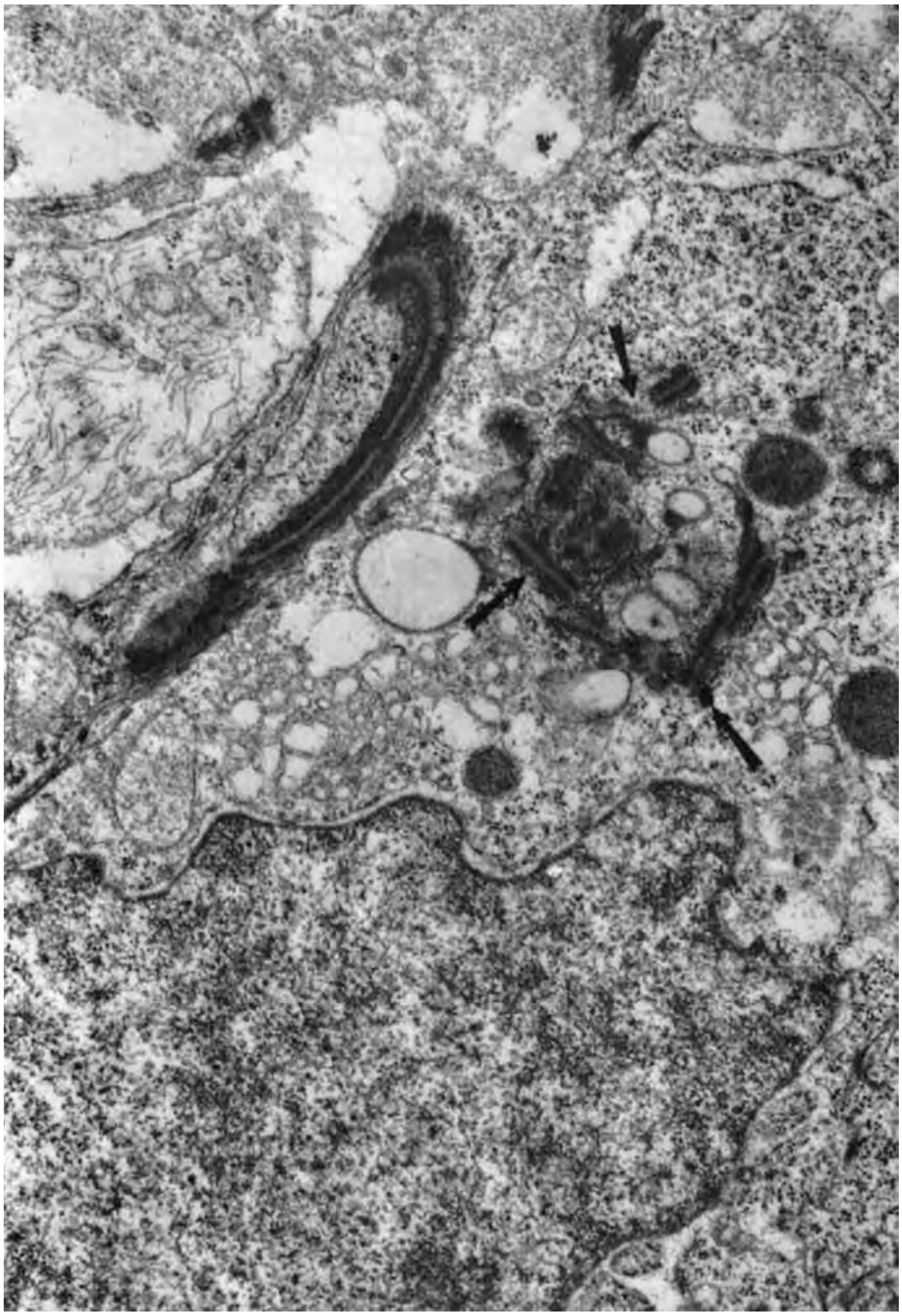


FIGURE EM-17. Squamous cell carcinoma. Desmosomes attached to tonofilaments (arrows) can be seen within the cytoplasm of the tumor cell.

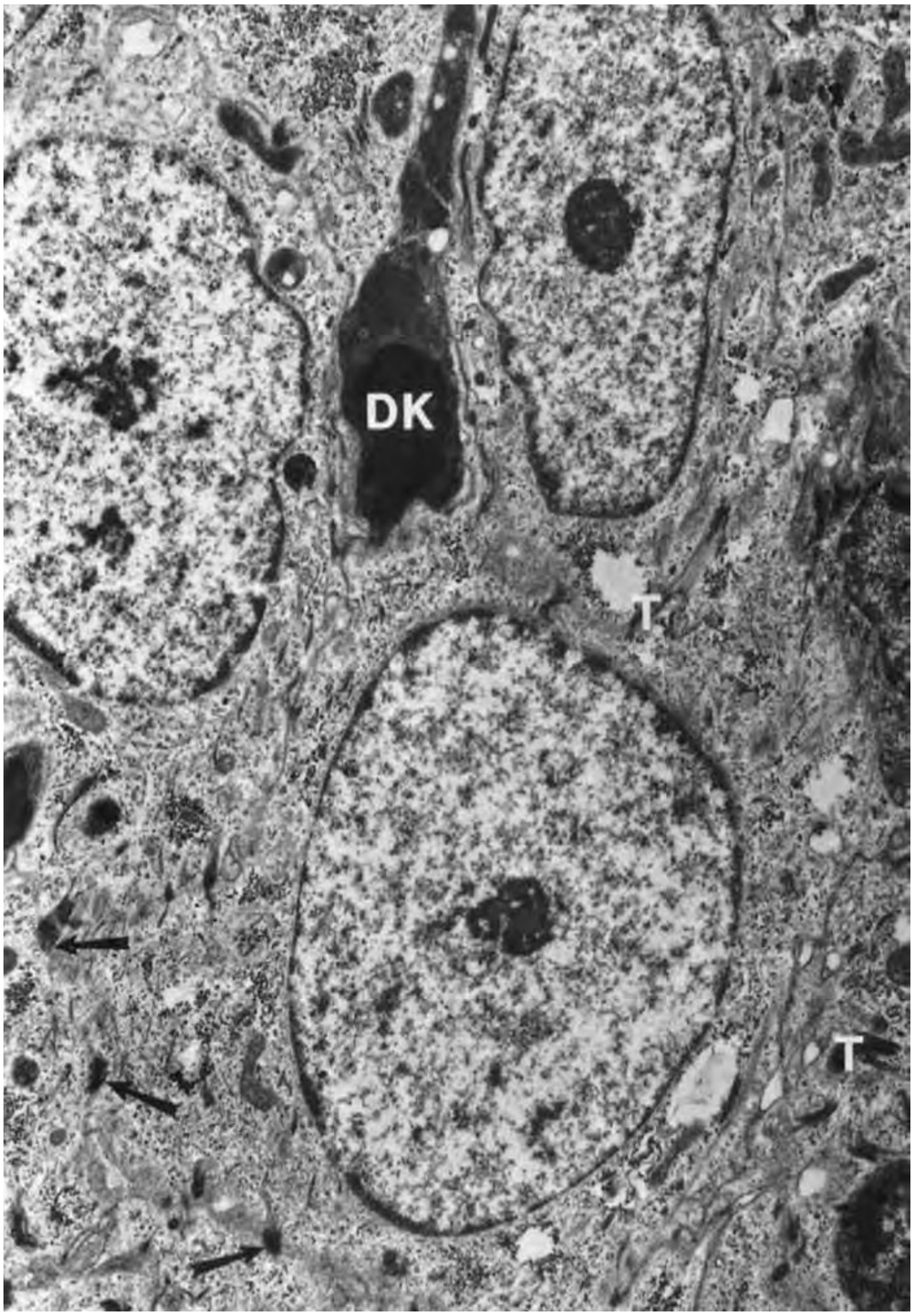


FIGURE EM-18. Basal cell epithelioma. The cells show evidence of keratinization. In addition to tonofilaments (T) and desmosomes (arrows), some dyskeratotic material (DK) is present.

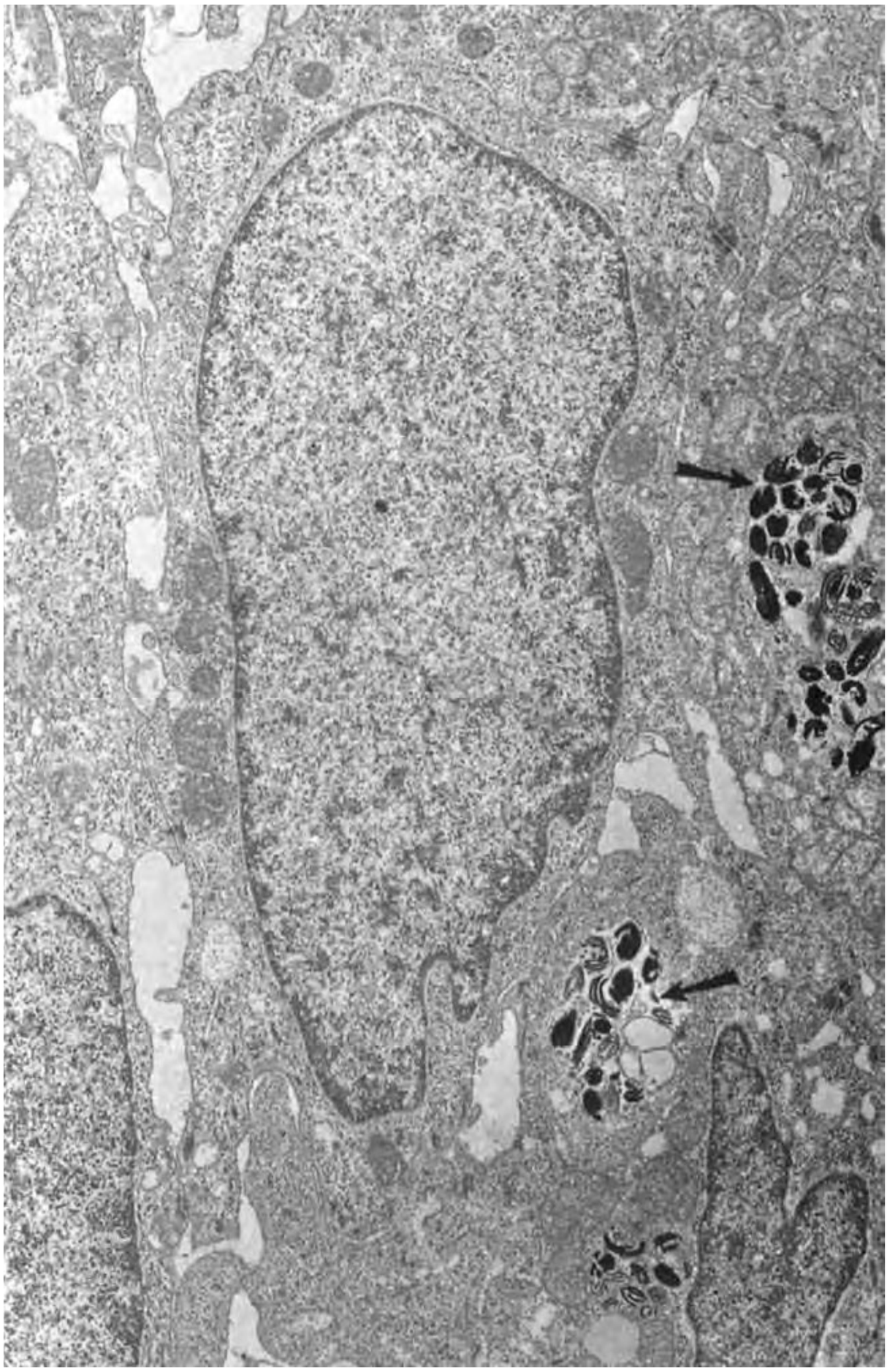


FIGURE EM-19. Pigmented basal cell carcinoma. Some of the tumor cells contain melanosome complexes located within lysosomes (arrows).

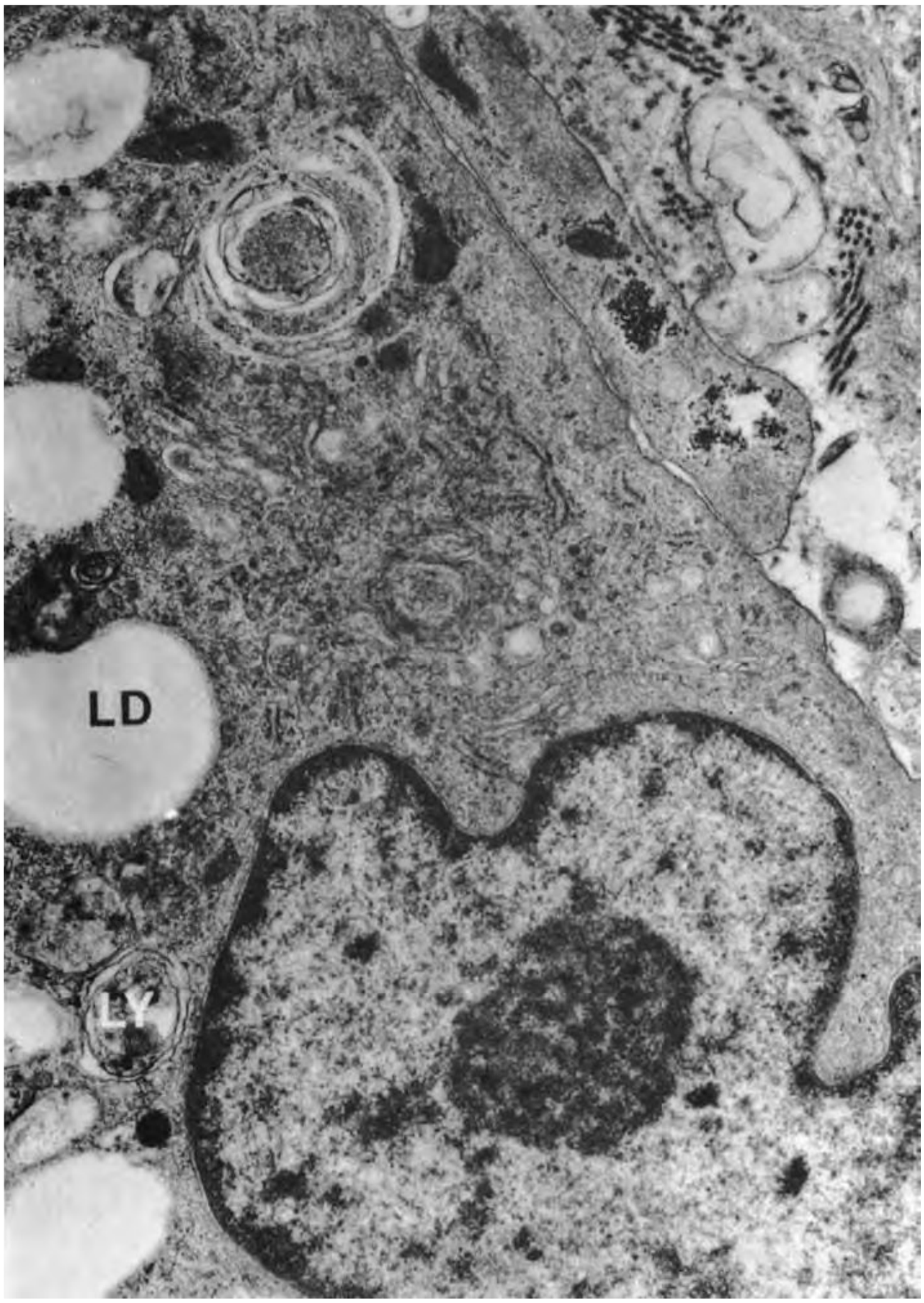


FIGURE EM-20. Dermatofibroma. The essential cells are fibroblasts, which, in addition to producing collagen, are engaged in phagocytosis and storage of lipid. LY, lysosome; LD, lipid droplets. (Courtesy of Dr. B. Mihatsch-Konz.)

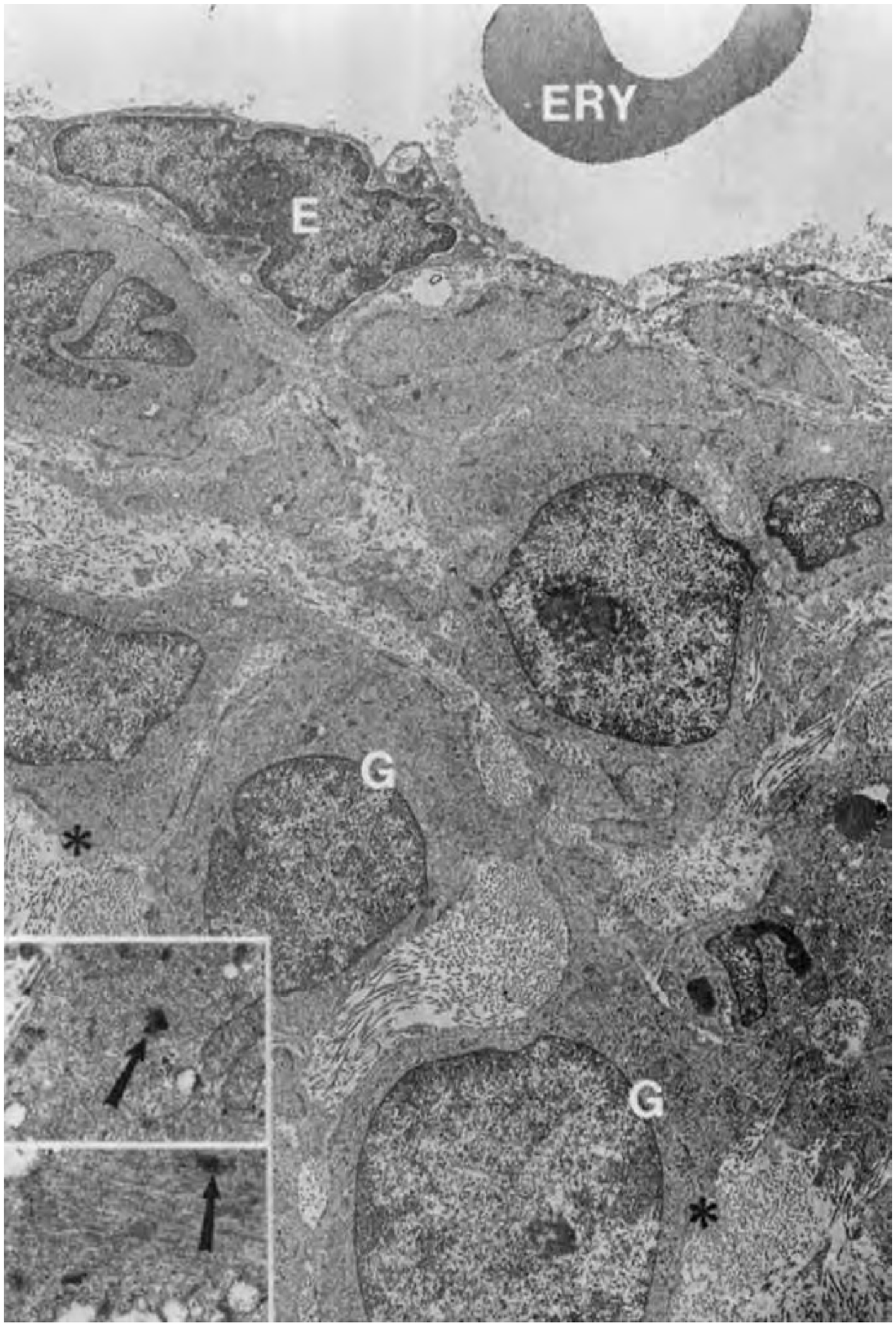


FIGURE EM-21. Glomus tumor. Inset: Myofilaments. The glomus cells are smooth muscle cells. Each glomus cell is surrounded by a basal lamina (asterisk). E, endothelial cell of capillary; G, glomus cell; ERY, erythrocyte within capillary lumen. Insets: The upper inset shows the myofilaments in cross-section, the lower inset in longitudinal section. Arrows point to so-called dense bodies.

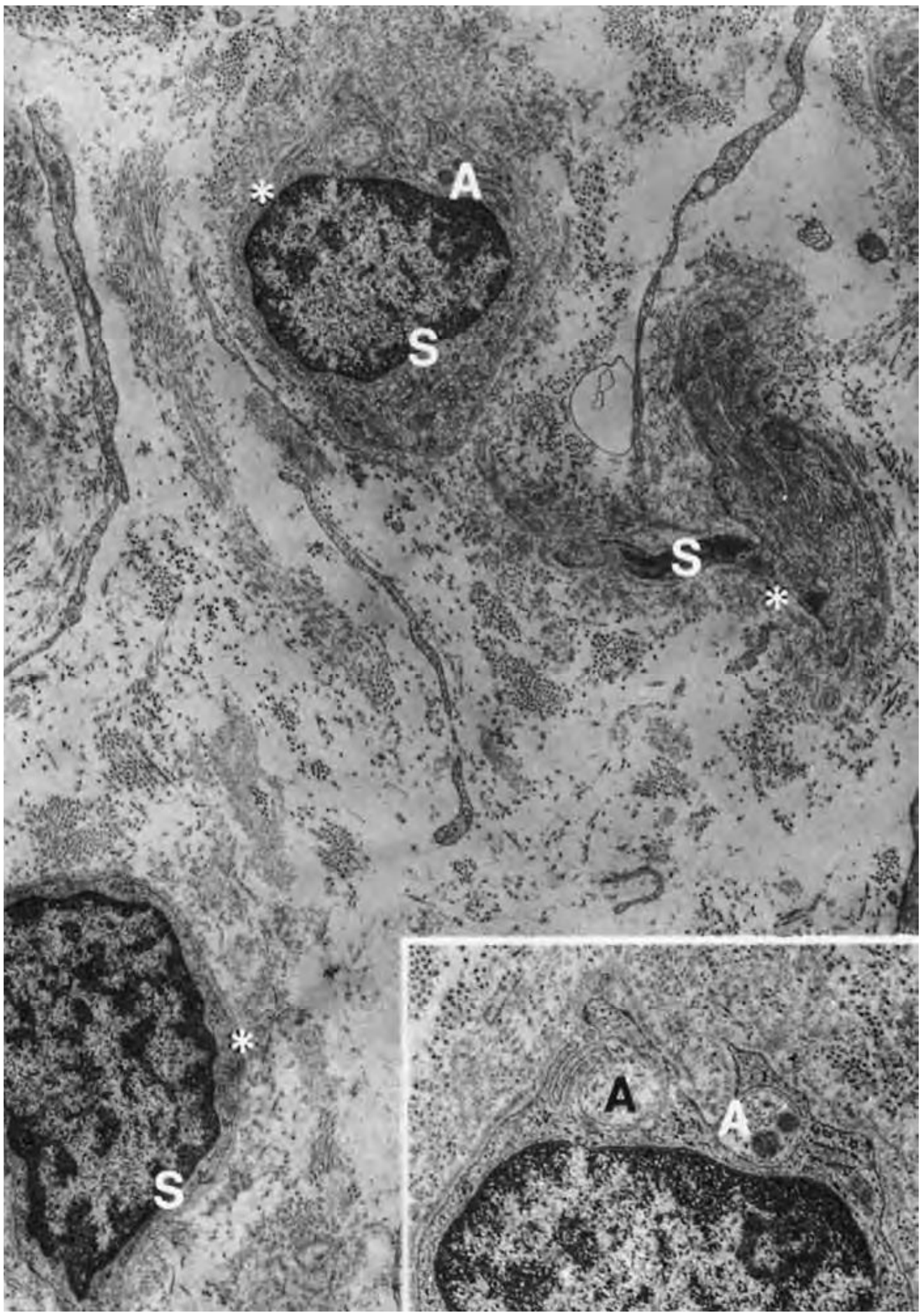


FIGURE EM-22. Neurofibroma. Inset: Axons in Schwann cell. The main cell type is the Schwann cell (S). Each cell is surrounded by a basal lamina (asterisks). Schwann cells contain axons (A) in their cytoplasm. Inset: Two axons (A) of the upper Schwann cell are shown at higher magnification.

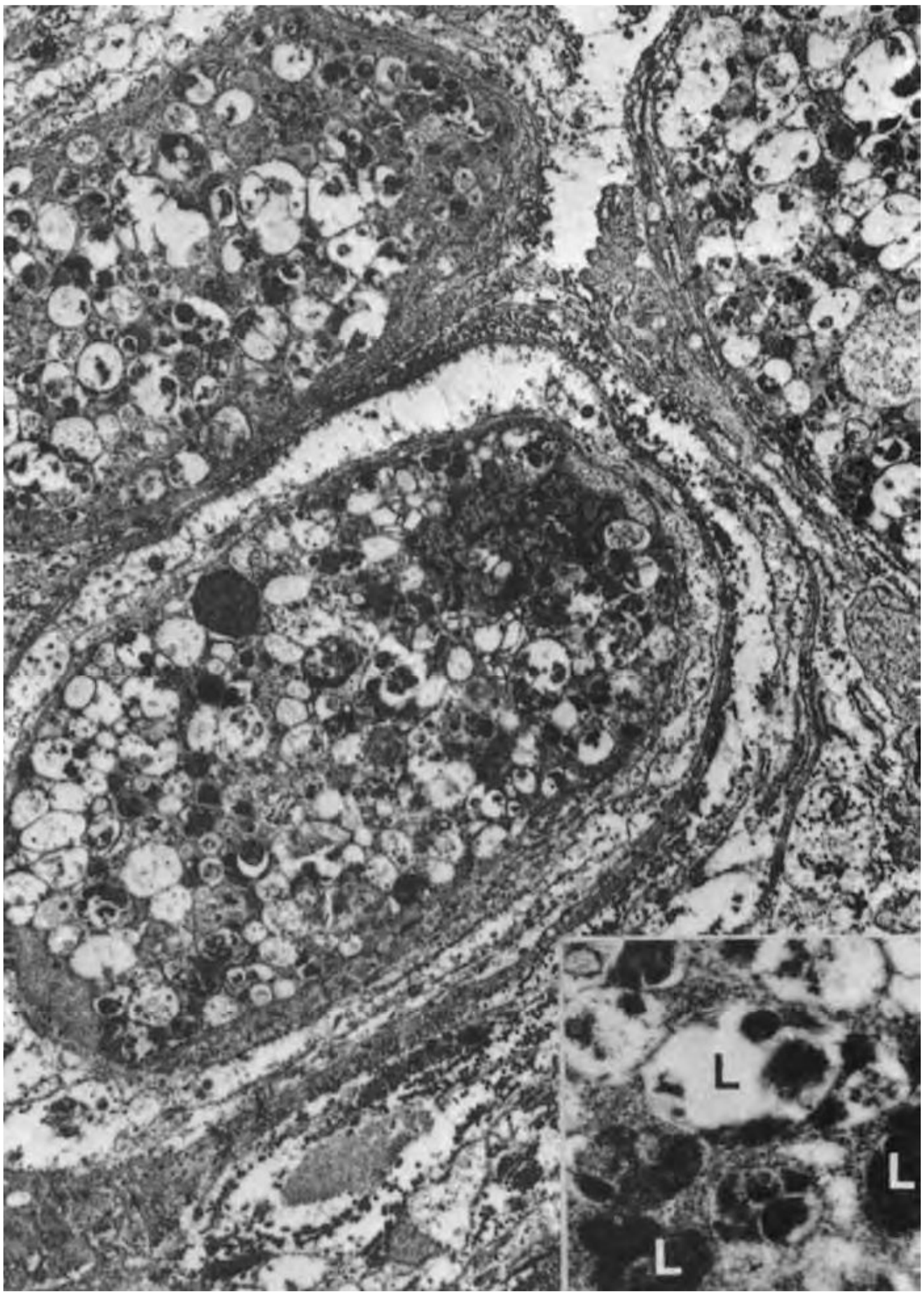


FIGURE EM-23. Granular cell tumor. Inset: Cytoplasmic granules. The cells contain numerous cytoplasmic granules, which are lysosomes. Inset: The lysosomes (L) are shown at higher magnification.

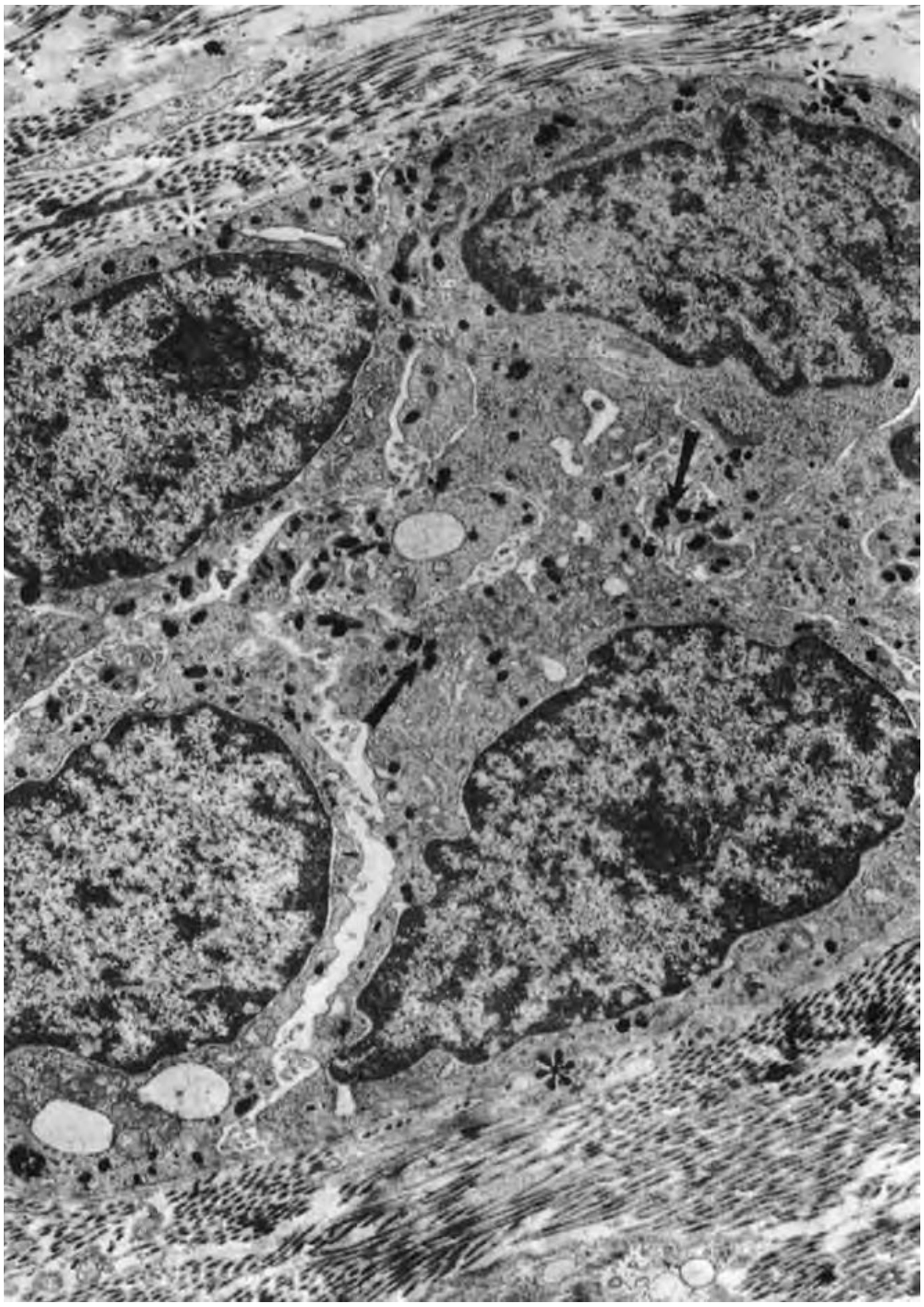


FIGURE EM-24. Intradermal nevus cell nest. The nevus cell nest is surrounded by a basal lamina (asterisk). There are no desmosomes between adjacent nevus cells. The nevus cells contain numerous melanosomes (arrows).

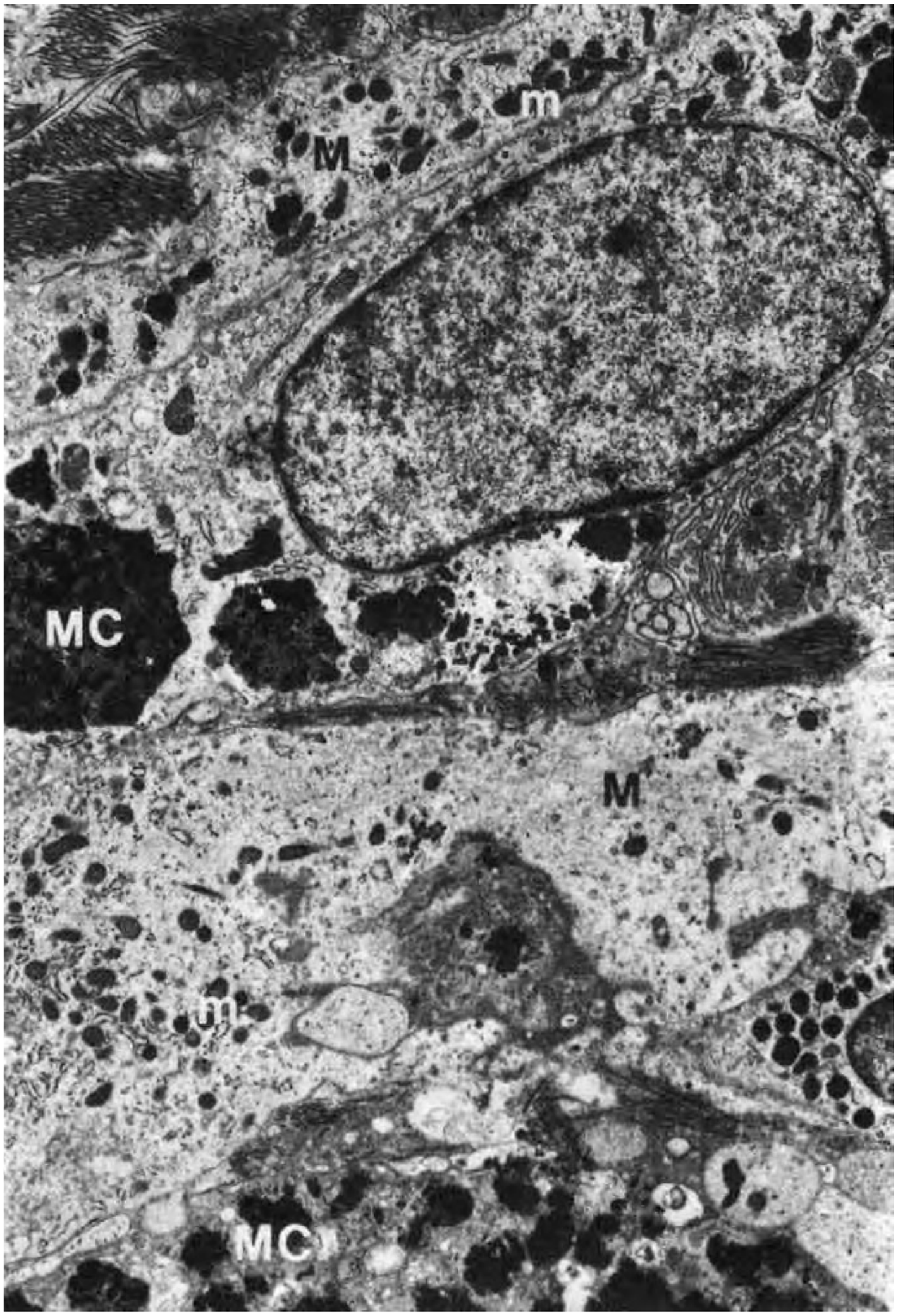


FIGURE EM-25. Malignant melanoma. In addition to malignant spindle-shaped melanocytes (M) containing an abundance of melanosomes (m), melanophages with melanosome complexes (MC) are found.

INDEX

Page number followed by "*f*" indicate figure; those followed by "*t*" indicate table.

AA. *See* Alopecia areata
AA amyloidosis. *See* Secondary systemic amyloidosis
AAT. *See* Alpha-1 antitrypsin
ABCD criteria
  for melanoma diagnosis, 740
  for nodular melanoma, 750
Abnormal apoproteins, 683
Abscess
  of acanthamoebiasis, 625
  of blastomycosis-like pyoderma, 546
  of botryomycosis, 573, 573*f*
  of chromomycosis, 607, 607*f*
  of coccidioidomycosis, 608–609
  of eumycetoma, 614
  of follicular occlusion triad (hidradenitis suppurativa, acne conglobata, perifolliculitis capitis abscedens et suffodiens), 544–545
  histopathology of, 117, 131
  injection, 558, 558*f,* 567–568, 568*f*
  of paracoccidioidomycosis, 606, 606*f*
  of subcutaneous phaeohyphomycosis, 602
Abt-Letterer-Siwe disease. *See* Acute disseminated LCD
Abtropfung, of compound nevus, 713
Acanthamoeba infection, 625, 625*f*
Acanthamoebiasis, 625, 625*f*
  differential diagnosis of, 625
  histopathology of, 625
Acantholysis, 11, 235
  acantholytic actinic keratosis and, 810
  Darier's disease and, 151, 794
  familial benign pemphigus with, 151
  irritated seborrheic keratosis and, 795
  pemphigus and, 245, 249
  pemphigus foliaceus and, 252
  pemphigus vegetans and, 250
  subcorneal pustular dermatosis and, 268
Acantholytic acanthoma, 794
  histopathology of, 794
Acantholytic actinic keratosis, 810, 810*f*
  histopathology of, 113–114
Acantholytic disorders, 85
  intraspinous keratinocyte separation
    acantholytic, 92, 92*f,* 113–114
    spongiotic, 92, 92*f,* 113
  subcorneal or intracorneal separation, 92, 92*f,* 112–113
  subepidermal vesicular dermatitis, 93, 93*f,* 114–115
  suprabasal keratinocyte separation, 93, 93*f,* 114
Acantholytic dyskeratosis, 794, 794*f*
  histopathology of, 794, 794*f*
Acantholytic dyskeratotic epidermal nevus, Darier's disease v., 149–150
Acantholytic keratinocytes, pemphigus vulgaris and, 247–248
Acantholytic solar keratosis, histopathology of, 93, 93*f*
Acantholytic squamous cell carcinoma, 821
  histopathology of, 114, 819*f,* 821
  pathogenesis of, 821
Acanthoma fissuratum, 357, 357*f*
  differential diagnosis of, 357
  histopathology of, 357, 357*f*
Acanthopodia, 625
Acanthosis
  acanthoma fissuratum and, 357
  with acral fibrokeratoma, 989
  of arsenical keratosis, 817
  with Becker's melanosis, 706
  Bowen's disease, 814
  of condyloma acuminatum, 654, 655*f*
  with erythema ab igne, 348
  Fox-Fordyce disease and, 492
  graft-*versus*-host disease and, 271
  granuloma gluteale infantum and, 381
  halogenodermas and, 326
  hyperkeratosis lenticularis perstans and, 398
  in hyperkeratotic seborrheic keratosis, 798
  ILVEN and, 194
  incontinentia pigmenti and, 161
  keratosis lichenoides chronica with, 192
  lichen planus and, 186
  with linear epidermal nevus, 791
  oculocutaneous tyrosinosis and, 452
  of oral focal epithelial hyperplasia, 657, 657*f*
  parapsoriasis and, 182
  of perioral dermatitis, 462
  photoallergic drug eruption and, 318
  with pinta, 585
  pityriasis rosea and, 183–184
  psoriasiform mycosis fungoides and, 941–942
  psoriasis vulgaris and, 176
  in sarcoidosis, 373
  seborrheic keratosis and, 795
  soft fibroma and, 981
  ultraviolet recall and, 346
  of verruca plana, 653, 653*f*
  of verruca vulgaris, 650, 651*f*
Acanthosis nigricans, 447–448, 448*f*–449*f*
  acanthosis nigricans-like mycosis fungoides v., 942
  differential diagnosis of, 448
  histogenesis of, 448
  histopathology of, 103, 105–106, 448, 449*f*
  Leser-Trélat sign with, 799
  linear epidermal nevus v., 792
Acanthosis nigricans-like mycosis fungoides, 942
Acanthotic seborrheic keratosis, 798
  pathogenesis of, 798
Accessory tragus, hair follicle nevus v., 854
Acetaminophen, acute generalized exanthematous pustulosis with, 314
Acetylsalicylic acid, fixed drug eruptions with, 314
Acid hydrolases, of azurophilic granules, 43
Acid mucopolysaccharides
  of ground substance, 48*f,* 49–50
  in hair follicles, 27
  of stratum spinosum, 10
Acid phosphatase, in syringoma, 885
Acne agminata. *See* Lupus miliaris disseminatus faciei
Acne conglobata
  in follicular occlusion triad, 544
  histopathology of, 120, 128
Acne fulminans, histopathology of, 128
Acne keloidalis, histopathology of, 99, 99*f,* 128
Acne keloidalis nuchae
  histopathology of, 117
  tufted hair folliculitis with, 487
Acne necrotica. *See also* Chronic superficial folliculitis
  histopathology of, 128
Acne rosacea, histopathology of, 115–116
Acne varioliformis. *See also* Chronic superficial folliculitis
  histopathology of, 128
Acne vulgaris, 459–461
  acne conglobata v., 544
  histopathology of, 127–128, 459, 460*f*
  pathogenesis of, 459–461
Acneiform folliculitis, Behçet's syndrome and, 413
Acneiform lesions, histopathology of, 128
Acquired digital fibrokeratoma. *See also* Acral fibrokeratoma
  histopathology of, 125
Acquired elastotic hemangioma, 1025–1026
  histopathology of, 1026, 1026*f*
Acquired hypogammaglobulinemia
  Behçet's syndrome v., 414
  Crohn's disease v., 416
Acquired ichthyosis, in HIV, 660
Acquired immunodeficiency syndrome (AIDS), 659–660
  acquired perforating dermatosis with, 396
  demodicidosis and, 465
  granuloma annulare and, 361
  histopathology of, 660
  human herpesvirus in, 646
  Kaposi's syndrome and, 1029–1030, 1030*f*
  Langerhans cells and, 21
  psoriasis and, 175
    histopathology of, 179
    pathogenesis of, 180–181
  sarcoidosis and, 370
  varicella with, 643
Acquired melanocytic nevi, 714–715
Acquired neuroma, 1135
  histopathology of, 1135, 1135*f*
Acquired perforating dermatosis (APD), 395–396
  differential diagnosis of, 393*t,* 396
  histogenesis of, 396
  histopathology of, 396
  perforating folliculitis v., 392
Acquired syphilis. *See* Venereal syphilis
Acquired vitamin B_3 deficiency. *See* Pellagra
Acral fibrokeratoma, 989–990
  differential diagnosis of, 989–990
  histopathology of, 989, 990*f*
Acral hyperpigmentation, 689
Acral lentiginous malignant melanoma, acantholytic dyskeratosis and, 794
Acral lentiginous melanoma, histopathology of, 123
Acral nevus of congenital origin, 728
Acral perineuriomas, 1133–1134
  intraneural perineurioma, 1133–1134, 1133*f*–1134*f*
  pacinian neurofibroma, 1133
Acral purpuric papulonodular lesions, Behçet's syndrome and, 413
Acral skin
  nevi of, 715–716
  of palms and soles, 56
  shave biopsy of, 6

Acral-lentiginous melanoma (ALM), 747–748
  biology of, 748–749
  classification of, 738, 739*f*
  differential diagnosis of, 749
  histopathology of, 105, 123, 748, 748*f*
Acral-lentiginous nevi, 716
  acral-lentiginous melanoma v., 749
Acremonium sp., 593
  nail unit and, 506–507
Acrodermatitis chronic atrophicans, 586–587, 587*f*
  histogenesis of, 587
  histopathology of, 108, 110, 117, 120, 587, 587*f*
  with Lyme disease, 587–588
  macular atrophy and, 400
Acrodermatitis continua of Hallopeau, 175
  localized, 178
Acrodermatitis enteropathica, 410, 410*f*
  differential diagnosis of, 410
  histopathology of, 103, 109, 112, 410, 410*f*
  necrolytic migratory erythema v., 409
  pathogenesis of, 410
  pellagra v., 408, 451
Acrokeratoelastoidosis, 138, 138*f*
  collagenous and elastotic marginal plaques of the hands v., 391
Acrokeratosis neoplastica, 419
  histopathology of, 103, 419
Acrokeratosis verruciformis of Hopf, 152, 152*f*
  Darier's disease v., 149, 151–152
  differential diagnosis of, 152
  histogenesis of, 152
  histopathology of, 152, 152*f*
  hyperkeratotic seborrheic keratosis v., 798
Acromegaly, soft fibroma and, 981
Acro-osteolysis, 401
  histogenesis of, 401
  histopathology of, 120, 401
Acropigmentation symmetrica of Dohi, 689
Acropustulosis of infancy, 267
  differential diagnosis of, 267
  histopathology of, 112, 267
  pathogenesis of, 267
Acrosclerosis
  dystrophic calcinosis cutis and, 436–437
  mixed connective tissue disease with, 292
  systemic scleroderma and, 299
Acrosyringeal lichen planus, 187
Acrosyringeal nevi, eccrine syringofibroadenoma v., 888
Actin, in epithelioid sarcoma, 996
Actinic comedonal plaques, 391
  histopathology of, 391
Actinic granuloma. *See also* Annular elastolytic giant cell granuloma
  histopathology of, 117, 120
Actinic keratosis, 807–811, 807*f*. *See also* Solar keratoses
  acantholytic squamous cell carcinoma from, 821
  cutaneous horn and, 811, 811*f*
  differential diagnosis of, 810–811
  histopathology of, 87, 87*f,* 104–107, 110, 808–810, 808*f*–810*f*
  pathogenesis of, 810
  solar lentigines v., 708
  squamous cell carcinoma v., 820–821
Actinic lentigo. *See also* Solar lentigo
  histopathology of, 87, 87*f,* 104
Actinic prurigo (AP), 335–336, 335*f*
  differential diagnosis of, 336
  histopathology of, 106, 108, 335–336, 335*f*–336*f*
  pathogenesis of, 336
  polymorphic light eruption v., 335
Actinic reticuloid syndrome. *See also* Chronic actinic dermatitis
  histopathology of, 111
  neutrophilic eccrine hidradenitis and, 491
Actinomyces israelii, 574
Actinomycetoma, 614
Actinomycosis, 574, 574*f*–575*f*
  histopathology of, 119, 574, 574*f*–575*f*
Acupuncture, silicone granuloma and, 374
Acute bacterial folliculitis, histopathology of, 128
Acute deep folliculitis, 543, 544*f*
  histopathology of, 543
Acute disseminated LCD, 668–669, 671
Acute febrile neutrophilic dermatosis
  histopathology of, 93, 93*f,* 115, 223, 223*f*
  pathogenesis of, 224
Acute generalized exanthematous pustulosis (AGEP), 314–315, 315*f*
  bowel-associated dermatosis-arthritis syndrome v., 412
  histopathology of, 109
Acute generalized pustular psoriasis of von Zumbusch, 175
Acute infantile hemorrhagic edema (AHE), Henoch-Schönlein purpura and, 219
Acute lymphoid, pyoderma gangrenosum with, 411
Acute meningococcemia, 546–547
  histopathology of, 546–547
  pathogenesis of, 547
Acute mucocutaneous candidiasis, 597–598, 597*f,* 598*t*
  histopathology of, 597–598
  pathogenesis of, 598
Acute myeloid leukemia, 957–958
  clinical features of, 957, 958*f*
  differential diagnosis of, 958
  histogenesis of, 958, 959*f*
  histopathology of, 958, 958*t,* 959*f*
Acute neutrophilic dermatosis, histopathology of, 94, 94*f,* 117
Acute pustular bacterid, bowel-associated dermatosis-arthritis syndrome v., 412–413
Acute radiation dermatitis, 348–352, 349*f*–351*f*
  histopathology of, 349
Acute septicemia, 546–548, 547*f*
  acute meningococcemia, 546–547
  Pseudomonas septicemia, 547–548, 547*f*
  Vibrio vulnificus septicemia, 548
Acute spongiotic dermatitis
  definition and evaluation of, 237, 239*f*
  differential diagnosis of, 243
Acute strongyloidiasis, 628
Acute superficial folliculitis, 542–543, 543*f*
  impetigo Bockhart, 542
  Pseudomonas folliculitis, 542–543
Acute ultraviolet burn, 346, 346*f*
Acute urticaria, 169
Acute weeping stage, of parapoxvirus infections, 648
Adalimumab, drug-induced lupus erythematosus with, 318
Addison's disease
  histogenesis of, 690
  histopathology of, 104, 690
  hyperpigmentation with, 690
  macular atrophy and, 400
Adenocarcinoma
  histopathology of, 122
  of mammary-like glands of the vulva, 1151
  metastatic, histopathology of, 97, 97*f,* 122
  primary, histopathology of, 122
  of skin, 1151
Adenocystic carcinoma, 1156
Adenoid basal cell carcinoma, 827*f*–828*f,* 830–831, 1156
Adenoid cystic carcinoma, 899
  additional studies of, 899
  histopathology of, 898*f*–899*f,* 899
Adenoid cystic eccrine carcinoma, histopathology of, 123
Adenoid seborrheic keratosis, 797–798
Adenoid squamous cell carcinoma, 818, 1156
  angiosarcoma v., 1043
Adenolipoma, 1060
  histopathology of, 1063, 1064*f*
Adenolymphoceles, 630
Adenomatous polyposis, desmoid-type fibromatosis and, 992
Adenopathy, urticarial vasculitis, 219
Adenosine triphosphatase (ATPase), Langerhans cells and, 19–21, 20*f*
Adenosquamous carcinoma
  histopathology of, 122
  mucin-producing squamous cell carcinoma and, 821
Adenoviridae, 637
Adhesion molecules, with solitary pagetoid reticulosis, 941
Adipocytes, 55. *See also* Subcutaneous fat
  with balloon cell nevus, 715
  in cutaneous γ/δ T-cell lymphoma, 951
  morphea and, 297, 297*f*–298*f*
Adipose tissue
  in chondroid lipoma, 1067
  eosinophilic fasciitis and, 303
  hormone production by, 535
  Jessner's lymphocytic infiltration of the skin and, 291
  in lipofibromatosis, 1070
  localized lipodystrophy and, 527
  lupus erythematosus profundus/panniculitis and, 283
  tumors of, 98, 98*f,* 126–127
Adiposis dolorosa, 534, 1061
  histopathology of, 1063
  lipedema and, 527
Adnexal carcinomas, 1151
Adnexotropic lesions, mycosis fungoides v., 944
Adnexotropic mycosis fungoides, 939–940, 940*f*
Adolescence, striae distensae and, 398
Adult colloid milium, 429
  histopathology of, 429–430, 430*f*
  pathogenesis of, 430
Adult T-cell leukemia/lymphoma (ATLL), 953–955
  clinical features of, 953–954
  differential diagnosis of, 955
  histogenesis of, 954
  histopathology of, 121, 954, 954*f*
  T-cell prolymphocytic leukemia v., 956
Adult-type rhabdomyoma, 1083
  histopathology of, 1084
Adverse cutaneous drug reactions, in HIV, 660
African histoplasmosis, 612
  histopathology of, 612
  pathogenesis of, 612
AFX. *See* Atypical fibroxanthoma
AGA. *See* Androgenetic alopecia
Agammaglobulinemia, 46
Age spots, 707
Aged skin, histopathology of, 108
AGEP. *See* Acute generalized exanthematous pustulosis
Age-related variations, in skin, 56, 56*f*
Aggressive digital papillary adenocarcinoma, 899–900
  histopathology of, 123, 899–900, 899*f*–900*f*
Aggressive fibromatosis. *See* Desmoid-type fibromatosis
Aggressive late-stage lesions, of Kaposi's sarcoma, 1033
Agminate folliculitis, 593
Agminated lentigines, 708
Agminated Spitz nevus, 718
AHE. *See* Acute infantile hemorrhagic edema
AHLE. *See* Angiolymphoid hyperplasia with eosinophilia
AHO. *See* Albright's hereditary osteodystrophy

AIDS. *See* Acquired immunodeficiency syndrome
AIDS-associated Kaposi's sarcoma, 1030, 1030*f,* 1034
AIMP. *See* Atypical intraepidermal melanocytic proliferation
AITL. *See* Angioimmunoblastic T-cell lymphoma
AJCC Melanoma Staging Committee, 763
AL amyloidosis. *See* Primary systemic amyloidosis
Albinism, 693
  histogenesis of, 693
  histopathology of, 104, 693
Albopapuloid, with nail unit, 506
Albright's hereditary osteodystrophy (AHO), 1086–1087, 1086*f*
  differential diagnosis of, 1087
  histopathology of, 127, 1087
  osteoma cutis v., 1087
  pathogenesis of, 1086–1087
Albright's syndrome, melanotic macules of, 705
Alcian blue reaction, 68–69, 69*t*
ALCL. *See* Anaplastic large cell lymphoma
Alcohol
  palmar fibromatosis and, 992
  for specimen processing, 68
Algae, *Prototheca,* 615–616, 616*f*
ALK protein
  anaplastic large cell lymphoma, 952–953
  in inflammatory pseudotumor, 994
Alkaline phosphatase/anti-alkaline phosphatase technique, 74–75
  generalized essential telangiectasia and, 1011
Alkaline phosphatase-streptavidin technique, 75
Alkaptonuric ochronosis, histopathology of, 104, 121
Allergic contact dermatitis, 237–239, 239*f*. *See also* Churg-Strauss vasculitis
  histopathology of, 89, 89*f,* 92, 92*f,* 108, 113, 238, 239*f*
  irritant contact dermatitis v., 240
  pathogenesis of, 238–239
  psoriasis vulgaris v., 181
  telogen effluvium and, 478
  transient acantholytic dermatosis with, 273
Allergic granulomatosis, histopathology of, 94, 94*f,* 116
Allergic granulomatous reactions to chemical agents, histopathology of, 118
Allergic rhinitis, Churg-Strauss syndrome and, 213
Allergic urticarial reaction, histopathology of, 107
Allescheria boydii, 614
Allopurinol
  DRESS with, 311
  eosinophilic pustular folliculitis and, 466
  SJS and TEN with, 313
  toxic epidermal necrolysis and, 269
ALM. *See* Acral-lentiginous melanoma
Alopecia, 470–490
  diagnosis of, 470–473
    parameters for, 473
    scalp biopsy, 470–472, 471*f*
    terminology for, 472–473, 472*f*–473*f*
  epidermolysis bullosa acquisita and, 261
  in generalized hair follicle hamartoma, 863
  kwashiorkor and, 410
  lichen planopilaris and, 188
  lipedematous, 489
  with mycosis fungoides, 936
  nonscarring, 473–481
    alopecia areata, 473–476, 474*f*–475*f*
    anagen effluvium, 478
    androgenetic alopecia, 479–481, 480*f*
    telogen effluvium, 478–479, 479*f*
    traction alopecia, 477–478, 478*f*
    trichotillomania, 476–477, 476*f*–477*f*
  porphyria cutanea tarda with, 433
  radiation dermatitis and, 348
  scalp biopsies for, 5
  scarring, 481–489, 482*f*–483*f*
    central centrifugal cicatricial alopecia, 485–487, 485*f*–486*f*
    classification of, 481–483
    end stage of, 482–483, 482*f*
    eosinophilic pustular folliculitis with, 466
    folliculitis decalvans, 486*f*–487*f,* 487
    histopathology of, 128
    postmenopausal frontal fibrosing alopecia, 488–489, 488*f*
    pseudopelade of Brocq, 483–485, 483*f*–484*f*
    scalp biopsies for, 5
    tufted hair folliculitis, 487–488, 487*f*–488*f*
  senescent, 489
  syringolymphoid hyperplasia with, 490–491, 490*f*
Alopecia areata (AA), 473–476, 474*f,* 694
  with follicular mucinosis, 468
  histopathology of, 99, 99*f,* 128, 474–475, 474*f*–475*f*
  pathogenesis of, 475–476
  trichotillomania v., 477
Alopecia mucinosa, 467–469, 468*f*
  histopathology of, 128, 468–469, 469*f*
  pathogenesis of, 469
  scurvy v., 407
Alopecia neoplastica, 1153
Alopecia syphilitica, alopecia areata v., 475
Alpha-1 antitrypsin (AAT), deficiency of
  pancreatic disease v., 529
  panniculitis with, 516–517, 516*f*–517*f*
  Weber-Christian disease v., 524
Alphonamides, acute generalized exanthematous pustulosis with, 314
Alternaria infection, 600*t,* 601, 603, 603*f*
Alternaria infectoria, 602
Alternaria sp., 593
Alternariosis, 600*t,* 603, 603*f*
Aluminum chloride
  reactions to, 376–377, 377*f*
  for shave biopsy, 6
Aluminum granuloma, 376–377, 377*f*
  histopathology of, 122, 376–377, 377*f*
  pathogenesis of, 377
Aluminum-zirconium complex, zirconium granuloma and, 376
Alveolar cellular blue nevus, 704
Alveolar rhabdomyosarcoma, 1085, 1085*f*
Amastigote stage, of *Leishmania,* 621, 623*f*
Amebic cysts, 625
Amelanotic blue nevus, histopathology of, 126
Amelanotic cellular blue nevus, 704
Amelanotic melanoma, 752
Aminopeptidase, Langerhans cells and, 21
Aminopyrine, erythema nodosum with, 515
Amiodarone
  drug-induced pigmentary alterations of, 692
  photodistributed hyperpigmentation and, 319, 319*f*–320*f*
Amitriptyline, drug-induced pigmentary alterations of, 692
Amniotic fluid, periderm and, 8
Amoebiasis, erythema nodosum with, 514
Amoxicillin clavulanate, exanthemic drug eruptions with, 312
Amphotericin B, 608
  for aspergillosis, 599
  exanthemic drug eruptions with, 312
Ampicillin
  acute generalized exanthematous pustulosis with, 314
  ultraviolet recall and, 346
Amylase, in pancreatic disease, 528
Amyloid, 425
  basal cell carcinoma presence of, 834
  polariscopic examination for, 70
  tonofilaments and, 429
Amyloidosis, 425–429. *See also* Macular amyloidosis
  amyloid, 425
  epidermolysis bullosa acquisita and, 261
  histopathology of, 107, 112, 116, 121
  primary localized cutaneous, 427–429
    lichen amyloidosis and macular amyloidosis, 427–429, 427*f*–428*f*
    nodular amyloidosis, 429
  primary systemic, 425–427, 426*f*
  with reactive angioendotheliomatosis, 1008
  secondary systemic, 427
  staining methods for, 67
Amyloidosis cutis nodularis atrophicans, 425
Amylophosphorylase reaction, papillary eccrine adenoma and, 891
Amyopathic dermatomyositis. *See* Dermatomyositis
Anagen effluvium, 478
  antineoplastic chemotherapeutic drugs and, 321
Anagen hair
  in alopecia areata, 474–475
  in growth cycle, 26–27, 29*f,* 31
  regional variation of, 30
Anal mucosa, dyskeratosis congenita, 139, 139*f*
Anaphylactic reaction
  eosinophils and, 43–44
  mast cells and, 41–42
Anaplastic large cell lymphoma (ALCL), 945–947, 952–953
  burn scars and, 346
  clinical features of, 952
  differential diagnosis of, 953
  histogenesis of, 952–953
  histopathology of, 117, 952, 953*f*
  peripheral T-cell lymphoma v., 952
Anaplastic meningiomas, 1142
ANAs. *See* Antinuclear antibodies
anatomic relationships with, 1107
ANCAs. *See* Antineutrophil cytoplasmic antibodies
Anchoring filaments, development of, 8
Ancylostoma braziliense, 627
Ancylostoma caninum, 627
Ancylostoma tubaeformis, 627
Androgenetic alopecia (AGA), 479
  histopathology of, 99, 99*f,* 127, 479–481, 480*f*
  pathogenesis of, 481
  postmenopausal frontal fibrosing alopecia and, 489
Androgenic hormones
  acne vulgaris and, 459–461
  androgenetic alopecia and, 481
Anemia
  with T-cell prolymphocytic leukemia, 955
  telogen effluvium and, 478
Anetoderma. *See also* Macular atrophy
  histopathology of, 120
Aneurysmal fibrous histiocytoma, 970, 972*f*
  histopathology of, 125
  Kaposi's sarcoma v., 1035
Angioblastoma. *See also* Tufted angioma
  giant cell, 1038–1039
  histopathology of, 126
Angiocentric lymphomas, histopathology of, 129
Angioedema, 169
  with hepatitis B, 661
  hereditary
    histopathology of, 169
    pathogenesis, 170
  histopathology of, 115, 169
Angioendotheliomatosis, 1007
  malignant, histopathology of, 126
  reactive, 1008–1010, 1009*f*
    histopathology of, 126
    intravascular large B-cell lymphoma v., 933

Angiofibroblastoma of the skin, 991
  differential diagnosis of, 991
  histogenesis of, 991
  histopathology of, 991
Angiofibromas, 987–988
  fibrous papule of the face, 988, 988*f*
  pearly penile papules, 988
  in tuberous sclerosis, 989
Angiogenic cells, tumors of, 98, 98*f,* 126
Angiohistiocytoma, Kaposi's sarcoma v., 1035
Angioimmunoblastic lymphadenopathy, histopathology of, 122
Angioimmunoblastic T-cell lymphoma (AITL), 952
  clinical features of, 952
  differential diagnosis of, 952
  histogenesis of, 952
  histopathology of, 952
Angiokeratoma, 1011
  histopathology of, 126, 1011, 1011*f*
  verrucous hemangioma v., 1020
Angiokeratoma corporis diffusum, 1011, 1176*f*
  polariscopic examination for, 70
Angiokeratoma of Fordyce, 1011
Angiokeratoma of Mibelli, 1011
Angioleiomyoma, 1077, 1078*f*
  with fat, 1060
  histopathology of, 126
  myopericytoma v., 1051
Angiolipoma, 1064–1066
  cutaneous angiolipoleiomyoma v., 1079
  differential diagnosis of, 1065–1066
  histopathology of, 126–127, 1065, 1065*f*
Angiolymphoid hyperplasia. *See also* Epithelioid hemangioma
  epithelioid hemangioma v., 1024–1025
  with follicular mucinosis, 468
  histopathology of, 95, 95*f,* 107
Angiolymphoid hyperplasia with eosinophilia (AHLE), histopathology of, 116, 119, 126
Angioma serpiginosum, 1012
  histogenesis of, 1012
  histopathology of, 126, 1012
Angiomatoid fibrous histiocytoma, 979, 994
  aneurysmal fibrous histiocytoma v., 970
  histogenesis of, 994
  histopathology of, 125, 994, 995*f*
Angiomatoid Spitz nevus, 722
Angiomatosis, 1027
  histopathology of, 126, 1027
  intravascular large B-cell lymphoma v., 933
  lymphangiomatosis v., 1046
Angiomatous lesions, graft-*versus*-host disease and, 271
Angiomyofibroblastoma, angiofibroblastoma v., 991
Angiomyofibroblastoma of the vulva, 990–991
  differential diagnosis of, 991
  histogenesis of, 991
  histopathology of, 991
Angiomyolipoma, histopathology of, 126, 1062–1063, 1064*f*
Angiomyxolipoma, 1065
Angiomyxoma, angiomyofibroblastoma of the vulva v., 991
Angioneurotic edema, celiac disease and, 417
Angiosarcomas, 1040–1043. *See also* Epithelioid angiosarcoma
  atypical vascular proliferation after radiotherapy v., 1046
  burn scars and, 346
  composite hemangioendothelioma and, 1037
  desmoplastic melanoma v., 756
  differential diagnosis of, 1043
  epithelioid hemangioma v., 1024
  following lymphedema, 1040–1041
  histogenesis of, 1042–1043
  histologic spectrum of, 1040–1041, 1041*f*
  histopathology of, 126, 1041–1042, 1041*f*–1042*f*
  intravascular large B-cell lymphoma v., 933
  intravascular papillary endothelial hyperplasia v., 1007
  Kaposi's sarcoma v., 1034
  postirradiation, 1041
  progressive lymphangioma v., 1045
  pyogenic granuloma v., 1018
  radiation-induced, 351–352
  retiform hemangioendothelioma v., 1036
  of the scalp and face, 1040, 1041*f*
  sinusoidal hemangioma v., 1019
  spindle cell hemangioma v., 1028
  symplastic hemangioma v., 1028
  tufted angioma v., 1016
Angiotensin-converting enzyme inhibitors, T-cell lymphomatoid hyperplasias and, 936
Angiotensin-converting enzyme test, for sarcoidosis, 372
Angiotropism, melanoma prognosis and, 768
Angular cheilitis, macular atrophy and, 400
Anhidrotic ectodermal dysplasia, eccrine glands and, 35–36
Animal-type melanoma, 757
  pigmented epithelioid melanocytoma and, 757
Annular elastolytic giant cell granuloma, 364–365, 364*f*–365*f*
  differential diagnosis of, 364–365
  histopathology of, 117, 119–120, 364, 364*f*–365*f*
  necrobiosis lipoidica v., 367
Annular plaques, of acquired perforating dermatosis, 396
Anogenital cancer
  giant condyloma acuminata of Buschke and Loewenstein in, 656
  human papillomavirus in, 650
Anogenital region, apocrine glands of, 35
Anogenital warts. *See* Condyloma acuminatum
Anorectal mucosa, mucosal lentiginous melanoma of, 749
Anorexia nervosa, pellagra and, 408, 451
Anorexia, polyarteritis nodosa and, 209
Anthill warts, 652
Anthrax, 567, 567*f*
  histopathology of, 120, 567, 567*f*
Antiarrhythmics, systemic lupus erythematosus and, 286–287, 286*t*
Antibiotics
  for acne vulgaris, 461
  acute generalized exanthematous pustulosis with, 314
  acute mucocutaneous candidiasis with use of, 597
  adverse reactions to, 660
  aspergillosis with use of, 599
  for bacillary angiomatosis, 573
  for blastomycosis-like pyoderma, 546
  for confluent and reticulated papillomatosis, 449
  herpetic folliculitis response to, 638
  infectious mononucleosis with, 644
  for Lyme disease, 585
  methicillin-resistant *Staphylococcus aureus* skin infections with use of, 542
  Pseudomonas septicemia with use of, 547
  radiation recall dermatitis and, 352
  for rickettsial infections, 568
  systemic lupus erythematosus and, 286–287, 286*t*
  toxic epidermal necrolysis and, 269
  toxicities of, 311
  ultraviolet recall and, 346
  for yaws, 584
Antibodies
  to cartilage, 494
  to melanocytes, 694
Anti-BP180 antibodies, assays for, 74, 74*t*
Anticardiolipin antibodies
  histopathology of, 116
  macular atrophy and, 400
α_1-antichymotrypsins, antibodies against, 76*t,* 78
Anticonvulsants
  interstitial granulomatous drug reaction and, 381
  pellagra and, 408
  systemic lupus erythematosus and, 286–287, 286*t*
  T-cell lymphomatoid hyperplasias and, 936
  toxic epidermal necrolysis and, 269
Antidepressants
  interstitial granulomatous drug reaction and, 381
  T-cell lymphomatoid hyperplasias and, 936
Antidesmoglein antibodies, assays for, 73–74
Antidesmoplakin antibodies, assays for, 73, 73*f*
Antiepileptics, toxicities of, 311
Antiepiligrin, assays for, 74
Antiepithelial antibodies, circulating, indirect immunofluorescence testing for, 73–74
Antifungal therapy, 596
  herpetic folliculitis response to, 638
Antigens
  for PAMS, 246*t,* 254
  of pemphigus, 245, 246*t*
  tumor detection of, 75, 76*t*
Antihistamines, interstitial granulomatous drug reaction and, 381
Antihistone antibodies, systemic scleroderma and, 301
Antihyperlipidemics, interstitial granulomatous drug reaction and, 381
Antihypertensive drugs
  interstitial granulomatous drug reaction and, 381
  lichenoid drug eruption and, 313
  systemic lupus erythematosus and, 286–287, 286*t*
Antimalarials, drug-induced pigmentary alterations of, 692
Antimony compounds, erythema nodosum with, 515
Antimycotics, 595
  for blastomycosis, 604
Antineoplastic chemotherapeutic drugs
  cutaneous reactions to, 321–322, 321*f*–322*f*
    histogenesis of, 322
    histopathology of, 321–322, 321*f*–322*f*
  drug-induced pigmentary alterations of, 692
Antineutrophil cytoplasmic antibodies (ANCAs), 207, 207*t*
  Churg-Strauss syndrome and, 213
  leukocytoclastic vasculitis and, 216
  Wegener's granulomatosis and, 214–215
Antinuclear antibodies (ANAs)
  drug-induced lupus erythematosus with, 318
  eosinophilic fasciitis and, 303
  systemic lupus erythematosus and, 288
  systemic scleroderma and, 301
Anti-p200 pemphigoid, 263
  histopathology of, 263
  immunofluorescence testing for, 263
Antiphospholipid antibodies, macular atrophy and, 400
Antiphospholipid syndrome
  chilblains v., 353
  histopathology of, 112
  with reactive angioendotheliomatosis, 1008
  systemic lupus erythematosus with, 288, 289*f*
Antiplakin antibodies, 73
Antiplectin antibodies, 74
Antiretroviral therapy, cutaneous manifestations of, 324
Antithyroid drugs, systemic lupus erythematosus and, 286–287, 286*t*
α_1-Antitrypsin, antibodies against, 76*t,* 78
α_1-Antitrypsin deficiency panniculitis, histopathology of, 130–131

Antituberculous medication, 552, 554
  radiation recall dermatitis and, 352
Anti-type IV collagen, assays for, 74, 74*t*
Anti-U1 ribonucleoprotein antibodies, mixed connective tissue disease with, 292–293
Antivirals, adverse reactions to, 660
Antoni A, schwannomas, 1116–1117
Antoni B, schwannomas, 1116–1117
Anus, cicatricial pemphigoid and, 259
AP. *See* Actinic prurigo
APD. *See* Acquired perforating dermatosis
Aphthosis. *See* Behçet's syndrome
Aplasia cutis congenita, 143, 143*f*
Aplasia cutis, histopathology of, 120
Aplastic anemia, eosinophilic fasciitis and, 303
Apocrine adenocarcinoma, histopathology of, 123
Apocrine adenoma, 880
  histopathology of, 880
Apocrine carcinomas, with nevus sebaceus, 872
Apocrine cystadenoma, median raphe cyst of the penis v., 805
Apocrine fibroadenoma, 880
  histopathology of, 880
Apocrine glands, 31–36
  carcinoma of, 895–896
  CEA in, 76
  collagen fibers and, 47
  in dermis, 57, 58*f*
  in dermoid cyst, 804
  embryology of, 32
  extramammary Paget's disease and, 840
  histopathology of, 99, 99*f,* 128–129
  inflammatory diseases of, 492
    Fox-Fordyce disease, 492
  inflammatory processes of, 85
  with nevus sebaceus, 871
  normal microanatomy of, 33–35, 34*f*–35*f*
  Paget's disease and, 838–839
  regional variation of, 35, 35*f*
  S100 protein in, 77
  special stains for, 34*f*–35*f,* 36
  specialized structure and function of, 35–36
  tumors of, 97, 97*f,* 123, 876–883
    apocrine adenoma; apocrine fibroadenoma, 880
    apocrine hidrocystoma, 877–878, 877*f*
    apocrine nevus, 876–877
    cylindroma, 881–883, 882*f*
    erosive adenomatosis of the nipple, 881, 881*f*
    hidradenoma papilliferum, 878, 878*f*
    malignant cylindroma, 883
    syringocystadenoma papilliferum, 878–880, 879*f*
    tubular apocrine adenoma, 880, 880*f*
Apocrine hidrocystoma, 877–878
  additional studies of, 877
  differential diagnosis of, 878
  histopathology of, 98, 98*f,* 123, 127, 877, 877*f*
Apocrine miliaria, histopathology of, 128
Apocrine nevus, 876–877
  histopathology of, 123, 876
  immunohistochemistry of, 877
Apocrine secretion, with apocrine glands, 36
Apoeccrine glands, 32
  Fox-Fordyce disease and, 492
Apoproteins, 680, 683
Apoptosis, of Spitz nevus, 721
Apoptotic keratinocytes
  actinic prurigo and, 336
  polymorphic light eruption and, 335
  ultraviolet recall and, 346
Appetite suppressants, drug-induced scleroderma with, 316
Apple-jelly nodules, 552
Areola
  hyperkeratosis of, 106
  nevoid hyperkeratosis of, 792–793
  Paget's disease of, 838–839
  sebaceous glands and, 31
  sebaceous hyperplasia in, 872
  smooth muscle of, 46
Argentaffin granules, 1157
Argyria, 327, 327*f*
  histopathology of, 121, 128, 327, 327*f*
  pathogenesis of, 327
Argyrophilia, for melanocytes, 16
Argyrophilic reticulum fibers, of dermis, 38, 46–47
Arms, lupus erythematosus profundus/panniculitis and, 283
Arrectores pilorum, 46
  smooth muscle tumors and, 1079–1080
Arsenical keratosis, 816–817
  histopathology of, 104, 817
  pathogenesis of, 817
Arsphenamine, erythema nodosum with, 515
ArteColl. *See* Polymethylmethacrylate
ArteFill. *See* Polymethylmethacrylate
Arteries
  calcification of, 435–436
  of dermal microvasculature, 50, 51*f*
Arterioles, calcification of, 435–436
Arteriolitis, systemic scleroderma and, 300
Arteriovenous anastomoses, glomus tumor v., 1049
Arteriovenous hemangioma, 1026–1027
  cutaneous angiolipoleiomyoma v., 1079
  histogenesis of, 1027
  histopathology of, 1026–1027, 1026*f*–1027*f*
Arteriovenous malformation, composite hemangioendothelioma and, 1037
Arthralgias
  with dermatomyositis, 293
  drug-induced lupus erythematosus with, 318
  erythema nodosum with, 514
  microscopic polyarteritis and, 212
  in pancreatic disease, 528
  polyarteritis nodosa and, 209
  with self-healing juvenile cutaneous mucinoses, 445
  subacute cutaneous lupus erythematosus with, 283
  urticarial vasculitis, 219
Arthritis
  with dermatomyositis, 293
  drug-induced lupus erythematosus with, 318
  fibroblastic rheumatism and, 307
  gout and, 438
  pityriasis rubra pilaris with, 195
  Reiter's disease and, 181
  systemic lupus erythematosus with, 288
Arthropathy
  with erythema nodosum, 511
  pityriasis rubra pilaris with, 195
Arthropod assault reactions, 634–635, 634*f*
  histopathology of, 634–635, 634*f*
  pathogenesis of, 635
Arthropod bites
  acute spongiotic dermatitis and, 243
  B-cell lymphomatoid hyperplasia and, 916
  eosinophilic panniculitis and, 515
  with follicular mucinosis, 468
  histopathology of, 89, 89*f,* 107, 109, 111, 130
  prurigo simplex v., 173
Arthrospores, 592*t*
Arylsulfatase, of eosinophils, 43
Aspergillosis, 599, 600*t,* 601*f*
  erythema nodosum with, 514
  histopathology of, 95, 95*f,* 119, 599, 601*f*
  subcutaneous phaeohyphomycosis v., 603
Aspergillus flavus, 599
Aspergillus fumigatus, 599
Aspergillus infections, 593, 604
Aspergillus niger, 593, 599
Asteatotic eczema, transient acantholytic dermatosis with, 273
Asteroid bodies
  of annular elastolytic giant cell granuloma, 364
  in necrobiosis lipoidica, 366
  in sarcoidosis, 371–372, 371*f*
  of sporotrichosis, 613
Asthma
  Churg-Strauss syndrome and, 213
  polyarteritis nodosa and, 210
Ataxia-telangiectasia, 145
Atherosclerosis, 230
ATLL. *See* Adult T-cell leukemia/lymphoma
Atopic dermatitis, 242
  acquired perforating dermatosis with, 396
  acropustulosis of infancy and, 267
  histopathology of, 113, 242
  Kaposi's varicelliform eruption with, 641
  with keratosis pilaris, 470
  Malassezia furfur in, 596
  pathogenesis of, 242
  psoriasis vulgaris v., 181
  Sézary syndrome v., 944
  xanthomas with, 686
Atopic eczema
  eczema herpeticum with, 638
  microorganisms and, 60
  transient acantholytic dermatosis with, 273
Atopy, alopecia areata and, 475
ATPase. *See* Adenosine triphosphatase
Atrichia with papular lesions, 490
  histopathology of, 490, 490*f*
  pathogenesis of, 490
Atrophic actinic keratosis, 809
Atrophic dermatitis, histopathology of, 90, 90*f,* 108–109
Atrophie blanche, 231–232, 231*f*
  histopathology of, 111, 116, 231–232, 231*f*
  malignant atrophic papulosis and, 232
  pathogenesis of, 232
Atrophoderma of Pasini and Pierini, 301–303
  histopathology of, 120, 301–302
  with Lyme disease, 587–588
  pathogenesis of, 303
Atrophying disorders, of Lyme disease, 587–588, 587*f*
  histopathology of, 588
Attenuated yaws, 584
Atypia
  of dysplastic nevus, 735–737
  malignant blue nevus and, 772
  in malignant eccrine poroma, 887–888
  of malignant proliferating trichilemmal tumor, 867
  melanoma and, 737
  of microvenular hemangioma, 1020
  nodular melanoma and, 750–751
  of superficial spreading melanoma, 744
Atypical cellular blue nevus, 704
Atypical fibrous histiocytoma, 970, 973*f*
Atypical fibroxanthoma (AFX), 978–979, 1100
  differential diagnosis of, 979, 979*f*
  extraskeletal osteosarcoma v., 1094
  factor XIIIa and, 78
  histogenesis of, 979
  histopathology of, 125, 978–979, 978*f*–979*f*
  leiomyosarcoma v., 1083
  pleomorphic fibroma v., 981
Atypical intraepidermal melanocytic proliferation (AIMP), 749
Atypical lipoma, 1072
Atypical lipomatous tumor, 1072
Atypical melanocytic hyperplasia. *See* Superficial spreading melanoma
Atypical mitoses, of Bowenoid papulosis of genitalia, 656

Atypical mole syndrome. *See* Dysplastic nevus
Atypical mycobacteria, histopathology of, 118–119
Atypical necrobiosis lipoidica of the face and scalp. *See* Annular elastolytic giant cell granuloma
Atypical schwannoma, histopathology of, 125
Atypical spindle cell tumors, differential diagnosis for, 75, 76*t*
Atypical vascular proliferation after radiotherapy, 1046
  differential diagnosis of, 1046
  histopathology of, 1046, 1046*f*–1047*f*
Auricle, pseudocyst of, 494, 494*f*
Autoimmune blistering disease
  direct immunofluorescence for, 71–72
  indirect immunofluorescence for, 73
Autoimmune diseases, 221
  vitiligo, 694
Autoimmune hemolysis, macular atrophy and, 400
Autoimmune sialadenitis, mucosa-associated lymphoid tissue lymphoma and, 920–921
Autoimmune thyroid disease, eosinophilic fasciitis and, 303
Autolysis, biopsy and, 6
Autosomal recessive ichthyosis, 135
  histopathology of, 135
Avidin-biotin peroxidase technique, 75
Axillae
  apocrine glands of, 35
  extramammary Paget's disease of, 839
Azathioprine
  for actinic prurigo, 335
  for chronic actinic dermatitis, 338
  for dermatomyositis, 294
  pellagra and, 408
Azurophilic granules, 43, 43*f*

B cells, 44
  B-cell lymphomatoid hyperplasia, 915–917, 915*f,* 916*t,* 917*f*
  exogenous plasmacytoma, 922
  identification of, 45
  infiltration patterns of, 911–913, 913*f,* 913*t*
    abnormal, 913–915, 914*f*
  mantle cell lymphoma, 928–930
  primary cutaneous diffuse large B-cell lymphoma
    leg type, 921–922
    other, 922
  primary cutaneous follicle center lymphoma, 917–920
  primary cutaneous marginal zone lymphoma, 920–921
  in skin, 911
  skin infiltration by, 44–45
Babesiosis, 585
Bacillary angiomatosis, 572–573, 572*f*
  cutaneous epithelioid angiomatous nodule v., 1025
  differential diagnosis of, 572–573
  histopathology of, 126, 572, 572*f*
  in HIV, 572, 659
  Kaposi's sarcoma v., 1035
  pyogenic granuloma v., 1018
Bacillus anthracis, histopathology of, 120
Bacterial abscesses, histopathology of, 95, 95*f,* 119, 132
Bacterial diseases, 539–575
  actinomycosis, 574, 574*f*–575*f*
  acute deep folliculitis, 543, 544*f*
  acute septicemia, 546–548, 547*f*
    acute meningococcemia, 546–547
    Pseudomonas septicemia, 547–548, 547*f*
    Vibrio vulnificus septicemia, 548
  acute superficial folliculitis, 542–543, 543*f*
    impetigo Bockhart, 542
    Pseudomonas folliculitis, 542–543
  anthrax, 567, 567*f*
  bacillary angiomatosis, 572–573, 572*f*
  blastomycosis-like pyoderma, 546
  botryomycosis, 573, 573*f*
  cat-scratch disease, 571–572
  chancroid, 569–570, 569*f*
  chronic deep folliculitis, 544
  chronic septicemia, 548–549, 548*f*
    chronic gonococcemia, 548–549
    chronic meningococcemia, 548, 548*f*
  chronic superficial folliculitis, 543
  ecthyma, 541
  erysipelas, 541
  follicular occlusion triad (hidradenitis suppurativa, acne conglobata, perifolliculitis capitis abscedens et suffodiens), 544–545, 545*f*
  granuloma inguinale, 570, 570*f*
  impetigo, 539–541, 540*f*
    bullous impetigo, 539–541
    impetigo contagiosa, 539, 540*f*
    staphylococcal scalded skin syndrome, 539–541
  injection abscess, 567–568, 568*f*
  leprosy, 558–567, 559*f*–565*f*
    borderline lepromatous leprosy, 559, 559*f,* 562
    borderline tuberculoid leprosy, 559, 559*f,* 562–563, 563*f*–564*f*
    clinical pathology of, 560
    electron microscopy of, 565
    histoid, 561–562, 562*f*
    histopathologic differential diagnosis of, 566
    HIV and, 566
    immunopathologic spectrum of, 559, 559*f*
    indeterminate, 559–560, 560*f*
    lepromatous leprosy, 559–562, 559*f,* 561*f*–562*f,* 566–567
    leprosy reactions, 564–567, 564*f*–565*f*
    midborderline leprosy, 559, 559*f,* 562
    peripheral nerve involvement in, 564
    staining of *Mycobacterium leprae,* 559–560
    tuberculoid leprosy, 559, 559*f,* 563, 566
  lymphogranuloma venereum, 571
  malakoplakia, 549, 549*f*
  methicillin-resistant *Staphylococcus aureus* skin infections, 542
  mycobacterial infections, 549–550
  necrotizing fasciitis, 541–542, 541*f*–542*f*
  nocardiosis, 574, 574*f*
  nontuberculosis mycobacteria infections, 555–558, 555*f*–558*f*
    Buruli ulcer, 556–558, 557*f*
    Mycobacterium avium-intracellulare, 555, 555*f*–556*f*
    Mycobacterium kansasii, 555, 555*f*
    Mycobacterium marinum, 555–556, 556*f*
    other, 558, 558*f*
  pseudofolliculitis of beard, 544
  rhinoscleroma, 570–571, 571*f*
  rickettsial infections, 568–569, 568*f*–569*f*
  toxic shock syndrome, 546
  tuberculosis, 550–555, 551*f*–554*f*
    erythema nodosum, 550
    lichen scrofulosorum, 550
    lupus vulgaris, 550, 551–552, 552*f*
    papulonecrotic tuberculid, 550
    primary, 550–551, 551*f*
    scrofuloderma, 550, 552
    tuberculids, 553–555, 554*f*
    tuberculosis cutis orificialis, 553
    tuberculosis verrucosa cutis, 550, 551, 551*f*
    tuberculous gumma, 552, 553*f*
  tularemia, 568
Bacterial endocarditis, palisaded neutrophilic and granulomatosis with, 369
Bacterial folliculitis, acute, histopathology of, 99, 99*f*
Bacterial impetigo, psoriasis vulgaris v., 181
Bacterial infections
  chronic
    with common variable immunodeficiency, 381
    histopathology of, 119
  erythema nodosum with, 514
  of the nail, 507–508, 508*f*
Bacterial lesions, 539–575
  of actinomycosis, 574, 574*f*–575*f*
  of acute deep folliculitis, 543, 544*f*
  of acute septicemia, 546–548, 547*f*
    acute meningococcemia, 546–547
    Pseudomonas septicemia, 547–548, 547*f*
    Vibrio vulnificus septicemia, 548
  of acute superficial folliculitis, 542–543, 543*f*
    impetigo Bockhart, 542
    Pseudomonas folliculitis, 542–543
  of anthrax, 567, 567*f*
  of bacillary angiomatosis, 572–573, 572*f*
  of blastomycosis-like pyoderma, 546
  of botryomycosis, 573, 573*f*
  of cat-scratch disease, 571–572
  of chancroid, 569–570, 569*f*
  of chronic deep folliculitis, 544
  of chronic septicemia, 548–549, 548*f*
    chronic gonococcemia, 548–549
    chronic meningococcemia, 548, 548*f*
  of chronic superficial folliculitis, 543
  of ecthyma, 541
  of erysipelas, 541
  of follicular occlusion triad (hidradenitis suppurativa, acne conglobata, perifolliculitis capitis abscedens et suffodiens), 544–545, 545*f*
  of granuloma inguinale, 570, 570*f*
  of impetigo, 539–541, 540*f*
    bullous impetigo, 539–541
    impetigo contagiosa, 539, 540*f*
    staphylococcal scalded skin syndrome, 539–541
  of injection abscess, 567–568, 568*f*
  of leprosy, 558–567, 559*f*–565*f*
    borderline lepromatous leprosy, 559, 559*f,* 562
    borderline tuberculoid leprosy, 559, 559*f,* 562–563, 563*f*–564*f*
    histoid, 561–562, 562*f*
    indeterminate, 559–560, 560*f*
    lepromatous leprosy, 559–562, 559*f,* 561*f*–562*f,* 566–567
    leprosy reactions, 564–567, 564*f*–565*f*
    midborderline leprosy, 559, 559*f,* 562
    tuberculoid leprosy, 559, 559*f,* 563, 566
  of lymphogranuloma venereum, 571
  of malakoplakia, 549, 549*f*
  of methicillin-resistant *Staphylococcus aureus* skin infections, 542
  of mycobacterial infections, 549–550
  of necrotizing fasciitis, 541–542, 541*f*–542*f*
  of nocardiosis, 574, 574*f*
  of nontuberculosis mycobacteria infections, 555–558, 555*f*–558*f*
    Buruli ulcer, 556–558, 557*f*
    Mycobacterium avium-intracellulare, 555, 555*f*–556*f*
    Mycobacterium kansasii, 555, 555*f*
    Mycobacterium marinum, 555–556, 556*f*
    other, 558, 558*f*
  of pseudofolliculitis of beard, 544
  of rhinoscleroma, 570–571, 571*f*
  of rickettsial infections, 568–569, 568*f*–569*f*
  of toxic shock syndrome, 546
  of tuberculosis, 550–555, 551*f*–554*f*
    erythema nodosum, 550
    lichen scrofulosorum, 550
    lupus vulgaris, 550, 551–552, 552*f*

papulonecrotic tuberculid, 550
primary, 550–551, 551*f*
scrofuloderma, 550, 552
tuberculids, 553–555, 554*f*
tuberculosis cutis orificialis, 553
tuberculosis verrucosa cutis, 550, 551, 551*f*
tuberculous gumma, 552, 553*f*
of tularemia, 568
BADS. *See* Blacklocks-albinism-deafness syndrome
Balamuthia mandrillaris, 625
Balanitis circumscripta plasmacellularis, 815–816
histopathology of, 816
pathogenesis of, 816
Balanitis xerotica obliterans. *See* Lichen sclerosus et atrophicus
B-ALL. *See* Precursor B-cell acute lymphoblastic lymphoma
Balloon cell melanoma, 749, 756–757
Balloon cell nevus, 715, 715*f*
histopathology of, 122, 715, 715*f*
Ballooning degeneration
of hand-foot-and-mouth disease, 658, 658*f*
in herpes simplex infection, 640–641, 640*f*
of Kaposi's varicelliform eruption, 642
of parapoxvirus infections, 648
of variola, 647
Bannayan-Riley-Ruvalcaba syndrome, Cowden's disease with, 869
Barbiturates, fixed drug eruptions with, 314
Bartholin's gland cyst, angiomyofibroblastoma of the vulva v., 990
Bartonella henselae, 571–572
in HIV, 659
Bartonella quintana, 572
in HIV, 659
Bart's syndrome. *See* Epidermolysis bullosa
Basal cell carcinoma, 823–835. *See also* Adenoid basal cell carcinoma; Fibrosing basal cell carcinoma; Superficial basal cell carcinoma
adenoid cystic carcinoma and, 899
amyloid presence in, 834
from arsenical keratosis, 817
in basaloid follicular hamartoma, 863
burn scars and, 346
clinical appearance of, 824–826, 824*f*–825*f*
differential diagnosis of, 834–835
eccrine poroma v., 887
electron microscopy of, 834
with follicular differentiation, 829*f,* 832
histopathology of, 88, 88*f,* 124, 826–832, 826*f*–829*f*
lack of autonomy of, 833
with matricial differentiation, 831
mucinous syringometaplasia v., 888
with nevus sebaceus, 871–872, 871*f*
occurrence of, 824
pathogenesis of, 833
pigmentary presentations of, 692
pilar differentiation, 833
predisposing factors for, 823–824
radiation-induced, 351
sebaceous carcinoma v., 876
site of origin of, 833–834
squamous cell carcinoma v., 821
stromal factor, 833
superficial, histopathology of, 106
trichoepithelioma and, 859
tumor of the follicular infundibulum v., 869–870
xeroderma pigmentosum with, 141
Basal cell epithelioma, 1179*f*
acantholytic dyskeratosis and, 794
Bowen's disease v., 813
cutaneous horn and, 811, 811*f*
in epidermal cysts, 802
pseudocarcinomatous hyperplasia and, 822
Basal lamina, hibernoma and, 1070
Basal layer
acantholytic actinic keratosis in, 810
atrophic actinic keratosis in, 809
bullous systemic lupus erythematosus and, 261
eccrine glands from, 32
erythema dyschromicum perstans and, 172
fixed drug eruptions and, 314
hemochromatosis and, 450
of keratinocytes, 7–10, 8*f*–11*f*
lichen planopilaris, 188
lichen planus and, 186
lichen sclerosus et atrophicus and, 305
melanin granules in, 16
melanocytes of, 14–15
mercury pigmentation in, 327–328
Merkel cells in, 18
pellagra and, 408
Basaloid carcinoma, cutaneous small cell undifferentiated carcinoma v., 1139
Basaloid cells
in acanthotic seborrheic keratosis, 798
in basaloid follicular hamartoma, 863
pilomatricoma and, 865, 865*f*
in sebaceoma, 874
in sebaceous adenoma, 873, 873*f*
in trichoblastoma, 860–861
Basaloid follicular hamartoma, 863
additional studies of, 863
differential diagnosis of, 863
histopathology of, 863, 863*f*–864*f*
Basaloid keratinocytes, in microcystic adnexal carcinoma, 897
Basement membrane zone, 21–24, 22*f*–23*f*
argyria in, 327
blisters at, 235
components of, 255–256, 256f
of dermal microvasculature, 50
development of, 7–8
direct immunofluorescence and, 71–73
discoid lupus erythematosus and, 280
of glomus cells, 52
hemochromatosis and, 450
ochronosis and, 440
p200 of, 263
PAS for, 68
in squamous cell carcinoma, 820
subepidermal bullous disease and, 255–256, 256*f*
superficial spreading melanoma in, 744
transient acantholytic dermatosis and, 273–274
Basilar keratinocytes, discoid lupus erythematosus and, 280–282
Basophilic cells, pilomatricoma and, 865, 865*f*
Basophilic granulocytes, 44
in trichoadenoma, 862
Basophilic small cells, immunohistochemistry of, 79, 79*t*
Bazex's syndrome, 826, 832. *See also* Acrokeratosis neoplastica
histopathology of, 103, 127
Bazin's disease. *See* Erythema induratum
B-cell follicles, 683, 684*f*
B-cell lymphoma
B-cell lymphomatoid hyperplasia v., 916
macular atrophy and, 400
B-cell lymphomatoid hyperplasia (B-CLH), 915–916
clinical features of, 915–916, 915*f*
differential diagnosis of, 916, 916*t*
histogenesis of, 916
histopathology of, 915*f,* 916, 917*f*
nodal follicular lymphoma v., 919*t,* 928
primary cutaneous marginal zone lymphoma v., 921
BCL2
diffuse large B-cell lymphoma, 930
lipofibromatosis, 1070
mantle cell lymphoma, 930
nodal follicular lymphoma, 928
primary cutaneous diffuse large B-cell lymphoma, leg type, 922
primary cutaneous follicle center lymphoma, 919, 920
primary cutaneous marginal zone lymphoma, 921
BCL6
diffuse large B-cell lymphoma, 930
primary cutaneous diffuse large B-cell lymphoma, leg type, 922
primary cutaneous follicle center lymphoma, 918, 920
primary cutaneous marginal zone lymphoma, 921
BCL10, primary cutaneous marginal zone lymphoma, 921
B-CLH. *See* B-cell lymphomatoid hyperplasia
Beard, pseudofolliculitis of, 544
histopathology of, 544
Becker nevus syndrome, 706
Becker's melanosis, 706, 710*t*
histopathology of, 104, 706
with smooth muscle hamartoma, 1075
Becker's pigmented hairy nevus. *See* Becker's melanosis
Bedbugs, reactions to bites of, 634–635, 634*f*
Bednar tumor, 975
Bees, reactions to stings of, 634–635, 634*f*
Behçet's syndrome, 221, 413–415, 413*f*–414*f*
bowel-associated dermatosis-arthritis syndrome v., 412–413
with chilblains, 353
differential diagnosis of, 414
erythema elevatum diutinum v., 221
erythema nodosum with, 514–515
hepatitis C with, 661
histopathology of, 116–117, 128, 221, 413–414, 413*f*–414*f*
neutrophilic eccrine hidradenitis and, 491
pathogenesis of, 221, 414–415
superficial migratory thrombophlebitis and, 517
Bejel. *See* Endemic syphilis
Benign appendageal tumors
classification of, 852–853, 852*t*
ontogeny of, 853
terminology for, 853
Benign cartilagenous tumors, 1094–1097
calcifying aponeurotic fibroma, 1096–1097, 1097*f*
soft tissue chondromas, 1094–1096, 1095*f*–1096*f*
Benign cephalic histiocytosis, 677–678, 677*f*
differential diagnosis of, 678
histopathology of, 124, 677–678, 677*f*
JXG v., 672
pathogenesis of, 678
Benign familial pemphigus
histopathology of, 114
Kaposi's varicelliform eruption with, 641
Benign fibrous histiocytoma, histopathology of, 98, 98*f,* 125
Benign gummatous syphilis, 583
Benign inherited acanthosis nigricans, 448
Benign juvenile melanoma. *See* Spitz nevus
Benign lichenoid keratosis. *See also* Lichen planus-like keratosis
actinic keratosis v., 811
postinflammatory pigmentary alteration with, 690
Benign lipoblastoma, 1070–1071
differential diagnosis of, 1071
histopathology of, 127, 1071, 1071*f*
Benign lymphangioendothelioma
histopathology of, 126
hobnail hemangioma v., 1022
Benign migratory glossitis, psoriasis vulgaris, 174, 174*f*
Benign mixed mesodermal proliferations, histopathology of, 126

Benign monoclonal gammopathy, diffuse normolipemic plane xanthoma with, 684
Benign pigmented lesions, 699–738
  blue nevi, 701–704
    cellular, 702–704, 703*f*
    combined, 704
    common, 701–702, 702*f*
  dermal melanocytoses and hamartomas, 699–701
    mongolian spot, 699–700
    nevi of Ota, Ito, and Hori; dermal melanocyte hamartoma, 700–701
  freckles and hyperpigmentations, 704–706
    Becker's melanosis, 706
    melanotic macules of Albright's syndrome, 705
    mucosal melanotic macules, 705–706
  lentigines, 706–709, 710*t*
    lentigo simplex, 708–709, 708*f,* 710*t*
    solar, 706–708, 707*f*
  melanocytic nevi, 710–738
    acquired, 714–715
    balloon cell nevus, 715, 715*f*
    common, 710–714
    congenital, 725–728, 726*f*
    deep penetrating nevus, 729–730, 729*f*
    dysplastic nevus, 733–738, 734*f*–735*f,* 736*t,* 737*t*
    halo nevus, 730–732, 731*f*
    melanonychia striata, 716
    nevi of acral skin, 715–716
    nevi of flexural sites, 718
    nevi of special sites, 715–716
    nevus of genital skin, 717–718, 718*f*
    pigmented spindle cell nevus, 724–725, 725*f*
    recurrent nevus, 732–733, 733*f*
    Spitz nevus, 718–724, 719*f*–720*f*
Benign polymorphous mesenchymal tumor, extraskeletal myxoid chondrosarcoma v., 1098
Benign symmetric lipomatosis, 1061–1062
Benign tertiary syphilis, 580
Benign Triton tumor, rhabdomyomatous mesenchymal hamartoma v., 1083
Benign tumors, description of, 791
Benoxaprofen, with solar urticaria, 340
Benzene, ochronosis and, 440
Benzocaine, granuloma gluteale infantum and, 381
Berloque dermatitis, 691
  histopathology of, 691
Berylliosis, 374, 377
  Crohn's disease v., 416
  histopathology of, 377
  pathogenesis of, 377
Bilateral pheochromocytoma, 1137
Bilharziasis cutanea tarda, 631, 632*f*
Bilharzides, 631
Bioplastique. *See* Polydimethylsiloxane
Biopsy
  for basal cell carcinoma, 835
  curettage, 6
  deep incisional, 5–6
  for direct immunofluorescence, 71
  for keratoacanthoma, 836
  of melanoma, 762
  nail plate, 595
  of the nail unit, 503
  for panniculitis, 511
  punch, 5
  scalp, 5
  scalpel, 5
  shave, 5–6
  techniques of, 5–6
    selection of, 5
Biphasic sarcomatoid carcinoma, 1099
Bipolaris infection, 601
Birbeck granule, 20*f,* 21, 669–671
Birt-Hogg-Dubé syndrome, 856–857
Bites, reactions to, 634–635, 634*f*
B-K mole syndrome. *See* Dysplastic nevus
Black fever, 624–625
Black flies, as onchocerciasis vector, 629
Black heel. *See* Calcaneal petechiae
Blacklocks-albinism-deafness syndrome (BADS), 693
Blastoconidia, 592*t*
Blastomyces dermatitidis, 603
  acanthamoebiasis v., 625
  cryptococcosis v., 611
  paracoccidioidomycosis v., 606
Blastomycosis
  Crohn's disease v., 416
  erythema nodosum with, 514
Blastomycosis-like pyoderma, 546
  differential diagnosis of, 546
  histopathology of, 546
  pathogenesis of, 546
  pemphigus vegetans v., 250
Blau syndrome, sarcoidosis v., 370
B-LBL. *See* Precursor B-cell lymphoblastic lymphoma
Blenorrhagicum, histopathology of, 109
Bleomycin
  drug-induced pigmentary alterations of, 692
  drug-induced scleroderma with, 316
  scleroderma and, 296
Blepharitis
  with acrodermatitis enteropathica, 410
  rosacea and, 463
Blindness, with onchocerciasis, 630
Blisters
  in arthropod assault reactions, 634*f*
  definition of, 235
  formation of, 235, 236*t*
  pathologic evaluation of, 235–237, 236*t*–238*t*
Blood group P antigen, 661
Blood, nodal follicular lymphoma of, 927
Blood vessels, collagen fibers and, 47
Bloom's syndrome, 144–145, 144*f*
  differential diagnosis of, 144–145
  histopathology of, 144
  pathogenesis of, 144
  poikiloderma atrophicans vasculare and, 295
Blue nevus, 701–704
  apocrine hidrocystoma v., 877
  cellular, 122, 126, 702–704, 703*f*
  combined, 704
  common, 122, 701–702, 702*f*
  deep penetrating nevus v., 728
  histogenesis of, 704
  malignant, 771–772, 771*f*–772*f*
  nevus of Ota and, 700
Blue rubber bleb nevus, 1019
  glomus tumor v., 1047, 1049
  histopathology of, 1019, 1019*f*
Blueberry muffin baby, 644, 1157
  congenital self-healing reticulohistiocytosis v., 669
Blunt trauma, histopathology of, 131
Bone
  epithelioid hemangioma of, 1023
  neurofibromatosis and, 1110–1111
Bone lesions
  of JXG, 672
  of yaws, 583
Bone marrow
  basophils from, 44
  Langerhans cells and, 19, 21
  macrophages and, 40
  mast cells from, 41
  nodal follicular lymphoma of, 927
  in precursor B-cell lymphoblastic lymphoma, 923–924
  T-cell prolymphocytic leukemia and, 955
Bone marrow-derived monocytes, in histiocytoses, 667
Borderline lepromatous leprosy, 559, 559*f,* 562
  histopathology of, 562
Borderline tuberculoid leprosy, 559, 559*f,* 562–563, 563*f*–564*f*
  histopathology of, 562–563, 563*f*–564*f*
Borrelia burgdorferi
  atrophoderma of Pasini and Pierini and, 303
  Lyme disease from, 585–589, 586*f*–587*f*
  morphea and, 297
  nodal follicular lymphoma and, 928
  primary cutaneous follicle center lymphoma and, 919
Borrelial lymphocytoma cutis, 588–589
  histopathology of, 122
Borrelioma, 588
Borreliosis, eosinophilic fasciitis and, 303
Borst-Jadassohn epithelioma, 832
Borst-Jadassohn phenomenon, of intraepithelial epitheliomas, 886
Botryoid rhabdomyosarcoma, 1085
Botryomycosis, 573, 573*f*
  histopathology of, 110, 119, 573, 573*f*
  pathogenesis of, 573
Boutonneuse fever, 568
Bovine collagen implants, 378–379
  histopathology of, 379
Bovine papular stomatitis pox, 647–648, 648*f*
Bowel arthrosis dermatosis syndrome
  Behçet's syndrome v., 414
  histopathology of, 117
Bowel bypass syndrome. *See* Bowel-associated dermatosis-arthritis syndrome
Bowel-associated dermatosis-arthritis syndrome, 412–413, 412*f*
  differential diagnosis of, 412–413
  histopathology of, 116, 224, 412, 412*f*
  pathogenesis of, 224, 412
Bowenoid actinic keratosis, 809, 809*f*
  Bowen's disease v., 815
Bowenoid papulosis
  of genitalia, 656–657, 657*f*
    differential diagnosis of, 656–657
    histogenesis of, 656
    histopathology of, 656, 657*f*
  histopathology of, 104, 106
Bowenoid transformation, with acanthotic seborrheic keratosis, 798
Bowen's disease, 813–815, 832
  arsenical keratosis and, 817
  balanitis circumscripta plasmacellularis v., 815
  bowenoid actinic keratosis v., 809
  Bowenoid papulosis of genitalia v., 656–657
  condyloma acuminatum in, 654
  differential diagnosis of, 815
  epidermal cysts with, 802
  in epidermodysplasia verruciformis, 653–654
  erythroplasia of Queyrat v., 815
  extramammary Paget's disease v., 840
  histopathology of, 104, 107, 111, 813–814, 814*f*
  lentigo maligna melanoma v., 745
  Paget's disease v., 839
  pathogenesis of, 814–815
  porokeratosis and, 139
  superficial spreading melanoma v., 744–745
BPAG1. *See* Bullous pemphigoid antigen 1
BPAG2. *See* Bullous pemphigoid antigen 2
BRAF
  compound nevus and, 713
  melanoma and, 743
Brain
  melanoma of, 700
  tuberous sclerosis in, 989
Breast
  apocrine glands of, 35, 35*f*
  Paget's disease of, 838–839

Breast carcinoma
  Cowden's disease with, 869
  EMA antibodies and, 76
  inflammatory, 1152
  metastatic carcinoma of skin, 1152–1154
    histopathology of, 1153–1154, 1153*f*–1154*f*
    immunoperoxidase studies, 1154
  signet ring cell of, 1153
  telangiectatic metastatic, 1152
Breast fibroademonas, Cowden's disease with, 869
Breslow's thickness of tumor, 765, 765*f*
Bromides
  erythema nodosum with, 515
  panniculitis with, 534
Bromocriptine, drug-induced scleroderma with, 316
Bromoderma, 326, 326*f*
Bronchial carcinoids, 1157
Bronchiolitis, PAMS and, 254
Bronchogenic duct cysts, 805
  histopathology of, 127, 805, 805*f*
  pathogenesis of, 805
  thyroglossal duct cysts v., 805
Bronchospasm, with solar urticaria, 340
Brooke-Spiegler syndrome, cylindroma and, 881
Brown OCA, 693
Brown recluse spider, reaction to bites of, 634–635
Brucellosis, erythema nodosum with, 514
Brunsting-Perry variant, of cicatricial pemphigoid, 259
Buerger's disease, 209, 210*f*
  differential diagnosis of, 209
  histopathology of, 111, 209, 210*f*
Bulbous diseases, verruciform xanthomas with, 685
Bullae
  of bullous impetigo, 539–540
  in coma, 316–317, 316*f*–317*f*
  definition of, 235
  with erythema ab igne, 347
  morphea and, 299
  polyarteritis nodosa and, 210
  urticaria pigmentosa and, 160
Bullous congenital ichthyosiform erythroderma. *See also* Epidermolytic hyperkeratosis
  epidermolytic hyperkeratosis in, 793
  hypertrophic actinic keratosis and, 809
Bullous dermatitis, histopathology of, 113
Bullous dermatosis of diabetes, histopathology of, 114
Bullous dermatosis of uremia, histopathology of, 114
Bullous disease
  drug-induced, 317–318, 317*t*
    histopathology of, 317
    pathogenesis of, 317–318
  immunohistochemistry for, 74
  of the nail, 506
Bullous drug eruption, histopathology of, 115
Bullous impetigo, 539–541
  differential diagnosis of, 541
  histopathology of, 112, 540
  pathogenesis of, 540
Bullous insect bite reaction, histopathology of, 115
Bullous lichen planus, histopathology of, 93, 93*f,* 114
Bullous lupus erythematosus, histopathology of, 114–115
Bullous mastocytosis, 158
  histopathology of, 93, 93*f,* 115
Bullous pemphigoid, 256–259, 257*f*–258*f,* 258*t,* 1169*f*–1170*f*
  clinical variants of, 259
    drug-associated, 259
    in lower extremities, 259
    vesicular pemphigoid, 259
  direct immunofluorescence and, 71, 257–258, 257*f,* 257*t*
  eosinophils and, 44
  histopathology of, 93, 93*f,* 107, 114–115, 256–257, 257*f*
  milia and, 802
  with nail unit, 506
  pathogenesis of, 258–259
  ultrastructural study of, 259
  vesicular pemphigoid v., 259
Bullous pemphigoid antigen 1 (BPAG1)
  of hemidesmosomes, 23
  herpes gestationis and, 260–261
Bullous pemphigoid antigen 2 (BPAG2)
  cicatricial pemphigoid and, 260
  of hemidesmosomes, 23
  herpes gestationis and, 260–261
Bullous systemic lupus erythematosus, 261–263, 262*f,* 286
  histopathology of, 261–263, 262*f,* 287, 287*f*–288*f*
  immunofluorescence testing for, 263
  ultrastructural study of, 263
Bullous vasculitis, histopathology of, 112, 115
Bullous/vesicular mycosis fungoides, 942
Bunostomum phlebotomum, 627
Bupropion, SJS and TEN with, 313
Burkitt lymphoma
  diffuse large B-cell lymphoma v., 931
  mantle cell lymphoma v., 929
  precursor B-cell lymphoblastic lymphoma v., 924*f,* 925
Burns. *See also* First-degree burns; Second-degree burns; Third-degree burns
  acute ultraviolet burn, 346, 346*f*
  basal cell carcinoma and, 824
  burn scar-associated malignancy, 346
  histopathology of, 343–346, 344*f*–345*f*
  radiation dermatitis v., 352
  squamous cell carcinoma from, 817
  ultraviolet recall, 346–347
Burrows
  of hookworm-related cutaneous larva migrans, 627, 627*f*
  of scabies, 626
Buruli ulcer, 556–558, 557*f*
  histopathology of, 120, 557, 557*f*
  pathogenesis of, 558
Buschke-Loewenstein tumor, 655*f,* 656
Buschke-Ollendorff syndrome. *See* Connective tissue nevus
Busulfan, drug-induced pigmentary alterations of, 692
Buttocks
  dermatitis herpetiformis and, 263
  lupus erythematosus profundus/panniculitis and, 283
Button osteomas on the calvarium, 1093

Cactus granuloma
  foreign-body reactions and, 374–375
  histopathology of, 375
CAD. *See* Chronic actinic dermatitis
N-Cadherin, desmoplastic melanoma and, 755
Cadherins, of desmosomes, 11
Cadmium selenide, tattoo reactions and, 377
CAF. *See* Calcifying aponeurotic fibroma
Café-au-lait spot
  histopathology of, 104
  of melanotic macules of Albright's syndrome, 705
  with neurofibromatosis, 1111
Calcaneal petechiae, 356, 356*f*
  histopathology of, 121, 356, 356*f*
Calcific elastosis, pseudoxanthoma elasticum v., 154
Calcification
  with dermatomyositis, 293
  of elastic fibers, 153–154
  with lipoid proteinosis, 430
  with metastatic calcinosis cutis, 435
  perforating calcific elastosis and, 397
  systemic scleroderma and, 300
Calcifying aponeurotic fibroma (CAF), 1096–1097, 1097*f*
  differential diagnosis of, 1097
Calcifying panniculitis, 530–531
  clinical features of, 530–531, 531*f*
  histopathology of, 131, 531, 531*f*
  pathogenesis of, 531
Calcineurin inhibitors
  for actinic prurigo, 335
  for chronic actinic dermatitis, 338
Calcinosis circumscripta, dystrophic calcinosis cutis and, 436–437
Calcinosis cutis, 435–438
  dystrophic, 436–437, 437*f*
  histopathology of, 121, 436–437, 436*f*
  idiopathic, 437
  metastatic, 435–436, 436*f*
  subepidermal calcified nodule, 437–438, 438*f*
Calcinosis universalis
  dystrophic calcinosis cutis and, 436, 437*f*
  histopathology of, 121
Calciphylaxis, 230, 230*f*
  calcifying panniculitis with, 531
  histopathology of, 94, 94*f,* 112, 116, 118–119, 230, 230*f*
  metastatic calcinosis cutis with, 435–436
  pathogenesis of, 230
Calcitonin gene-related peptide (CGRP)
  in dermis, 54
  Merkel cells and, 19
  prurigo nodularis and, 174
Calcium
  calciphylaxis and, 230
  dystrophic calcinosis cutis and, 436
  eccrine glands and, 35
  metastatic calcinosis cutis and, 435–436
  in pilomatricoma, 865
  in subcutaneous fat necrosis, 529–530, 530*f*
  subepidermal calcified nodule and, 438
Calcium channel blockers, T-cell lymphomatoid hyperplasias and, 936
C-ALCL. *See* Cutaneous anaplastic large cell lymphoma
Callus, of deep palmoplantar warts, 652
Calvarium, button osteomas on, 1093
Calymmatobacterium granulomatis, 570, 570*f*
  histopathology of, 120
  leishmaniasis v., 622
Campylobacter, Reiter's disease and, 182
c-ANCAs. *See* Cytoplasmic antineutrophil cytoplasmic antibodies
Candida albicans, 593, 598, 604
  acrodermatitis enteropathica and, 410
  erythroplakia of oral mucosa and, 812
  granuloma gluteale infantum and, 381
  lingua geographica and, 795
  necrolytic migratory erythema and, 409
  oral leukoplakia and, 812
Candida endocrinopathy syndrome, alopecia areata and, 475
Candida glabrata, 598
Candida granuloma, 598
Candida infections
  of nail, 507, 507*f,* 593, 595
  oral hairy leukoplakia with, 645
Candida krusei, 604
Candida onychomycosis, 599
  histopathology of, 599
Candida parapsilosis, nail unit and, 507, 507*f*
Candida sp.
  nail unit and, 507, 507*f*
  perioral dermatitis and, 463
Candida tropicalis, 604

Candidal granuloma, histopathology of, 119
Candidiasis, 597–599, 597*f,* 598*t*
  acropustulosis of infancy v., 267
  acute mucocutaneous candidiasis, 597–598, 597*f,* 598*t*
  Candida onychomycosis, 599
  chronic mucocutaneous candidiasis, 598
  disseminated candidiasis, 598–599
  histopathology of, 107, 109, 112
  in HIV, 597–598, 659, 660
  psoriasis vulgaris v., 181
Capecitabine therapy, pyogenic granuloma and, 1018
Capillary hemangioma variants, 1014–1016. *See also* Pyogenic granuloma
  cherry hemangioma, 1015
  infantile hemangioma, 1014–1015, 1014*f*–1015*f*
  tufted angioma, 1015–1016, 1015*f*–1016*f*
  tufted angioma v., 1016
Captopril
  drug-induced pemphigus and, 253
  lichenoid drug eruption and, 313
Carbamazepine
  DRESS with, 311
  drug-induced pseudolymphoma syndrome with, 320
  eosinophilic pustular folliculitis and, 466
  SJS and TEN with, 313
Carbidopa, scleroderma and, 296
Carbuncle, histopathology of, 128
Carcinoembryonic antigen (CEA)
  antibodies against, 76, 76*t*
  chondroid syringoma and, 894
  in nodular hidradenoma, 892
  nodular melanoma and, 752
  with Paget's disease, 838–839
  signet cell melanoma and, 757
Carcinoid carcinomas, metastatic carcinoma of skin, 1157–1158
  histopathology of, 1157–1158
  immunoperoxidase and electron microscopy studies, 1158
Carcinoid metastases, 1157
Carcinoid syndrome
  pellagra and, 408, 451
  scleroderma and, 296
Carcinoid tumors, 1154
Carcinoma. *See also* Adenocystic carcinoma; Adenoid cystic carcinoma; adenosquamous carcinoma; Basaloid carcinoma; Biphasic sarcomatoid carcinoma; Breast carcinoma; Colon carcinoma; Colorectal carcinoma; Eccrine sweat gland carcinoma; Gastric carcinoma; Gastrointestinal carcinoma; Intraductal carcinoma; Lung carcinoma; Lymphoepithelioma-like carcinoma; Metastatic carcinoma; Metastatic neuroendocrine carcinoma; Mixed carcinoma; Mucin-producing squamous cell carcinoma; Mucoepidermoid carcinoma; Nodular basal cell carcinoma; Oat cell carcinoma; Pagetoid squamous cell carcinoma; Pancreatic carcinoma; Pigmented basal cell carcinoma; Pigmented epidermotropic metastatic breast carcinoma; Pilomatric carcinoma; Pilomatrix carcinoma; Primary cutaneous signet ring cell carcinoma; Renal cell carcinoma; Sebaceous carcinoma; Small cell carcinomas; Squamous cell carcinoma; Sweat gland carcinoma; Syringoid eccrine carcinoma; Trichilemmal carcinoma; Verrucous carcinoma; Visceral carcinoma
  of apocrine glands, 895–896
  definition of, 853
  of eccrine glands, 895–900
  adenoid cystic carcinoma, 898*f*–899*f,* 899
  aggressive digital papillary adenocarcinoma, 899–900, 899*f*–900*f*
  classic type of, 896
  microcystic adnexal carcinoma, 896–897, 897*f*
  mucinous eccrine carcinoma, 898, 898*f*
  mucoepidermoid carcinoma, 898–899
  syringoid eccrine carcinoma, 896, 896*f*–897*f*
  of the inframammary crease, 1152–1153
Carcinoma en cuirasse, 1152–1153
Carcinoma *in situ,* verruciform xanthomas in, 685
Carcinosarcoma, 1093–1094, 1099
Cardiac failure, hereditary hemochromatosis and, 449
Cardiovascular syphilis, 583
Carmustine, drug-induced pigmentary alterations of, 692
Carney complex, 709
  cutaneous myxoma and, 997
  pigmented epithelioid melanocytoma and, 757
Cartilage
  antibodies to, 494
  inflammatory diseases of, 492–494
  chondrodermatitis nodularis helicis, 492–493, 493*f*
  pseudocyst of the auricle, 494, 494*f*
  relapsing polychondritis, 493–494
Cartilaginous tissue, tumors of, 98, 98*f,* 127
Caseation necrosis, rosacea and, 463–464
Caspases, androgenetic alopecia and, 481
Caspofungin, for aspergillosis, 599
Castleman's disease
  diffuse normolipemic plane xanthoma with, 684
  glomeruloid hemangioma with, 1010
  paraneoplastic autoimmune multiorgan syndrome and, 254
Cat hookworm, cutaneous larva migrans, 627–628, 627*f*
Catagen hair
  in alopecia areata, 474–475
  in growth cycle, 26–27, 29*f,* 31
Cationic proteins, of azurophilic granules, 43
Cats, exposure to, 571–573, 647
Cat-scratch disease, 571–572
  histopathology of, 119, 572
Cattle ringworm, 593
Cauliflower-like lesions
  Buschke-Loewenstein tumor, 656
  of condyloma acuminatum, 654, 655*f*
Cavernous hemangioma, 1019–1020
  blue rubber bleb nevus, 1019, 1019*f*
  cutaneous angiolipoleiomyoma v., 1079
  histopathology of, 126
  Maffucci's syndrome, 1019
  sinusoidal hemangioma, 1019–1020, 1019*f*–1020*f*
Cavernous lymphangioma, 1044
  differential diagnosis of, 1044
  histopathology of, 126, 1044, 1044*f*
CBH. *See* Cephalic brain-like hamartoma
CBN. *See* Cellular blue nevus
CCCA. *See* Central centrifugal cicatricial alopecia
CD1, precursor plasmacytoid dendritic cell lineage, 960
CD1a, antibodies against, 76*t,* 78
CD2
  with adult T-cell leukemia/lymphoma, 954
  cutaneous γ/δ T-cell lymphoma, 951
  mycosis fungoides, 942
  of primary cutaneous aggressive CD8-positive T-cell lymphoma, 950
  Sézary syndrome, 944
  subcutaneous panniculitis-like T-cell lymphoma, 948
CD3
  with adult T-cell leukemia/lymphoma, 954
  with angioimmunoblastic T-cell lymphoma, 952
  cutaneous γ/δ T-cell lymphoma, 951
  lymphomatoid granulomatosis, 933
  mycosis fungoides, 942
  precursor plasmacytoid dendritic cell lineage, 960
  of primary cutaneous aggressive CD8-positive T-cell lymphoma, 950
  primary cutaneous CD4-positive small-/ medium-sized pleomorphic T-cell lymphoma, 950
  Sézary syndrome, 944
  subcutaneous panniculitis-like T-cell lymphoma, 948
  T-cell prolymphocytic leukemia, 955
CD4
  with adult T-cell leukemia/lymphoma, 954
  with angioimmunoblastic T-cell lymphoma, 952
  cutaneous γ/δ T-cell lymphoma, 951
  lymphomatoid granulomatosis, 933
  mycosis fungoides, 942
  precursor plasmacytoid dendritic cell lineage, 959–960
  of primary cutaneous aggressive CD8-positive T-cell lymphoma, 950
  primary cutaneous CD4-positive small-/ medium-sized pleomorphic T-cell lymphoma, 950
  Sézary syndrome, 944
  subcutaneous panniculitis-like T-cell lymphoma, 948
  T-cell prolymphocytic leukemia, 955–956
CD5
  with adult T-cell leukemia/lymphoma, 954
  in chronic lymphocytic lymphoma/small lymphocytic lymphoma, 925
  cutaneous γ/δ T-cell lymphoma, 951
  diffuse large B-cell lymphoma, 930
  intravascular large B-cell lymphoma, 932
  mantle cell lymphoma, 930
  mycosis fungoides, 942
  nodal follicular lymphoma, 928
  primary cutaneous follicle center lymphoma, 918, 920
  primary cutaneous marginal zone lymphoma, 921
  Sézary syndrome, 944
  subcutaneous panniculitis-like T-cell lymphoma, 948
CD7
  cutaneous γ/δ T-cell lymphoma, 951
  of primary cutaneous aggressive CD8-positive T-cell lymphoma, 950
  Sézary syndrome, 944
CD8
  with angioimmunoblastic T-cell lymphoma, 952
  cutaneous γ/δ T-cell lymphoma, 951
  lymphomatoid granulomatosis, 933
  mycosis fungoides, 942
  primary cutaneous aggressive CD8-positive T-cell lymphoma, 949–950
  primary cutaneous CD4-positive small-/ medium-sized pleomorphic T-cell lymphoma, 950
  Sézary syndrome, 944
  subcutaneous panniculitis-like T-cell lymphoma, 948
  T-cell prolymphocytic leukemia, 955–956
CD10
  in chronic lymphocytic lymphoma/small lymphocytic lymphoma, 925
  intravascular large B-cell lymphoma, 932
  mantle cell lymphoma, 930
  neurothekeoma, 1129
  nodal follicular lymphoma, 928
  precursor B-cell lymphoblastic lymphoma, 924–925
  primary cutaneous diffuse large B-cell lymphoma, leg type, 922
  primary cutaneous follicle center lymphoma, 918, 920
  primary cutaneous marginal zone lymphoma, 921

CD11a, intravascular large B-cell lymphoma, 932
CD11c
  in chronic lymphocytic lymphoma/small lymphocytic lymphoma, 925
  myeloid sarcoma, 957
CD13
  myeloid sarcoma, 957
  precursor plasmacytoid dendritic cell lineage, 960
CD14, myeloid sarcoma, 957
CD15
  lymphomatoid granulomatosis, 933
  precursor plasmacytoid dendritic cell lineage, 960
CD18, intravascular large B-cell lymphoma, 932
CD19
  in chronic lymphocytic lymphoma/small lymphocytic lymphoma, 925
  diffuse large B-cell lymphoma, 930
  nodal follicular lymphoma, 928
  precursor B-cell lymphoblastic lymphoma, 924–925
  primary cutaneous follicle center lymphoma, 918
CD20
  in chronic lymphocytic lymphoma/small lymphocytic lymphoma, 925
  diffuse large B-cell lymphoma, 930
  intravascular large B-cell lymphoma, 932
  lymphomatoid granulomatosis, 933
  mantle cell lymphoma, 930
  nodal follicular lymphoma, 928
  precursor B-cell lymphoblastic lymphoma, 924–925
  primary cutaneous follicle center lymphoma, 918
  primary cutaneous marginal zone lymphoma, 921
CD21, primary cutaneous marginal zone lymphoma, 921
CD22
  in chronic lymphocytic lymphoma/small lymphocytic lymphoma, 925
  diffuse large B-cell lymphoma, 930
  nodal follicular lymphoma, 928
  precursor B-cell lymphoblastic lymphoma, 924–925
  primary cutaneous follicle center lymphoma, 918
CD23
  in chronic lymphocytic lymphoma/small lymphocytic lymphoma, 925
  mantle cell lymphoma, 930
  primary cutaneous marginal zone lymphoma, 921
CD24, precursor B-cell lymphoblastic lymphoma, 924–925
CD25, with adult T-cell leukemia/lymphoma, 954
CD30
  with adult T-cell leukemia/lymphoma, 954
  anaplastic large cell lymphoma, 952
  diffuse large B-cell lymphoma, 930
  lymphomatoid granulomatosis, 933
  mycosis fungoides, 942
  primary cutaneous CD4-positive small-/medium-sized pleomorphic T-cell lymphoma, 950
CD31
  angiosarcoma, 1042
  antibodies against, 76*t,* 78, 78*f*
  composite hemangioendothelioma and, 1037
  epithelioid angiosarcoma, 1043
  epithelioid hemangioendothelioma, 1040
  Kaposi's sarcoma, 1033
CD33, myeloid sarcoma, 957
CD34
  angiosarcoma, 1042
  antibodies against, 76*t,* 77–78
  composite hemangioendothelioma and, 1037
  epithelioid angiosarcoma, 1043
  epithelioid hemangioendothelioma, 1040
  in epithelioid sarcoma, 996
  giant cell fibroblastoma, 977
  Kaposi's sarcoma, 1033
  lipofibromatosis, 1070
  microvenular hemangioma, 1021
CD35, primary cutaneous marginal zone lymphoma, 921
CD43
  in chronic lymphocytic lymphoma/small lymphocytic lymphoma, 925
  mantle cell lymphoma, 930
  myeloid sarcoma, 957
  nodal follicular lymphoma, 928
CD45. *See also* Leukocyte common antigen
  of primary cutaneous aggressive CD8-positive T-cell lymphoma, 950
CD56
  cutaneous γ/δ T-cell lymphoma, 951
  precursor plasmacytoid dendritic cell lineage, 959–960
CD57
  cutaneous small cell undifferentiated carcinoma, 1139
  granular cell epulis of infancy, 1131
  lipofibromatosis, 1070
  neurothekeoma, 1129
CD68
  anaplastic large cell lymphoma, 953
  myeloid sarcoma, 957
CD79, primary cutaneous marginal zone lymphoma, 921
CD79a
  in chronic lymphocytic lymphoma/small lymphocytic lymphoma, 925
  diffuse large B-cell lymphoma, 930
  nodal follicular lymphoma, 928
  precursor B-cell lymphoblastic lymphoma, 924–925
  primary cutaneous follicle center lymphoma, 918
CD99
  lipofibromatosis, 1070
  pacinian perineural cell fibroma, 1134–1135
CD116, myeloid sarcoma, 957
CD117. *See also* c-kit
  myeloid sarcoma, 957
  schwannoma and, 1119
CD123, precursor plasmacytoid dendritic cell lineage, 960
CD179a/b, precursor B-cell lymphoblastic lymphoma, 924–925
CEA. *See* Carcinoembryonic antigen
Celiac disease, 417
  dermatitis herpetiformis and, 265
Cellular angiofibroma, 988
Cellular blue nevus (CBN), 702–704
  deep penetrating nevus v., 730
  histopathology of, 122, 126, 702–704, 703*f*
  Kaposi's sarcoma v., 1035
  pigmented epithelioid melanocytoma and, 757
  types of, 704
Cellular fibrous histiocytoma, 969, 972*f*
  dermatofibroma v., 973
  plexiform fibrohistiocytic tumor v., 977
Cellular myxoma, neurothekeoma v., 1129
Cellular neurothekeoma, histopathology of, 125
Cellular schwannoma (CS), 1118–1119, 1118*f*–1119*f*
  histopathology of, 125
Cellular schwannoma of Woodruff, 1122
Cellular stroma, pilomatricoma and, 865
Cellulite, lipedema and, 527
Cellulitis
  histopathology of, 115, 117
  radiation recall dermatitis and, 352
Central centrifugal cicatricial alopecia (CCCA), 485–487, 485*f*
  histopathology of, 485–487, 485*f*–486*f*
Central nervous system, extracutaneous melanomas in, 726
Centroblasts
  histopathology of, 122
  in primary cutaneous follicle center lymphoma, 918
Centrocyte
  nodal follicular lymphoma, 926, 928
  in primary cutaneous follicle center lymphoma, 918
Cephalic brain-like hamartoma (CBH), histopathology of, 125
Cercariae, of *Schistosoma,* 631
Cerebral cysticercosis, 632
Cerebriform congenital nevus, 725, 728
Ceruminal glands, extramammary Paget's disease of, 839
Cervical cancer
  condyloma acuminatum in, 654
  human papillomavirus in, 650
Cervical intraepithelial neoplasia (CIN), giant condyloma acuminata of Buschke and Loewenstein in, 656
CGD-TCL. *See* Cutaneous γ/δ T-cell lymphoma
CGRP. *See* Calcitonin gene-related peptide
Chanarin-Dorfman syndrome, 135
Chancre. *See also* Syphilitic chancre
  tuberculous, 550–551
Chancroid, 569–570, 569*f*
  chancre v., 581
  histopathology of, 120, 569–570, 569*f*
Chediak-Higashi syndrome, 693, 694–695
  histogenesis of, 695
  histopathology of, 104, 695
Cheilitis glandularis, 380–381
  histopathology of, 99, 99*f,* 129, 380–381
  pathogenesis of, 381
Cheilitis granulomatosa, 380, 380*f*
  histopathology of, 118, 380, 380*f*
  pathogenesis of, 380
Cheilitis, necrolytic migratory erythema, 409
Chemical agents, panniculitis due to, 525–526, 526*f*
Chemical burns, 343, 345
Chemical depigmentation, 691
  histopathology of, 104, 691
Chemokines, allergic contact dermatitis and, 239
Chemotherapeutic agents
  acute mucocutaneous candidiasis with use of, 597
  for diffuse large B-cell lymphoma, 930
  drug-induced pigmentary alterations of, 692
  herpes zoster with use of, 643
  for histiocytic cytophagic panniculitis, 533
  for leprosy, 559, 561, 563–564
  neutrophilic eccrine hidradenitis and, 491–492
  nontuberculosis mycobacteria infections with, 555
  radiation recall dermatitis and, 352
  ultraviolet recall and, 346
Cherry hemangioma, 1015
  differential diagnosis of, 1015
  histopathology of, 126, 1015
Chest, lupus erythematosus profundus/panniculitis and, 283
Chicken pox. *See* Varicella
Chilblain lupus erythematosus. *See* Chilblains
Chilblains, 352–355, 353*f*–354*f*
  differential diagnosis of, 355
  histopathology of, 115–116, 353, 353*f*–354*f*
  polymorphic light eruption v., 335
CHILD syndrome. *See* Congenital hemidysplasia with ichthyosiform erythrodermal and limb defects
Childbirth, telogen effluvium and, 478
Childhood diabetes mellitus, scleroderma and, 296
Childhood granulomatous periorificial dermatitis, 462–463
  histopathology of, 462
  pathogenesis of, 463
CHL. *See* Classical Hodgkin's lymphoma

Chlamydia infection, erythema nodosum with, 514
Chlamydia trachomatis, 571
  histopathology of, 120
  Reiter's disease and, 182
Chlorambucin, for dermatomyositis, 294
Chloramphenicol
  pellagra and, 408
  for rickettsial infections, 568
Chlorine, eccrine glands and, 35
Chloroma, myeloid sarcoma v., 957
Chloroquine
  lichenoid drug eruption and, 313
  for reticular erythematous mucinoses, 444
Chlorothiazide, photoallergic drug eruption and, 318
Chlorpromazine
  drug-induced lupus erythematosus with, 318
  photoallergic drug eruption and, 318
  photodistributed hyperpigmentation and, 319, 319*f*–320*f*
Chlorpromazine pigmentation, histopathology of, 107
Cholangiocarcinomas, 1156
Cholestanolemia, histopathology of, 124
Cholestasis, palmar xanthomas with, 680
Cholesterol
  sebaceous gland and, 30
  in xanthomas, 682–683
Cholesterol clefts
  in necrobiosis lipoidica, 366–367
  of necrobiotic xanthogranuloma with paraproteinemia, 683
  in xanthomas, 682, 682*f*
Cholesterol emboli, histopathology of, 112
Cholinergic stimulation, of eccrine glands, 35
Chondroblasts, in chondroid lipoma, 1067
Chondrocytes
  S100 protein in, 77
  of soft tissue chondromas, 1094
Chondrodermatitis nodularis helicis (CNH), 492–493, 493*f*
  acanthoma fissuratum v., 357
  histopathology of, 120, 492–493, 493*f*
  pathogenesis of, 493
Chondroid lipoma, 1067–1068, 1068*f*
  differential diagnosis of, 1067
  histopathology of, 127, 1067, 1068*f*
  pathogenesis of, 1067–1068
Chondroid syringoma, 893–894
  additional studies of, 894
  differential diagnosis of, 894
  histopathology of, 123, 893–894, 893*f*–894*f*
  with nevus sebaceus, 871
Chondroitin sulfate, PAS and, 69, 69*t*
Chondro-osseus tumors, 1086–1100
  benign cartilagenous tumors, 1094–1097
    calcifying aponeurotic fibroma, 1096–1097, 1097*f*
    soft tissue chondromas, 1094–1096, 1095*f*–1096*f*
  cutaneous ossification, 1086–1094
    Albright's hereditary osteodystrophy, 1086–1087, 1086*f*
    extraskeletal osteosarcoma, 1093–1094, 1093*f*
    metaplastic or secondary ossification, 1089–1090, 1090*f*
    osteoma cutis, 1087–1089, 1088*f*–1089*f*
    postinjury ossification, 1090–1093, 1091*f*–1092*f*
  extraskeletal myxoid chondrosarcoma, 1097–1098, 1098*f*
    in chondroid lipoma, 1067
    differential diagnosis of, 1098
    histopathology of, 1098, 1098*f*
    pathogenesis of, 1098
  mesenchymal chondrosarcoma, 1098–1099, 1099*f*
    differential diagnosis of, 1099
    myopericytoma and, 1049
    pathogenesis of, 1099
  osseous and chondroid lesions, 1099–1100, 1100*f*
Chondrosarcoma
  extraskeletal myxoid chondrosarcoma, 1097–1098, 1098*f*
  histopathology of, 127
  mesenchymal chondrosarcoma, 1098–1099, 1099*f*
  radiation-induced, 351
Chordoid sarcoma, 1097
Choriocarcinoma, 1158
Chorionic gonadotropin antigen, 1158
Chorioretinitis, with onchocerciasis, 630
Choroid, melanoma of, 700
Chrome green, tattoo reactions and, 377
Chromoblastomycosis, histopathology of, 118–119, 132
Chromogranin A, Merkel cells and, 19
Chromogranin, antibodies against, 76*t,* 77
Chromomycosis, 600*t,* 601, 607–608, 607*f*
  histopathology of, 119, 607, 607*f*
  pathogenesis of, 608
Chronic actinic damage, histopathology of, 108
Chronic actinic dermatitis (CAD), 338–340, 338*f*–340*f*
  histopathology of, 108, 111, 117
  in HIV, 660
Chronic allergic dermatitis, histopathology of, 109
Chronic atopic dermatitis, histopathology of, 90, 90*f,* 109
Chronic bullous dermatosis of childhood. *See* Linear IgA dermatosis, childhood type
Chronic cutaneous leishmaniasis, 621, 623–624
  differential diagnosis of, 624
  histopathology of, 623–624
Chronic cutaneous lupus erythematosus, 280–283, 281*f*–282*f,* 284*f*
  discoid lupus erythematosus, 280–283, 281*f*–282*f*
  lupus erythematosus profundus/panniculitis, 283, 284*f*
  tumid lupus erythematosus, 283, 284*f*
  verrucous lupus erythematosus, 282*f,* 283
Chronic deep folliculitis, 544
  histopathology of, 544
Chronic eczema, actinic prurigo v., 336
Chronic erythema nodosum, histopathology of, 131
Chronic fibrosing alveolitis, ulcerative colitis with, 416
Chronic focal LCD, 669
Chronic gonococcemia, 548–549
  histopathology of, 548–549
  pathogenesis of, 549
Chronic granulomatous disease, 245
Chronic lymphocytic leukemia (CLL), 925–926
  clinical features of, 925
  differential diagnosis of, 919*t,* 926
  histogenesis of, 925–926
  histopathology of, 925, 926*f*
  paraneoplastic autoimmune multiorgan syndrome and, 254
  primary cutaneous follicle center lymphoma v., 919
  with relapsing polychondritis, 493
Chronic meningococcemia, 548, 548*f*
  histopathology of, 548, 548*f*
Chronic mucocutaneous candidiasis (CMC), 598
  histopathology of, 598
Chronic multifocal LCD, 669
Chronic myelogenous leukemia, histopathology of, 122
Chronic myeloid leukemia, 957–958
  clinical features of, 957, 958*f*
  differential diagnosis of, 958
  histogenesis of, 958, 959*f*
  histopathology of, 958, 958*t,* 959*f*
Chronic radiation dermatitis, 348–352, 349*f*–351*f*
  differential diagnosis of, 352
  histopathology of, 349–351, 349*f*–350*f*
Chronic septicemia, 548–549, 548*f*
  chronic gonococcemia, 548–549
  chronic meningococcemia, 548, 548*f*
Chronic spongiotic dermatitis
  definition and evaluation of, 237, 240*f*
  differential diagnosis of, 244
  histopathology of, 109
Chronic strongyloidiasis, 628
Chronic subcutaneous zygomycosis, 601
Chronic superficial folliculitis, 543
  histopathology of, 543
Chronic ulcerative herpes simplex, 639, 641
Chronic ulcers
  graft-*versus*-host disease and, 271
  histopathology of, 106
Chronic urticaria, 169
  celiac disease and, 417
  with strongyloidiasis, 628
Chrysiasis, 327
  histogenesis of, 327
  histopathology of, 121, 327
CHS1/LYST gene, 695
Churg-Strauss granuloma. *See also* Palisaded neutrophilic and granulomatosis
  Behçet's syndrome v., 414
Churg-Strauss syndrome (CSS), 213–214, 214*f*
  clinical features of, 213
  differential diagnosis of, 214
  granulomatous vasculitis and, 213
  histopathology of, 213–214, 214*f*
  palisaded neutrophilic and granulomatosis v., 370
  p-ANCA for, 207, 207*t*
  Wegener's granulomatosis v., 215
Churg-Strauss vasculitis, histopathology of, 91, 91*f,* 100, 100*f,* 111, 116, 130
Chylomicronemia, eruptive xanthomas with, 680
Chymase, mast cells and, 41
Cicatricial alopecia, 480
  graft-*versus*-host disease and, 271
Cicatricial pemphigoid, 258*t*, 259–260, 260*f*
  histopathology of, 115, 259–260, 260*f*
  immunofluorescent testing for, 258*t,* 260
  with nail unit, 506
  ultrastructural study of, 260
Cilia
  in bronchogenic duct cysts, 805
  in cutaneous ciliated cyst, 805
  in thyroglossal duct cysts, 805
CIN. *See* Cervical intraepithelial neoplasia
Cinnabar, tattoo reactions and, 377
Ciprofloxacin, drug-induced pseudoporphyria with, 320
Circumorificial plasmacytosis, 816
  histopathology of, 117
Circumscripta, histopathology of, 121
Cirrhosis, with reactive angioendotheliomatosis, 1008
Cirsoid aneurysm. *See also* Arteriovenous hemangioma
  histopathology of, 126
  symplastic hemangioma v., 1028
Citrulline, basal cell carcinoma and, 833
Civatte bodies
  discoid lupus erythematosus and, 281–282
  fixed drug eruptions and, 314
  with lichen planus of the nail, 505
CK20, cutaneous small cell undifferentiated carcinoma, 1139
c-kit, antibodies against, 76*t,* 78
CKs. *See* Cytokeratins
CLA. *See* Cutaneous lymphocyte-associated antigen
Cladosporium carrionii, 607
Cladosporium sp., 593
Clark's levels of invasion, 764–765
Clark's nevus, dysplastic nevus v., 734
Classic Kaposi's sarcoma, 1029, 1030*f*
Classic polyarteritis nodosa, 211–212

Classic Sweet's syndrome. *See* Acute febrile neutrophilic dermatosis
Classical Hodgkin's lymphoma (CHL), 933
Classification
  of histiocytes, 668*t*
  of leishmaniasis, 621, 622*t*
Claudin-1
  pacinian perineural cell fibroma, 1134–1135
  storiform perineural cell fibroma, 1132
Clear cell acanthoma, 799–800, 800*f*
  histopathology of, 104, 800, 800*f*
  pathogenesis of, 800
Clear cell adenocarcinoma, 1156
Clear cell atypical fibroxanthoma, 978–979
Clear cell basal cell carcinoma, 831
Clear cell fibrous papule, 988
Clear cell hidradenoma, 891
Clear cell myoepithelioma, 891
Clear cells
  sebaceous carcinoma and, 876
  of secretory portion of eccrine glands, 32
  in solitary trichilemmoma, 869
Clear cells of Toker, superficial spreading melanoma and, 745
Clinical pathology, of leprosy, 560
Clitoris, mucocutaneous end-organs in, 54
CLL. *See* Chronic lymphocytic leukemia
Clofazimine-induced pigmentation, 325, 692
  histopathology of, 325
  pathogenesis of, 325
Clonal nevi, deep penetrating nevus v., 730
Clonal seborrheic keratosis, 796*f,* 798, 832
  histopathology of, 105
Clonidine patch, drug-induced pseudolymphoma syndrome with, 320
Clostridium novyi, in injection abscesses, 567
Clostridium perfringens, in injection abscesses, 567, 568*f*
CMC. *See* Chronic mucocutaneous candidiasis
CMV. *See* Cytomegalovirus
CNH. *See* Chondrodermatitis nodularis helicis
Coagulation necrosis, with chemical burns, 346
Coagulopathies, 228–230, 229*f*
  histopathology of, 228–230
Cobalt blue, tattoo reactions and, 377
Cobb syndrome, verrucous hemangioma v., 1020
Cocaine, drug-induced scleroderma with, 316
Coccidioides immitis, 608
Coccidioidin skin test, 608
Coccidioidomycosis, 600*t,* 608–609, 608*f*
  erythema nodosum with, 514
  histopathology of, 118–119, 132, 608–609
  in HIV, 608, 659
  rhinosporidiosis v., 615
Cochayne-Touraine, with nail unit, 506
Codeine, radiation recall dermatitis and, 352
Cold injury, 352–355
  cryotherapy-induced, 355, 355*f*
  frostbite, 352
  panniculitis and, 526
  pernio, 352–355, 353*f*–354*f*
Cold panniculitis, histopathology of, 130–131
Cold sores. *See* Herpes labialis
Colitis, epidermolysis bullosa acquisita and, 261
Collagen fibers, 46–49, 47*f*–48*f*
  acquired perforating dermatosis and, 396
  aging of, 56
  atrophoderma of Pasini and Pierini and, 301–302
  biosynthesis of, 47–48
  connective tissue nevus with, 154
  cross-striations of, 48–49
  Ehlers-Danlos syndrome and, 156
  in elastofibroma dorsi, 987
  fibroblastic rheumatism and, 307
  granuloma annulare and, 362
  Kyrle's disease and, 392
  late-onset focal dermal elastosis and, 397
  lichen myxedematosus and, 443
  lichen sclerosus et atrophicus and, 305–306
  lipoid proteinosis and, 431
  locations of, 46–47, 47*f*
  microvenular hemangioma and, 1020
  morphea and, 297–298, 297*f*–298*f*
  nerve sheath myxoma and, 1127
  ochronosis and, 440–441
  pachydermoperiostosis and, 158
  perforating calcific elastosis and, 397
  perforating folliculitis and, 393
  pretibial myxedema and, 442
  reactive perforating collagenosis and, 395
  scleredema and, 446–447
  scurvy and, 407
  solar elastosis and, 389
  striae distensae and, 398
  in synovial sarcoma, 995
  systemic scleroderma and, 300–301
  types of, 49
Collagen implant granuloma, histopathology of, 118
Collagen necrosis, of Buruli ulcer, 556–557, 557*f*
Collagenous and elastotic marginal plaques of the hands, 391
  histopathology of, 391
Collagenous fibroma, 983
  histopathology of, 983, 983*f*
Collagenous spherulosis, epithelioid schwannoma v., 1120
Collarette, with clear cell acanthoma, 799
Colloid bodies
  adult colloid milium and, 430
  basal cell carcinoma presence of, 834
  discoid lupus erythematosus and, 281–282
  fixed drug eruptions and, 314
  juvenile colloid milium and, 429–430
  neonatal lupus erythematosus and, 285
  nodular colloid degeneration and, 430
Colloid milium, 429–430, 430*f*
  histopathology of, 121, 429–430, 430*f*
Colon carcinoma, 1155
  with Muir-Torre syndrome, 875
Colonic polyps, soft fibroma and, 981
Colony-stimulating factors (CSFs), of keratinocytes, 13
Colorectal carcinoma, 1156
Coma blister, 273
  histopathology of, 128, 273
  pathogenesis of, 273
Coma bullae
  histopathology of, 113
  sweat gland necrosis in, 316–317, 316*f*–317*f*
Combined nevus, 704
  deep penetrating nevus v., 729–730
  histopathology of, 704
Comedones
  of acne vulgaris, 459, 460*f*
  of trichostasis spinulosa, 470
Common blue nevus, 701–702, 702*f*
  deep penetrating nevus v., 730
  histopathology of, 122, 701–702, 702*f*
Common melanocytic nevi, 710–714
  histopathology of, 711–714, 711*f*–713*f*
Common tumorigenic melanoma, 749–753, 751*f*
  differential diagnosis of, 752
  histopathology of, 750–751
    architectural features, 750, 751*f*
    cytological features, 750–752, 751*f*
  immunohistochemistry of, 752–753
Common variable immunodeficiency, 381
Common wart. *See* Verruca vulgaris
Community-acquired methicillin-resistant *Staphylococcus aureus,* 542
Composite hemangioendothelioma, 1037
  histopathology of, 1037, 1037*f*
Compound melanocytic nevus, histopathology of, 122
Compound nevus, 738
  histopathology of, 105, 712–714, 712*f*–713*f,* 726–729, 727*f*
Compromised hosts
  herpes simplex in, 639
  herpes zoster in, 643–644
  varicella in, 643
Concentric fibroplasia, dysplastic nevus and, 735
Condyloma acuminatum, 654–656, 655*f*
  histopathology of, 105, 654–656, 655*f*
Condyloma lata, histopathology of, 90, 90*f*
Condylomata lata
  of endemic syphilis, 585
  of secondary syphilis, 582
Confluent papillomatosis, 449, 449*f*
  histogenesis of, 449
  histopathology of, 106, 449
  Malassezia furfur in, 596
Congenital acral melanocytic nevus, 725
Congenital cutaneous candidiasis, 597
Congenital cytomegalovirus, 644
Congenital diffuse melanosis, 689
  histogenesis of, 589
  histopathology of, 589
Congenital diseases, 133–162
  acrokeratoelastoidosis, 138, 138*f*
  acrokeratosis verruciformis of Hopf, 152, 152*f*
  aplasia cutis congenita, 143, 143*f*
  ataxia-telangiectasia, 145
  Bloom's syndrome, 144–145, 144*f*
  connective tissue nevus, 154–155, 154*f*–155*f*
  cutis laxa, 157–158, 157*f*
  Darier's disease, 149–152, 150*f*–151*f*
  dyskeratosis congenita, 139, 139*f*
  ectodermal dysplasia, 141–142, 142*f*
  Ehlers-Danlos syndrome, 155–156, 155*f*
  epidermolysis bullosa, 145–148, 145*t*
  familial benign pemphigus, 148–149, 149*f*
  focal dermal hypoplasia syndrome, 142–143, 143*f*
  hypomelanosis of Ito, 161–162, 161*f*
  ichthyosis, 133–137
    autosomal recessive, 135
    CHILD syndrome, 135–136, 135*f*
    epidermolytic hyperkeratosis, 134–135, 134*f*
    erythrokeratodermia variabilis, 136
    harlequin, 136
    linearis circumflexa, 136
    syndromes associated with, 136–137
    vulgaris, 133
    X-linked, 133
  incontinentia pigmenti, 160–161, 161*f*
  keratosis palmaris et plantaris, 137, 137*f*
  linear melorheostotic scleroderma, 155
  pachydermoperiostosis, 158
  pachyonychia congenita, 138–139, 138*f*
  poikiloderma congenitale, 143–144
  porokeratosis, 139–141, 140*f*
  pseudoxanthoma elasticum, 152–154, 153*f*
  urticaria pigmentosa, 158–160, 158*f*–159*f*
  Werner's syndrome, 145
  Winchester syndrome, 155
  xeroderma pigmentosum, 141
Congenital hemangiomas, 1013–1014
  noninvoluting, 1013–1014, 1014*f*
  rapidly involuting, 1013, 1013*f*
Congenital hemidysplasia with ichthyosiform erythrodermal and limb defects (CHILD syndrome), 135–136, 135*f*
  verruciform xanthomas with, 685
Congenital herpes simplex, 639
Congenital ichthyosiform erythroderma, 135

Congenital leukemic infiltrates, congenital self-healing reticulohistiocytosis v., 669
Congenital melanocytic nevi, 725–729, 726*f*
  histopathology of, 122, 726–729, 727*f*
  incidence of, 726, 726*f*
Congenital nevi
  melanoma in, 728–729
  proliferative nodules in, 729
Congenital self-healing reticulohistiocytosis (CSHRH), 669–671
  histopathology of, 124
Congenital syphilis, 580
Congenital telangiectatic erythema. *See* Bloom's syndrome
Congenital vitamin B_3 deficiency. *See* Hartnup's disease
Conjunctivae, argyria of, 327
Conjunctivitis
  with acrodermatitis enteropathica, 410
  Reiter's disease and, 181
  rosacea and, 463
Connective tissue deficiencies, 231
  histopathology of, 231
Connective tissue disease, 220–221, 279–307
  atrophoderma of Pasini and Pierini, 301–303
  dermatomyositis, 293–295, 294*f*
  eosinophilic fasciitis, 303, 304*f*
  erythema chronicum migrans v., 586
  fibroblastic rheumatism, 307
  giant cell arteritis v., 208
  histopathology of, 107–108, 110–112
  lichen sclerosus et atrophicus, 303–307, 305*f*–306*f*
  lupus erythematosus, 279–292
    chronic cutaneous, 280–283, 281*f*–282*f*, 284*f*
    Jessner's lymphocytic infiltration of skin, 291–292, 292*f*
    neonatal, 283–285, 285*f*
    subacute cutaneous, 283, 285*f*
    systemic, 285–291, 286*t*, 287*f*–289*f*, 289*t*–291*t*
  lymphocytoma cutis v., 588
  mixed, 292–293
  of the nail, 506
  nephrogenic systemic fibrosis, 301, 302*f*
  poikiloderma atrophicans vasculare, 295, 296*f*
  pyoderma gangrenosum with, 224
  scleroderma, 295–301
  secondary syphilis v., 583
Connective tissue nevus, 154–155, 154*f*–155*f*
  differential diagnosis for, 155
  histopathology for, 155, 155*f*
  pathogenesis for, 155
Connective tissue panniculitis, localized lipoatrophy with, 527
Conradi-Hunermann syndrome, 136
Constipation, Behçet's syndrome and, 413
Contact dermatitis
  chronic actinic dermatitis v., 338
  xanthomas with, 686
Contact hypersensitivity, T cells in, 913
Contact reactions, lymphocytoma cutis v., 588
Copper metabolism
  Ehlers-Danlos syndrome and, 156
  elastosis perforans serpiginosa and, 395
Copper pennies, of chromomycosis, 607, 607*f*
Coral bead sign, 675
Cordylobia anthropophaga, as myiasis vector, 632–633
Corneal clouding, mucopolysaccharidosis and, 447
Corneal opacities
  with acrodermatitis enteropathica, 410
  Winchester syndrome and, 155
Cornu cutaneum. *See* Cutaneous horn
Corticosteroids, 380
  aspergillosis with use of, 599
  cryptococcosis with, 609
  for dermatomyositis, 294
  eosinophilic pustular folliculitis and, 466
  for erythema induratum, 521
  for follicular occlusion triad (hidradenitis suppurativa, acne conglobata, perifolliculitis capitis abscedens et suffodiens), 545
  granuloma gluteale infantum and, 381
  histopathology of, 380
  hyperlipidemia from, 680
  Langerhans cells and, 21
  perioral dermatitis and, 463
  SJS and TEN with, 313
  sporotrichosis with use of, 613
  steroid acne and, 461–462, 461*f*
Cosmetics, androgenetic alopecia and, 481
Coumarin necrosis, histopathology of, 116
Cowden's disease
  multiple trichilemmoma in, 869
  tumor of the follicular infundibulum v., 869
Cowden's syndrome, 1062
Cowpox
  histopathology of, 114
  human infection, 647
Coxsackie A16 virus, Kaposi's varicelliform eruption with, 641
Coxsackie virus, 658, 658*f*
  histopathology of, 114
Crab yaws, 583
Cranial fasciitis, 984
  histopathology of, 125
Creeping eruptions, of hookworm-related cutaneous larva migrans, 627
Creeping myiasis, 632–633
CREST syndrome, 437
  primary biliary cirrhosis with, 417
  systemic scleroderma and, 299
Creutzfeldt-Jakob disease, malignant atrophic papulosis and, 232
Criteria for the Classification of Systemic Lupus Erythematosus, 279
Crohn's disease, 415–416, 415*f*
  acrodermatitis enteropathica and, 410
  Behçet's syndrome v., 414
  cheilitis granulomatosa v., 380
  differential diagnosis of, 416
  erythema nodosum with, 514
  histopathology of, 118, 130, 415–416, 415*f*
  palisaded granulomatous panniculitis with, 525
  pathogenesis of, 416
  pyoderma gangrenosum with, 411
Cross syndrome, 693
Crush artifact
  in curettage, 6
  in punch biopsies, 5
Crusted scabies, 626
Cryofibrinogenemia, chilblains v., 353
Cryoglobulinemia, 219–220, 220*f*
  acro-osteolysis and, 401
  with chilblains, 353
  diffuse normolipemic plane xanthoma with, 684
  histopathology of, 111–112, 116, 121, 220
  leukocytoclastic vasculitis and, 216, 219–220, 220*f*
  with reactive angioendotheliomatosis, 1008
Cryoglobulins, 219–220, 220*f*
Cryoproteins, bowel-associated dermatosis-arthritis syndrome with, 412
Cryotherapy, injury induced by, 355, 355*f*
Cryptococcal cellulitis, 610
Cryptococcosis, 600*t*, 609–611, 610*f*
  differential diagnosis of, 611
  histopathology of, 117–119, 610, 610*f*
  molluscum contagiosum v., 649
  pathogenesis of, 610–611
  rheumatoid nodules v., 368
Cryptococcus, in HIV, 609, 659
Cryptococcus neoformans, 600*t*, 604, 609–611, 610*f*
  histoplasmosis v., 312
  paracoccidioidomycosis v., 606
CS. *See* Cellular schwannomas
CSCUC. *See* Cutaneous small cell undifferentiated carcinoma
CSFs. *See* Colony-stimulating factors
CSHRH. *See* Congenital self-healing reticulohistiocytosis
CSS. *See* Churg-Strauss syndrome
CTCL. *See* Cutaneous T-cell lymphoma
Culicosis bullosa, in arthropod assault reactions, 634*f*
Curettage
  histologic examination and, 6
  injury caused by, 357, 358*f*–359*f*
  for keratoacanthoma, 836
  of melanoma, 762
Cushing's disease, striae distensae and, 398
Cutaneous acanthamebiasis, in HIV, 660
Cutaneous alternariosis, 600*t*, 603, 603*f*
  histopathology of, 119, 132, 603
Cutaneous anaplastic large cell lymphoma (C-ALCL), 945–947
  histopathology of, 97, 97*f*, 124
Cutaneous angiolipoleiomyoma, 1060, 1076
Cutaneous angiomyolipoma, 1060
Cutaneous B-cell lymphoma, histopathology of, 121
Cutaneous calculi. *See* Subepidermal calcified nodule
Cutaneous cholesterol embolism, 230–231
  histopathology of, 231
Cutaneous chondroma, 1094
Cutaneous ciliated cyst, 805
  histopathology of, 127, 805
  pathogenesis of, 805
Cutaneous collagenous vasculopathy, 1011–1012
  histopathology of, 1012
Cutaneous disease. *See also* Dermatoses
  pigmentary presentations of, 692–693
    histogenesis of, 693
    histopathology of, 692–693
Cutaneous endometriosis, histopathology of, 127
Cutaneous epithelioid angiomatous nodule, 1025
  differential diagnosis of, 1025
  histopathology of, 1025, 1025*f*–1026*f*
Cutaneous extravascular necrotizing granuloma. *See* Palisaded neutrophilic and granulomatosis
Cutaneous follicular lymphoma, primary, histopathology of, 122
Cutaneous γ/δ T-cell lymphoma (CGD-TCL), 950–951
  clinical features of, 950–951
  differential diagnosis of, 951
  histogenesis of, 951
  histopathology of, 951
Cutaneous horn, 811, 811*f*
  histopathology of, 103, 811, 811*f*
Cutaneous larva migrans, 627–628, 627*f*
Cutaneous LCD, 669
Cutaneous leiomyosarcoma, 1080, 1081*f*
  histopathology of, 1080–1082, 1081*f*–1082*f*
Cutaneous leishmaniasis, 621
  chronic, histopathology of, 118
  histopathology of, 117, 120
  histoplasmosis v., 312
Cutaneous lesions, linear IgA dermatosis and, 265
Cutaneous lymphocyte-associated antigen (CLA)
  mycosis fungoides, 942
  with solitary pagetoid reticulosis, 941
Cutaneous lymphoid hyperplasia
  histopathology of, 94, 94*f*, 96, 96*f*, 117, 122
  macular atrophy and, 400
Cutaneous lymphomas. *See also* Lymphoproliferative disease
  chilblains v., 353

Cutaneous meningiomas, 1141–1143
differential diagnosis of, 1143
histogenesis of, 1142–1143
histopathology of, 125, 1142, 1142*f*
Cutaneous metastatic calcinosis, 435
Cutaneous myoepitheliomas, extraskeletal myxoid chondrosarcoma v., 1098
Cutaneous myxoma, 997
differential diagnosis of, 997
histopathology of, 121, 125, 997, 997*f*
Cutaneous necrosis/calcification syndrome, histopathology of, 118
Cutaneous necrotizing vasculitis, histopathology of, 91, 91*f,* 111
Cutaneous ossification, 1086–1094
Albright's hereditary osteodystrophy, 1086–1087, 1086*f*
extraskeletal osteosarcoma, 1093–1094, 1093*f*
metaplastic or secondary ossification, 1089–1090, 1090*f*
osteoma cutis, 1087–1089, 1088*f*–1089*f*
postinjury ossification, 1090–1093, 1091*f*–1092*f*
Cutaneous palisading granulomatous inflammation, microscopic polyarteritis and, 212
Cutaneous plasmacytoma, histopathology of, 96, 96*f,* 122
Cutaneous polyarteritis nodosa, erythema nodosum v., 515
Cutaneous porphyria, direct immunofluorescence for, 71, 73
Cutaneous protothecosis, 615–616, 616*f*
histopathology of, 616, 616*f*
pathogenesis of, 616
Cutaneous reactions to cytokines, histopathology of, 117
Cutaneous signet-ring carcinoma, 1151
Cutaneous small cell undifferentiated carcinoma (CSCUC), 1138–1140
differential diagnosis of, 1139
histogenesis of, 1139
histopathology of, 122, 1138–1139, 1138*f*–1139*f*
Cutaneous T-cell lymphoma (CTCL)
eosinophilic fasciitis and, 303
granuloma annulare v., 363
histopathology of, 109, 111, 121, 128
polymorphic light eruption v., 335
primary cutaneous diffuse large B-cell lymphoma, leg type v., 921
primary cutaneous peripheral T-cell lymphoma of, 949
Sézary syndrome of, 944
with syringolymphoid hyperplasia, 490–491
Cutaneous toxicities of drugs, 311–328
acute generalized exanthematous pustulosis, 314–315, 315*f*
antineoplastic chemotherapeutic drugs, 321–322, 321*f*–322*f*
antiretroviral therapy, 324
argyria, 327, 327*f*
bullous disorders, 317–318, 317*t*
chrysiasis, 327
clofazimine-induced pigmentation, 325
in coma, 316–317, 316*f*–317*f*
drug-induced Sweet's syndrome-like eruption, 315
erythema multiforme, 312, 312*f*
exanthemic drug eruptions, 311–312, 312*f*
fixed drug eruption, 314, 314*f*
halogen eruptions, 326–327, 326*f*
from human recombinant proteins, 322–324, 323*f*–324*f,* 323*t*
interface dermatitis, 312
lichenoid drug eruption, 313–314, 313*f*
lupus erythematosus, 318, 318*f*
mercury pigmentation, 327–328, 328*f*
minocycline pigmentation, 324–325, 324*f*
nephrotic systemic fibrosis, 316, 316*f*
neutrophilic drug eruptions, 314
penicillamine-induced dermatoses, 325–326, 325*f*–326*f*
photodistributed hyperpigmentation, 319–320, 319*f*–320*f*
photosensitivity, 318–319, 319*f*
pseudolymphoma syndrome, 320, 320*f*
pseudoporphyria, 320–321
scleroderma-like conditions, 315–316
TEN and SJS, 312–313, 313*f*
toxic acral erythema, 315
Cutaneous vasculitides, direct immunofluorescence for, 71–73
Cuticle, anatomy of, 36–37, 36*f*–37*f*
Cuticular system, anatomy of, 36–37, 36*f*–37*f*
Cutis laxa, 157–158, 157*f*
histogenesis of, 157–158
histopathology of, 96, 96*f,* 115, 120, 157, 157*f*
Cutis rhomboidalis nuchae, 390
Cyclin antibodies, for Spitz nevus, 722
Cyclin D1
acral-lentiginous melanoma and, 748
in chronic lymphocytic lymphoma/small lymphocytic lymphoma, 925
Cyclooxygenase inhibitors, SJS and TEN with, 313
Cyclophosphamide
for dermatomyositis, 294
drug-induced pigmentary alterations of, 692
Cyclospora, Reiter's disease and, 182
Cyclosporine
for actinic prurigo, 335
for chronic actinic dermatitis, 338
for dermatomyositis, 294
Cylindroma, 881–883, 882*f*
additional studies of, 882–883
histopathology of, 123, 882, 882*f*
with trichoepithelioma, 857
Cyrano sign, 672
Cystic hygroma, 1044
differential diagnosis of, 1044
histopathology of, 126, 1044, 1044*f*
Cysts
amebic, 625
of epidermis. *See* Epidermis, tumors and cysts of
of rhinosporidiosis, 615
Cytarabine, toxic acral erythema with, 315
Cytokeratins (CKs)
antibodies against, 75, 76*t*
chondroid syringoma and, 894
eccrine and apocrine glands, 34*f,* 36
epithelioid angiosarcoma, 1043
in epithelioid sarcoma, 996–997
in eruptive vellus hair cysts, 806
granuloma annulare and, 364
immunohistochemistry for, 18
in malignant chondroid syringoma, 895
Merkel cells and, 18–19
in syringocystadenoma papilliferum, 879
Cytokines
alopecia areata and, 476
cutaneous reactions to, 117
graft-*versus*-host disease and, 272
middermal elastolysis and, 399
T cells and, 45
Cytolysis, 235
Cytolytic blister, histopathology of, 113
Cytolytic substance secretion, of scabies, 627
Cytomegalovirus (CMV), 644–646, 645*f*–646*f*
Epstein-Barr virus, 644–645, 646*f*
erythema multiforme and, 268
histogenesis and viral identification of, 644
histopathology of, 644, 645*f*
in HIV, 644, 659
human herpesvirus-6, -7, -8, 645–646
Cytomegalovirus inclusion disease, 645*f*
histopathology of, 107, 116
Cytophagic histiocytic panniculitis, histopathology of, 101, 101*f,* 130
Cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCAs), for proteinase 3, 207, 207*t*
Cytoreductive therapy, graft-*versus*-host disease and, 272
Cytoskeletal antigens, antibodies against, 75
Cytotoxic dermatitis
T cells in, 913
ultraviolet recall and, 346
Cytotoxic drug eruptions, histopathology of, 91, 91*f,* 112
Cytotoxic drugs, tuberculosis with, 550
Cytotoxics, drug-induced pigmentary alterations of, 692
Cytotrophoblasts, 1158

D2-40, lymphatic vessels and, 768
Dabska's tumor, 1022. *See also* Papillary intralymphatic angioendothelioma
histopathology of, 126
retiform hemangioendothelioma v., 1036
Dapsone, drug-induced pseudoporphyria with, 320
Darier's disease, 85, 149–152, 150*f*–151*f*
acantholysis and, 151, 794
acantholytic actinic keratosis v., 810
acrokeratosis verruciformis of Hopf v., 149, 151–152
Bowen's disease v., 815
differential diagnosis of, 152
eczema herpeticum with, 638
familial benign pemphigus v., 149
folliculitis decalvans and, 487
histopathology of, 100, 100*f,* 113–114, 129, 150–151, 150*f*–151*f*
Kaposi's varicelliform eruption with, 641
pathogenesis of, 151–152
pigmentary presentations of, 692–693
transient acantholytic dermatosis v., 273–274
types of, 149–150
warty dyskeratoma v., 807
Darier-White disease, 506
Dark cells, of secretory portion of eccrine glands, 32
Daughter yaws, 583
Daunorubicin, drug-induced pigmentary alterations of, 692
De Sanctis-Cacchione syndrome, 141
Decapitation secretion
by apocrine glands, 33
in papillary eccrine adenoma, 890
in tubular apocrine adenoma, 880
Deep benign fibrous histiocytoma, myopericytoma and, 1049
Deep fibrous histiocytoma, 971–972
Deep fibrous nodules, of progressive nodular histiocytosis, 677
Deep folliculitis, histopathology of, 128
Deep granuloma annulare, 361
Deep incisional biopsy, 5–6
Deep JXG, 672
Deep palmoplantar warts, 652–653, 652*f*
histogenesis and viral identification of, 653
histopathology of, 652–653, 652*f*
Deep penetrating nevus, 729–730
differential diagnosis of, 730
histopathology of, 122, 729–730, 729*f*
Deep shave biopsy, 5–6
Deep vascular plexus, of dermal microvasculature, 50
Deep venous thrombosis, systemic lupus erythematosus and, 288

Degenerative collagenous plaques of the hands. *See* Collagenous and elastotic marginal plaques of the hands
Dego's disease, 232–233. *See also* Malignant atrophic papulosis
  Behçet's syndrome v., 414
  histopathology of, 94, 94*f,* 111, 116, 232–233, 232*f*
  pathogenesis of, 233
Dematiaceous fungi, 591, 592*t*
Demeclocycline hydrochloride, phototoxic drug eruption and, 319
Dementia, pellagra and, 408, 451
Demerol. *See* Meperidine hydrochloride
Demodex brevis, in demodicidosis, 464–465
Demodex folliculorum
  in demodicidosis, 464–465
  in skin, 60, 60*f*
Demodex mites, in HIV, 660
Demodex sp.
  androgenetic alopecia and, 481
  demodicidosis and, 464–465
  with eosinophilic pustular folliculitis, 467
  perioral dermatitis, 463
  rosacea and, 464
Demodicidosis, 464–465
  forms of, 464–465
  histopathology of, 465, 465*f*
  in HIV, 465, 660
  pathogenesis of, 465
Demodicidosis gravis, 464
Dendritic cells, 39–40, 39*f*
  aging of, 56
  in histiocytoses, 667
  melanoma v., 770
  in skin, 911
Dendritic processes, melanin transfer by, 15, 18
  in hair, 28
Dendrophages, 40
Depigmentation
  in halo nevus, 730, 732
  localized or diffuse, 87, 87*f*
  with piebaldism, 693
Depigmented extramammary Paget's disease, 692–693
Dermabrasion, milia and, 802
Dermal atrophying, of Lyme disease, 586–587, 587*f*
Dermal dendrocytes, 39–40, 39*f*
Dermal dendrocytoma, 678, 972
Dermal duct nevus, 793
  histopathology of, 793
Dermal erythropoiesis, extramedullary hematopoiesis and, 956
Dermal fasciitis, 984
Dermal fibroblasts, 38, 39*f*
  dermal muscle cells, 46
  emigrant inflammatory cells, 42–46, 42*f*–43*f,* 45*f*
    basophilic granulocytes, 44
    eosinophilic granulocytes, 43–44
    lymphocytes, 42*f*–43*f,* 44–46, 45*f*
    neutrophilic granulocytes, 42–43, 42*f*–43*f*
    plasma cells, 42*f,* 46
  mast cells, 41–42, 41*f*
  perivascular and interstitial dendritic cells, 39–40, 39*f*
  phagocytic macrophages, 40–41, 40*f*
Dermal fibrosis
  actinic prurigo and, 336
  mercury pigmentation and, 328, 328*f*
Dermal hair papilla, of hair follicles, 25
Dermal hematopoiesis, histopathology of, 117
Dermal hypersensitivity, chilblains v., 355
Dermal lymphatics, of dermal microvascular unit, 51*f,* 53
Dermal melanocytic hamartoma, 700–701
  histogenesis of, 701
  histopathology of, 117
Dermal melanocytic nevus, histopathology of, 122
Dermal melanocytic tumors of uncertain malignant potential (MELTUMP), histopathology of, 123
Dermal melanocytoses
  mongolian spot, 699–700
  nevi of Ota, Ito, and Hori; dermal melanocyte hamartoma, 700–701
Dermal microvascular unit, 50–55
  dermal lymphatics of, 51*f,* 53
  endothelial cells of, 50–52, 51*f*
  glomus cells of, 52–53, 53*f*
  neural network of, 53–55, 54*f*
Dermal muscle cells, 46
Dermal nevus, histopathology of, 105
Dermal papillae, psoriasis vulgaris and, 176–177
Dermal pigments, histopathology of, 121
Dermal recurrent melanocytic nevus, histopathology of, 122
Dermal/interstitial dendritic cell
  in histiocytoses, 667
  xanthogranuloma cells from, 671
Dermatan sulfate, mucopolysaccharidosis and, 447
Dermatitis. *See also* Allergic contact dermatitis; Atopic dermatitis; Chronic radiation dermatitis; Chronic spongiotic dermatitis; Contact dermatitis; Dyshidrotic dermatitis; Exfoliative dermatitis; Irritant contact dermatitis; Photoallergic dermatitis; Seborrheic dermatitis; Stasis dermatitis
  basophils and, 44
  mycosis fungoides v., 944
  pellagra and, 408, 451
  relapsing polychondritis with, 494
Dermatitis herpetiformis, 263–265, 264*f,* 1171*f*
  bullous systemic lupus erythematosus v., 263
  celiac disease with, 417
  direct immunofluorescence for, 71
  histopathology of, 93, 93*f,* 115, 263–264, 264*f*
  immunofluorescence testing for, 264–265, 264*f*
  pathogenesis of, 265
  prurigo simplex v., 173
  sclerosing cholangitis with, 417
  ultrastructural study of, 265
  vesicular pemphigoid v., 259
Dermatitis schistosomica, 631
Dermatobia hominis, as myiasis vector, 632–633
Dermatofibroma, 969, 971*f,* 1181*f*
  acantholytic dyskeratosis and, 794
  aneurysmal fibrous histiocytoma, 970, 972*f*
  atypical fibrous histiocytoma, 970, 973*f*
  basal cell carcinoma v., 827*f*
  cellular fibrous histiocytoma, 969, 972*f*
  common blue nevus v., 701
  deep fibrous histiocytoma, 971–972
  dermal dendrocytes and, 39
  differential diagnosis of, 973–974
  enzyme histochemistry of, 972–973
  epithelioid fibrous histiocytoma, 970–971, 973*f*
  extraneural sporadic cutaneous neurofibromas v., 1110
  extraskeletal osteosarcoma v., 1094
  histogenesis of, 972
  histopathology of, 98, 98*f,* 106, 124, 969, 971*f*
  inflammatory pseudotumor v., 994
  juvenile xanthogranuloma v., 673
  neoplasm *versus* reactive process, 972
  papular xanthoma v., 674
  pleomorphic fibroma v., 981
Dermatofibrosarcoma protuberans (DFSP), 974–976, 1115–1116
  cellular fibrous histiocytoma v., 969
  dermatofibroma v., 973
  differential diagnosis of, 976, 976*f*
  giant cell fibroblastoma v., 977
  histogenesis of, 975–976
  histopathology of, 125, 974–975, 975*f*
  storiform perineural cell fibroma v., 1133
Dermatomycosis, 591, 592*t*
Dermatomyofibroma, 980–981
  differential diagnosis of, 981
  histogenesis of, 980
  histopathology of, 125–126, 980, 981*f*
  plexiform fibrohistiocytic tumor v., 977
Dermatomyositis, 293–295, 294*f*
  celiac disease and, 417
  differential diagnosis of, 294–295
  direct immunofluorescence for, 71–72, 72*f*
  histogenesis of, 294
  histopathology of, 91, 91*f,* 107–108, 112, 294, 294*f*
  malignant atrophic papulosis and, 232
  of nail unit, 506
  necrolytic migratory erythema v., 409
  pathogenesis of, 293–294
  poikiloderma atrophicans vasculare and, 295
  reticulohistiocytosis v., 676
  systemic lesions with, 294
  systemic lupus erythematosus with, 286
Dermatomyositis sine myositis. *See* Dermatomyositis
Dermatopathia pigmentosa reticularis, 689–690
Dermatopathologic diagnosis
  biological relevance of, 4
  difficulties with, 2–3
  introduction to, 1
  prognostication, 3–4
  sensitivity and specificity of, 1–2
Dermatophyte infection
  acute spongiotic dermatitis and, 243
  subacute spongiotic dermatitis and, 243
Dermatophytes, 591–595, 592*t,* 593*t,* 594*f*–595*f*
Dermatophytid. *See* Id reaction
Dermatophytosis, 591–595, 593*t,* 594*f*–595*f,* 598*t*
  erythema nodosum with, 514
  histopathology of, 86, 86*f,* 103, 108–109, 113, 593–595, 594*f*–595*f*
  pathogenesis of, 595
Dermatoradiology, 1057, 1058*t*
Dermatoses. *See also* Inflammatory dermatoses
  histopathologic diagnoses of, 1–4
  penicillamine-induced, 325–326, 325*f*–326*f*
  prognostication of, 3–4
Dermatosis. *See* Intraepidermal neutrophilic dermatosis; Linear IgA dermatosis
Dermatosis papulosa nigra, 795, 797*f,* 799
  histopathology of, 104, 799
Dermis
  aging of, 56
  apocrine glands in, 57, 58*f*
  dermal fibroblasts of, 38–46, 39*f*–43*f,* 45*f*
    dermal muscle cells, 46, 57
    emigrant inflammatory cells, 42–46, 42*f*–43*f,* 45*f*
    mast cells, 41–42, 41*f*
    perivascular and interstitial dendritic cells, 39–40, 39*f*
    phagocytic macrophages, 40–41, 40*f*
  dermal microvascular unit, 50–55
    dermal lymphatics, 51*f,* 53
    endothelial cells, 50–52, 51*f*
    glomus cells, 52–53, 53*f*
    neural network, 53–55, 54*f*
  extracellular matrix of, 46–50, 47*f*–48*f*
    collagen fibers, 46–49, 47*f*–48*f*
    elastic fibers, 49
    ground substance, 49–50
  tumors of, 96–98, 96*f*–98*f*
    cysts of dermis and subcutis, 98, 98*f,* 127
    large polygonal and round cell, 97, 97*f,* 122–125
    small cell, 96, 96*f,* 121–122

spindle cell, pleomorphic, and connective tissue tumors, 98, 98*f,* 125–127
Dermis adjacent to folliculitis, histopathology of, 117
Dermoid cyst, 804
histopathology of, 127, 804, 804*f*–805*f*
pathogenesis of, 804
Desipramine, photodistributed hyperpigmentation and, 319, 319*f*–320*f*
Desmin
angiomyofibroblastoma of the vulva and, 991
schwannoma and, 1119
spindle cell hemangioma, 1028
Desmocollins, 11
pemphigus and, 245
Desmogleins, 11
pemphigus and, 245, 247, 249
pemphigus herpetiformis and, 253
Desmoid tumor. *See also* Desmoid-type fibromatosis
histopathology of, 125
Desmoid-type fibromatosis, 992
histogenesis of, 992
histopathology of, 992, 992*f*
Desmoplakin, 11
pemphigus and, 245
Desmoplastic blue nevi, 701
Desmoplastic cutaneous leiomyosarcoma, radiation-induced, 351
Desmoplastic fibroblastoma. *See* Collagenous fibroma
Desmoplastic hairless hypopigmented nevus, 725, 728
Desmoplastic leiomyosarcoma, 1081
Desmoplastic melanoma, 749, 753–756, 754*f*–755*f*
differential diagnosis of, 756
histopathology of, 98, 98*f,* 123, 126, 753–755, 754*f*
immunohistochemistry of, 755
reexcision specimens of, 755
Desmoplastic Spitz nevi, 722
Desmoplastic stroma, in desmoplastic trichoepithelioma, 860
Desmoplastic trichilemmoma, 868, 868*f*
Desmoplastic trichoepithelioma, 859–860
differential diagnosis of, 860
histopathology of, 123, 860, 860*f*
microcystic adnexal carcinoma v., 897
Desmosomes
Bowen's disease and, 815
Darier's disease and, 151–152
in eccrine poroma, 887
familial benign pemphigus with, 151
of keratinocytes, 7–11, 10*f*
keratoacanthoma and, 837
of oral mucosa, 12
in Paget's disease, 838
pemphigus and, 245, 247, 247*f*
in pilomatricoma, 865
in squamous cell carcinoma, 820
transient acantholytic dermatosis and, 273
Desquamation, radiation dermatitis and, 348
DFSP. *See* Dermatofibrosarcoma protuberans
DHT. *See* Dihydrotestosterone
Diabetes mellitus
acanthosis nigricans and, 448
acquired perforating dermatosis and, 395–396
alopecia areata and, 475
granuloma annulare and, 361
hereditary hemochromatosis and, 449
with Kyrle's disease, 392
lipomembranous panniculitis with, 531
localized lipodystrophy with, 526–527
necrobiosis lipoidica and, 365, 367
palisaded neutrophilic and granulomatosis with, 369
palmar fibromatosis and, 992
scleredema and, 446
soft fibroma and, 981
Diabetic bullae, 273
friction blisters v., 357
Diagnosis. *See* Histologic diagnosis
Diarrhea
acrodermatitis enteropathica and, 410
Behçet's syndrome and, 413
with common variable immunodeficiency, 381
pellagra and, 408, 451
Differential diagnosis
biopsy with, 5–6
for difficult cases, 2
Diffuse alimentary tract ganglioneuromatosis, 1137
Diffuse articular lipomatosis. *See* Lipoma arborescens
Diffuse (acute) cutaneous leishmaniasis, 621–623, 622*t,* 624*f*
histopathology of, 622–623
Diffuse large B-cell lymphoma (DLBCL), 930–932
clinical features of, 930
differential diagnosis of, 931–932
histogenesis of, 930–931, 931*f*
histopathology of, 122, 930, 931*f*
Hodgkin's lymphoma v., 935
intravascular large B-cell lymphoma of, 932
Diffuse leprosy, 560, 562, 565–566, 565*f*
Diffuse lipomatosis, 1062
Diffuse normolipemic plane xanthoma (DNPX), 684–685, 685*f*
differential diagnosis of, 685
histopathology of, 124, 684–685, 685*f*
papular xanthoma v., 674
pathogenesis of, 685
Diffuse pattern, of benign cephalic histiocytosis, 677–678
Diffuse plane xanthomas, 680
Diffuse systemic scleroderma, systemic scleroderma and, 299
Digital mucous cyst, 997
histogenesis of, 997
histopathology of, 125, 997, 998*f*
Digital mucous cyst/myxoid cyst, histopathology of, 121
Dihydrotestosterone (DHT)
acne vulgaris and, 460–461
androgenetic alopecia and, 481
Dihydroxyphenylalanine reaction, for melanocytes, 16
Dilated pore of Winer, 855
histopathology of, 123, 127, 855, 855*f*–856*f*
Diltiazem
acute generalized exanthematous pustulosis with, 314
photodistributed hyperpigmentation and, 319–320
Dimorphic fungi, 592*t*
Diphosphopyridine nucleotide diaphorase, in nodular hidradenoma, 892
Diplococcus pneumoniae, acute septicemia from, 546–547
Diptera, as myiasis vector, 632
Dirofilaria immitis, 628
Dirofilaria repens, 628
Dirofilaria sp., 628–629, 629*f*
Dirofilaria subdermata, 628
Dirofilaria tenuis, 628
Dirofilaria ursi, 628
Dirofilariasis. *See* Subcutaneous dirofilariasis
Discoid lupus erythematosus (DLE), 280–283, 281*f*–282*f,* 1177*f*
differential diagnosis of, 282–283
with follicular mucinosis, 468
histopathology of, 93, 93*f,* 115, 128, 280–283, 281*f*–282*f*
Jessner's lymphocytic infiltration of the skin v., 292
lichen planopilaris v., 190–191
systemic lupus erythematosus v., 285–286
tumid lupus erythematosus v., 283
verruciform xanthomas with, 685
verrucous lupus erythematosus v., 283
Disease listings by site, pattern, and cytology, 103–132
of epidermis and stratum corneum, 103–104
Dissecting cellulitis of the scalp
histopathology of, 131
tufted hair folliculitis with, 487
Disseminated acanthamoebiasis, 625
in HIV, 660
Disseminated acantholytic acanthoma, 794
Disseminated anergic cutaneous leishmaniasis. *See* Diffuse (acute) cutaneous leishmaniasis
Disseminated candidiasis, 598–599
histopathology of, 598–599
Disseminated epidermolytic acanthoma, 793
differential diagnosis of, 793
histopathology of, 793
Disseminated gonococcal infection. *See* Chronic gonococcemia
Disseminated histoplasmosis, 611–612
Disseminated intravascular coagulation
histopathology of, 91, 91*f,* 94, 94*f,* 111, 116
systemic lupus erythematosus and, 288
Disseminated LCD, 669
Disseminated nevus anelasticus, middermal elastolysis and, 399
Disseminated strongyloidiasis, 628, 629*f*
Disseminated superficial actinic porokeratosis, 139
Distal and lateral subungual onychomycosis (DLSO), 593
DLBCL. *See* Diffuse large B-cell lymphoma
DLE. *See* Discoid lupus erythematosus
DLSO. *See* Distal and lateral subungual onychomycosis
DNA repair, dysplastic nevus and, 738
DNA topoisomerase I, systemic scleroderma and, 301
DNPX. *See* Diffuse normolipemic plane xanthoma
Docetaxel
drug-induced lupus erythematosus with, 318
drug-induced scleroderma with, 316
toxic acral erythema with, 315
Dog hookworm, cutaneous larva migrans, 627–628, 627*f*
Donovan bodies, 570
Donovanosis. *See* Granuloma inguinale
DOPA reaction, 701
malignant blue nevus and, 772
Dopa, tyrosinase and, 17–18
Double refraction, of foreign bodies, 374
Dowling-Degos disease, 689–690
histopathology of, 109
Downgrading reactions, 564
Down's syndrome
alopecia areata and, 475
elastosis perforans serpiginosa and, 394
macular atrophy and, 400
Doxorubicin, drug-induced pigmentary alterations of, 692
Doxycycline
phototoxic drug eruption and, 319
SJS and TEN with, 313
DRESS. *See* Drug rash with eosinophilia and systemic symptoms
Drug(s)
B-cell lymphomatoid hyperplasia and, 916
coma blister and, 273
cutaneous toxicities of, 311–328
acute generalized exanthematous pustulosis, 314–315, 315*f*
antineoplastic chemotherapeutic drugs, 321–322, 321*f*–322*f*
antiretroviral therapy, 324
argyria, 327, 327*f*
bullous disorders, 317–318, 317*t*
chrysiasis, 327

Drug(s) (*continued*)
clofazimine-induced pigmentation, 325
in coma, 316–317, 316*f*–317*f*
drug-induced Sweet's syndrome-like eruption, 315
erythema multiforme, 312, 312*f*
exanthemic drug eruptions, 311–312, 312*f*
fixed drug eruption, 314, 314*f*
halogen eruptions, 326–327, 326*f*
from human recombinant proteins, 322–324, 323*f*–324*f*, 323*t*
interface dermatitis, 312
lichenoid drug eruption, 313–314, 313*f*
lupus erythematosus, 318, 318*f*
mercury pigmentation, 327–328, 328*f*
minocycline pigmentation, 324–325, 324*f*
nephrotic systemic fibrosis, 316, 316*f*
neutrophilic drug eruptions, 314
penicillamine-induced dermatoses, 325–326, 325*f*–326*f*
photodistributed hyperpigmentation, 319–320, 319*f*–320*f*
photosensitivity, 318–319, 319*f*
pseudolymphoma syndrome, 320, 320*f*
pseudoporphyria, 320–321
scleroderma-like conditions, 315–316
TEN and SJS, 312–313, 313*f*
toxic acral erythema, 315
erythema nodosum and, 514–515
systemic lupus erythematosus and, 286–287, 286*t*
toxic epidermal necrolysis and, 269
Drug eruptions, postinflammatory pigmentary alteration with, 690
Drug hypersensitivity, lymphocytoma cutis v., 588
Drug injections
eosinophilic panniculitis and, 515
panniculitis and, 525
Drug rash with eosinophilia and systemic symptoms (DRESS), 311
Drug reactions, granuloma annulare v., 363
Drug-associated bullous pemphigoid, 259
Drug-associated linear IgA dermatosis, 266
Drug-induced lupus, histopathology of, 112
Drug-induced pemphigus, 253
histopathology of, 114, 253
immunofluorescence testing of, 253
pathogenesis of, 253
Drug-induced pigmentary alterations, 692
histopathology of, 692
Drug-induced pseudolymphoma, histopathology of, 122
Drug-induced pseudoporphyria, histopathology of, 114
Drug-induced vasculitis, 221
Duct ectasia, cheilitis glandularis and, 381
Ductal cells, of eccrine hidrocystoma, 884
Ductal eccrine carcinoma, malignant eccrine poroma and, 888
Dupuytren's contracture. *See also* Palmar fibromatosis
knuckle pads and, 993
Durcum's disease, 534. *See also* Adiposis dolorosa
lipedema and, 527
Dwarfism
mucopolysaccharidosis and, 447
Winchester syndrome and, 155
Dysbetalipoproteinemia, 680
Dyschromatosis symmetrica hereditaria. *See* Acropigmentation symmetrica of Dohi
Dyschromia, radiation dermatitis and, 348
Dyshidrotic dermatitis, 240–241, 241*f*
histopathology of, 108, 241, 241*f*
Dyskeratosis. *See also* Focal acantholytic dyskeratosis
acantholysis with, 794
in acantholytic squamous cell carcinoma, 821
PAMS and, 254
transient acantholytic dermatosis with, 273
ultraviolet recall and, 346
Dyskeratosis congenita, 139, 139*f*, 689–690
poikiloderma atrophicans vasculare and, 295
Dyskeratotic acanthoma, 794
Dyskeratotic keratinocytes
of Bowenoid papulosis of genitalia, 656
fixed drug eruptions and, 314
ultraviolet recall and, 346
in verrucous lupus erythematosus, 283
Dyskerin, 139
Dysmaturation, ultraviolet recall and, 346
Dyspareunia, necrolytic migratory erythema, 409
Dysplastic nevus, 733–738, 734*f*–735*f*, 736*t*, 737*t*
differential diagnosis and management of, 737*t*, 738
grading of, 735–737, 736*t*
histopathology of, 105, 122, 733–737, 734*f*–735*f*, 736*t*
junctional nevus v., 712
melanoma risk and, 760
melanoma v., 749
nevi of acral skin v., 715
nevi of flexural sites and, 718
pathobiology of, 736*t*, 737–738, 737*t*
pigmented spindle cell nevus v., 724–725
radial growth phase melanoma v., 737*t*, 738
Spitz nevi v., 723–724
Dystrophic calcinosis cutis, 436–437, 437*f*
with burn scars, 346
histopathology of, 437
Dystrophic epidermolysis bullosa
milia and, 802
with nail unit, 506

Early spongiotic dermatitis, histopathology of, 113
Ears
discoid lupus erythematosus and, 280
relapsing polychondritis and, 493
vellus hairs, 57
EB. *See* Epidermolysis bullosa
EBA. *See* Epidermolysis bullosa acquisita
EBV. *See* Epstein-Barr virus
Ecchymoses, Ehlers-Danlos syndrome and, 156
Eccrine acrospiroma, 891
Eccrine adenocarcinoma, histopathology of, 123
Eccrine angiomatous hamartoma, 883
histopathology of, 128
Eccrine glands, 31–36
with adnexotropic mycosis fungoides, 939
carcinomas of, 895–900
adenoid cystic carcinoma, 898*f*–899*f*, 899
aggressive digital papillary adenocarcinoma, 899–900, 899*f*–900*f*
classic type of, 896
microcystic adnexal carcinoma, 896–897, 897*f*
mucinous eccrine carcinoma, 898, 898*f*
mucoepidermoid carcinoma, 898–899
syringoid eccrine carcinoma, 896, 896*f*–897*f*
CEA in, 76
chilblains and, 353, 353*f*–354*f*, 355
collagen fibers and, 47
coma blister and, 273
in dermoid cyst, 804
discoid lupus erythematosus and, 280
embryology of, 32
histopathology of, 99, 99*f*, 128–129
inflammatory diseases of, 490–492
neutrophilic eccrine hidradenitis, 491–492, 491*f*
syringolymphoid hyperplasia with alopecia, 490–491, 490*f*
inflammatory processes of, 85
morphea and, 297–298, 297*f*–298*f*
normal microanatomy of, 32–33, 33*f*
Paget's disease and, 838–839
porokeratotic eccrine ostial and dermal duct nevus of, 793
regional variation of, 35, 35*f*
S100 protein in, 77
special stains for, 34*f*–35*f*, 36
specialized structure and function of, 35–36
tumors of, 97, 97*f*, 123, 883–895
chondroid syringoma, 893–894, 893*f*–894*f*
eccrine hidrocystoma, 884, 884*f*
eccrine nevus, 883, 883*f*
eccrine poroma, 885–887, 886*f*
eccrine spiradenoma, 888–889, 889*f*
eccrine syringofibroadenoma, 888, 888*f*
malignant chondroid syringoma, 894–895, 895*f*
malignant eccrine poroma, 887–888, 887*f*
malignant eccrine spiradenoma, 890, 890*f*
malignant nodular hidradenoma, 892, 892*f*–893*f*
mucinous syringometaplasia, 888
nodular hidradenoma, 891–892, 891*f*
papillary eccrine adenoma, 890–891, 890*f*
syringoma, 884–885, 884*f*–885*f*
Eccrine glandular ridges, Merkel cells at, 18
Eccrine hidrocystoma, 884
additional studies of, 884
apocrine hidrocystoma v., 878
differential diagnosis of, 884
histopathology of, 98, 98*f*, 127, 884, 884*f*
Eccrine nevus, 883, 883*f*
histopathology of, 99, 99*f*, 123, 128, 883, 883*f*
Eccrine poroma, 885–887
additional studies of, 887
differential diagnosis of, 887
histopathology of, 104, 886–887, 886*f*
nodular hidradenoma v., 892
Eccrine poromatosis, 886
Eccrine spiradenoma, 888–889
additional studies of, 889
cylindroma and, 881
glomus tumor v., 1049
histopathology of, 96, 96*f*, 122–123, 889, 889*f*
nodular hidradenoma v., 892
Eccrine sweat gland adenoma of the clear cell type, 891
Eccrine sweat gland carcinoma, 1158
Eccrine syringofibroadenoma, 888
additional studies of, 888
histopathology of, 888, 888*f*
Eccrine syringometaplasia, histopathology of, 123
ECM1. *See* Extracellular matrix protein 1 gene
Ecthyma, 541
histopathology of, 120, 541
Ecthyma gangrenosum, 547
histopathology of, 115, 120, 131
Ectodermal cells, epidermis from, 7
Ectodermal dysplasia
forms of, 141–142, 142*f*
histopathology of, 142
Ectopic ependymomas, 1143
Ectothrix infections, 594
Eczema. *See also* Spongiotic dermatitis
actinic prurigo v., 336
chronic actinic dermatitis v., 338, 340
Eczema herpeticum. *See* Kaposi's varicelliform eruption
Eczema vaccinatum, 642, 647
Eczematous dermatitis, 503–504
histopathology of, 108
Eczematous nevus, histopathology of, 108
Edema blisters, 273
histopathology of, 273
Edematous mucocutaneous leishmaniasis, 624
EDS. *See* Ehlers-Danlos syndrome
EED. *See* Erythema elevatum diutinum
EFH. *See* Epithelioid fibrous histiocytoma
EGFR. *See* Epidermal growth factor receptor

Egg shells, of scabies, 627
Ehlers-Danlos syndrome (EDS), 155–156, 155*f*
  dystrophic calcinosis cutis and, 437
  elastosis perforans serpiginosa and, 394
  histogenesis of, 156
  histopathology of, 120, 156
  types of, 156
Ehrlichia chaffeensis, Lyme disease from, 585
EIN. *See* Intraepidermal neutrophilic dermatosis
Elastases
  macular atrophy and, 400–401
  middermal elastolysis and, 399
Elastic fibers
  acquired perforating dermatosis and, 396
  in adult colloid milium, 430
  aging of, 56
  argyria and, 327
  calcification of, 153–154
  connective tissue nevus with, 154
  cutis laxa and, 157–158
  of dermis, 49
  elastosis perforans serpiginosa and, 393, 395
  erythema ab igne and, 348
  fibroblastic rheumatism and, 307
  granuloma annulare and, 362
  of lamina densa, 24
  linear focal elastosis and, 398–399
  macular atrophy and, 400–401
  middermal elastolysis and, 399
  morphea and, 297*f*–298*f,* 298
  mucopolysaccharidosis and, 447
  ochronosis and, 440
  papillary dermal elastolysis and, 399
  perforating calcific elastosis and, 396
  perforating folliculitis and, 393
  perifollicular elastolysis and, 401
  pseudoxanthoma elasticum and, 152–153
  solar elastosis and, 389
  staining of, 69, 69*t,* 70*f*
  striae distensae and, 398
Elastin
  in elastofibroma dorsi, 987
  late-onset focal dermal elastosis and, 397
  papillary dermal elastolysis and, 399
Elasto-collagenous plaques of the hands. *See* Collagenous and elastotic marginal plaques of the hands
Elastofibroma dorsi, 987
  differential diagnosis of, 987
  histogenesis of, 987
  histopathology of, 987, 987*f*
Elastofibroma, histopathology of, 125
Elastogenesis, papillary dermal elastolysis and, 399
Elastolysis. *See* Cutis laxa
Elastophagocytosis
  of annular elastolytic giant cell granuloma, 365
  giant cell arteritis and, 208
  middermal elastolysis and, 399
  of sarcoidosis, 372
Elastosis perforans serpiginosa (EPS), 393–395
  acquired perforating dermatosis v., 396
  differential diagnosis of, 393*t,* 395
  histogenesis of, 395
  histopathology of, 96, 96*f,* 120, 325, 325*f*–326*f,* 394–395, 394*f*
  Kyrle's disease and, 392
  pathogenesis of, 326
  penicillamine-induced, 325–326, 325*f*–326*f*
  pseudoxanthoma elasticum and, 153
Elastosis, solar, 56, 56*f*
Elastotic degeneration, of elastic fibers, 49
Elastotic material, solar elastosis and, 389–390, 390*f*
Elastotic nodules of the ears, 390, 391*f*
Elastotic striae. *See* Linear focal elastosis
Elaunin fibers
  of lamina densa, 24
  solar elastosis and, 389
Elbows, dermatitis herpetiformis and, 263
Electrical burns, 274, 275*f,* 343
  histopathology of, 114, 274, 275*f*
Electrocautery, for shave biopsy, 6
Electrodesiccation, for recurrent nevus, 732
Electrodesiccation-induced injury, 357, 358*f*–359*f*
  differential diagnosis of, 357
  histopathology of, 357, 358*f*–359*f*
Electron micrographs, 1162–1186
Electron microscopy
  for diagnosis, 79–80
  of leprosy, 565
  for lichen planus, 189
  for psoriasis vulgaris, 179
ELISA. *See* Enzyme linked immunosorbent assay
EM. *See* Erythema multiforme
EMA. *See* Epithelial membrane antigen
Embolic phenomena, 206
Embryonal rhabdomyosarcoma, 1085
Emigrant inflammatory cells, 42–46, 42*f*–43*f,* 45*f*
  basophilic granulocytes, 44
  eosinophilic granulocytes, 43–44
  lymphocytes, 42*f*–43*f,* 44–46, 45*f*
  neutrophilic granulocytes, 42–43, 42*f*–43*f*
  plasma cells, 42*f,* 46
Emperipolesis, of lymphocytes, 679, 679*f*
Encapsulated angiolipoma, 1066
Encephalocele
  heterotopias v., 1141
  histopathology of, 125
Encephalocraniocutaneous lipomatosis, 1062
Enchondromas, 1094
Endarteritis obliterans, of syphilis, 580, 580*f,* 582
Endemic African Kaposi's sarcoma, 1029–1030, 1030*f*
Endemic syphilis, 585
  histopathology of, 585
Endocarditis, with reactive angioendotheliomatosis, 1008
Endocytosis, of viruses, 637
Endogenous ochronosis, 440
Endoneural variants, of neurofibromatosis, 1111–1113
Endoneurium, anatomic relationships with, 1107
Endothelial cells, of dermal microvascular unit, 50–52, 51*f*
Endothelial nitric oxide synthase (eNOS), Behçet's syndrome and, 415
Endothrix infections, 594, 594*f*
ENL. *See* Erythema nodosum leprosum
Enolase, Merkel cells and, 19
eNOS. *See* Endothelial nitric oxide synthase
Ensheathed neuroma, 1138
Entamoeba histolytica, 625
Enteritis, epidermolysis bullosa acquisita and, 261
Enterobacter cloacae, neutrophilic eccrine hidradenitis and, 491
Enterocutaneous fistula, histopathology of, 120
Entomophthorales infection, 599
Environmental effects, in histologic diagnosis, 3
Environmental-related variations, in skin, 56, 56*f*
Enzyme activity
  in keratinocytes, 12–13
  in melanocytes, 17
  specimen demonstration of, 67
Enzyme linked immunosorbent assay (ELISA), 74
  with ANCAs, 207
Eosinophil(s)
  actinic prurigo and, 335
  acute generalized exanthematous pustulosis with, 315, 315*f*
  in arthropod assault reactions, 634
  chronic actinic dermatitis and, 339
  cicatricial pemphigoid and, 259–260
  dermatitis herpetiformis and, 264
  eosinophilic fasciitis and, 303
  with eosinophilic pustular folliculitis, 466
  of eosinophilic ulcer of the tongue, 813
  epidermolysis bullosa acquisita and, 261
  in epithelioid fibrous histiocytoma, 970
  erythema nodosum and, 511–512
  erythema toxicum neonatorum and, 267
  with exanthemic drug eruptions, 311–312
  graft-*versus*-host disease and, 272
  granuloma annulare and, 361
  granuloma gluteale infantum and, 381
  in halogenodermas, 326
  herpes gestationis and, 261
  incontinentia pigmenti and, 161
  macular atrophy and, 400
  in mycosis fungoides, 937
  in myeloid leukemias, 958
  polymorphic light eruption with, 333
  prurigo nodularis and, 174
  prurigo simplex and, 173
  PUPPP and, 170
  solar urticaria and, 340
  with syringolymphoid hyperplasia, 491
  transient acantholytic dermatosis and, 273
  transient neonatal pustular melanosis and, 267
  in trichoadenoma, 862
  urticaria pigmentosa and, 159–160
Eosinophilia
  eosinophilic pustular folliculitis with, 466
  erythema toxicum neonatorum and, 267
  with minocycline pigmentation, 324
Eosinophilia-myalgia syndrome, scleroderma and, 296
Eosinophilic cellulitis
  bullous pemphigoid v., 256
  histopathology of, 94, 94*f,* 117
  vesicular pemphigoid and, 259
Eosinophilic fasciitis, 303, 304*f,* 515–516, 515*f*
  clinical features of, 515
  differential diagnosis of, 515–516
  histopathology of, 101, 101*f,* 116, 120, 130, 303, 304*f,* 515, 515*f*
  with Lyme disease, 587–588
  nephrogenic systemic fibrosis and, 301
  pathogenesis of, 303
  systemic lupus erythematosus with, 286
Eosinophilic granulocytes, 43–44
Eosinophilic granuloma, 669
Eosinophilic granuloma of histiocytosis X, eosinophilic ulcer of the tongue v., 813
Eosinophilic inclusion bodies
  of deep palmoplantar warts, 652, 652*f*
  of parapoxvirus infections, 648, 648*f*
Eosinophilic keratin, in proliferating trichilemmal cyst, 867
Eosinophilic leukemia, eosinophilic panniculitis and, 515
Eosinophilic panniculitis, 515–516, 515*f*
  clinical features of, 515
  differential diagnosis of, 515–516
  histopathology of, 130, 515, 515*f*
Eosinophilic pneumonitis, Churg-Strauss syndrome and, 213
Eosinophilic pustular folliculitis (EPF), 466–467
  erythema toxicum neonatorum v., 267
  with follicular mucinosis, 468
  histopathology of, 99, 99*f,* 113, 128, 466–467, 467*f*
  in HIV, 466, 660
  pathogenesis of, 467
Eosinophilic spongiosis
  bullous pemphigoid and, 256–257, 257*f*
  drug-induced pemphigus and, 253
  pemphigus foliaceus and, 251

Eosinophilic ulcer of the tongue, 813
  differential diagnosis of, 813
  histopathology of, 120, 813
Eosinophil-rich granulomata, with strongyloidiasis, 628
EPF. *See* Eosinophilic pustular folliculitis
Ephelide. *See* Freckles
Epidermal appendages, tumors of, 851–900
  classification of, 851–853, 852*t*
  terminology for, 853
Epidermal atypia, of Bowenoid papulosis of genitalia, 656
Epidermal cysts, 800–802, 801*f*
  dermoid cyst v., 804
  histopathology of, 98, 98*f,* 127, 801–802, 801*f*
  pathogenesis of, 802
  pilar or trichilemmal cyst v., 802
Epidermal dysmaturation, histopathology of, 103
Epidermal epidermolysis bullosa, 146–147
Epidermal growth factor receptor (EGFR), cutaneous eruptions with, 323, 323*t*
Epidermal necrosis, histopathology of, 114
Epidermal nevus, 690. *See also* Linear epidermal nevus
  histopathology of, 88, 88*f,* 103–106
Epidermis
  aging of, 56, 56*f*
  basement membrane zone of, 21–24, 22*f*–23*f*
  disorders of, 86–87, 86*f*–87*f*
    hyperkeratosis with hypogranulosis, 86, 86*f,* 103
    hyperkeratosis with normal or hypergranulosis, 86, 86*f,* 103
    hyperkeratosis with parakeratosis, 86, 86*f,* 103
    localized or diffuse hypopigmentation/depigmentation, 87, 87*f,* 104
  eccrine and apocrine glands of, 31–36
    embryology of, 32
    normal microanatomy of, 32–35, 33*f*–35*f*
    regional variation, 35, 35*f*
    special stains, 34*f*–35*f,* 36
    specialized structure and function, 35–36
  of eyelid, 57, 58*f*
  hair follicles of, 24–31, 24*f*–29*f*
    embryology, 24–25, 24*f*–25*f*
    normal microanatomy, 25–30, 25*f*–29*f*
    regional variation, 30–31
    sebaceous glands, 28*f,* 30
    specialized structure and function, 31
  keratinocytes of, 7–14, 8*f*–11*f,* 13*f*
    embryology, 7–8, 8*f*
    normal microanatomy of, 8–12, 9*f*–11*f*
    specialized structure and function, 11*f,* 12–14, 13*f*
  Langerhans cells of, 19–21, 20*f*
    embryology, 19–20, 20*f*
    normal microanatomy, 20–21, 20*f*
    regional variation, 21
    specialized structure and function, 21
  melanocytes of, 14–18
    embryology, 14
    normal microanatomy, 14–16, 14*f*–15*f*
    regional and racial variation, 17
    specialized structure and function, 17–18
    in sun-exposed areas, 15*f,* 17
    ultrastructure, 15*f,* 17
  Merkel cells of, 18–19, 19*f*
    embryology of, 18
    normal microanatomy of, 18–19, 19*f*
    regional variation of, 19
    specialized structure and function of, 19
  nails of, 36–38, 36*f*–37*f*
  neoplastic localized proliferations of, 85, 87–89, 87*f*–89*f*
    irregular proliferations, 88, 88*f,* 106
    localized irregular thickening, 87, 87*f,* 104–105
    localized lesions with elongated rete ridges, 88, 88*f,* 105
    localized lesions with pagetoid epithelial proliferation, 88, 88*f,* 105
    localized lesions with thinning, 87, 87*f,* 105
    localized papillomatous epithelial lesions, 88, 88*f,* 105–106
    superficial polypoid lesions, 89, 89*f,* 106
  Spitz nevus in, 721
  subcorneal pustular dermatosis and, 268
  tumors and cysts of, 791–840
    acantholytic squamous cell carcinoma, 821
    actinic keratosis, 807–811, 807*f*–810*f*
    arsenical keratosis and carcinoma, 816–817
    balanitis circumscripta plasmacellularis, 815–816
    basal cell carcinoma, 823–835, 824*f*–829*f*
    Bowen's disease, 813–815, 814*f*
    bronchogenic and thyroglossal duct cysts, 805, 805*f*
    classification of, 791
    clear cell acanthoma, 799–800, 800*f*
    cutaneous ciliated cyst, 805
    cutaneous horn, 811, 811*f*
    dermatosis papulosa nigra, 799
    dermoid cyst, 804, 804*f*–805*f*
    eosinophilic ulcer of the tongue, 813
    epidermal or infundibular cysts, 800–802, 801*f*
    eruptive vellus hair cysts, 806
    erythroplasia of Queyrat, 815
    extramammary Paget's disease, 839–840
    in immunosuppressed hosts, 835, 835*f*
    incidental epidermolytic hyperkeratosis, 793–794
    incidental focal acantholytic dyskeratosis, 794, 794*f*
    isolated and disseminated acantholytic acanthoma, 794
    isolated and disseminated epidermolytic acanthoma, 793
    keratoacanthoma, 835–837, 835*f*–837*f*
    large cell acanthoma, 799, 799*f*
    Leser-Trélat sign, 799
    leukoedema of the oral mucosa, 794–795
    linear epidermal nevus, 791
    lingua geographica, 795
    median raphe cyst of the penis, 805–806, 805*f*
    milia, 802
    mucin-producing squamous cell carcinoma, 821–822
    necrotizing sialometaplasia, 813
    nevoid hyperkeratosis of nipple and areola, 792–793
    nevus comedonicus, 793
    oral leukoplakia, 811–812, 812*f*
    oral white sponge nevus, 794
    Paget's disease, 838–839, 838*f*
    pigmented follicular cyst, 804
    pilar or trichilemmal cyst, 802–803, 802*f*–803*f*
    porokeratotic eccrine ostial and dermal duct nevus, 793
    pseudocarcinomatous hyperplasia, 822–823, 823*f*
    seborrheic keratosis, 795–798, 795*f*
    squamous cell carcinoma, 817–821, 818*f*–819*f,* 821*f*
    squamous intraepithelial neoplasia, 816
    steatocystoma multiplex, 803–804, 803*f*–804*f*
    stucco keratosis, 797*f,* 799
    verrucous carcinoma, 822
    verrucous hyperplasia, verrucous carcinoma of the oral mucosa, 812–813
    warty dyskeratoma, 806–807, 806*f*–807*f*
Epidermis above granular cell tumor, histopathology of, 104
Epidermis adjacent to folliculitis, histopathology of, 113
Epidermodysplasia verruciformis (EV), 653–654, 654*f*
  Bowen's disease and, 813
  histogenesis of, 654
  histopathology of, 654, 654*f*
Epidermoid, foreign-body reactions and, 373
Epidermolysis bullosa (EB), 145–148, 145*t*
  acquisita, 147–148, 148*f*
  aplasia cutis congenita v., 143
  friction blisters v., 357
  groups of, 145–146, 145*t*
  histopathogenesis of, 147
  histopathology of, 129, 146–147
  with nail unit, 506
Epidermolysis bullosa acquisita (EBA), 147–148, 148*f,* 261, 262*f*
  assays for, 74
  Crohn's disease with, 415
  friction blisters v., 357
  histopathology of, 114–115, 261, 262*f*
  immunofluorescence testing for, 261, 262*f*
  relapsing polychondritis with, 494
Epidermolysis bullosa dystrophica-recessive, 146–147
Epidermolysis bullosa herpetiformis, 146–147
Epidermolysis bullosa letalis, 146–147
  histopathology of, 114
Epidermolysis bullosa simplex, 1165*f*
  histopathology of, 114
Epidermolytic acanthoma, histopathology of, 103, 113
Epidermolytic hyperkeratosis, 29, 134–135, 134*f,* 793–794
  acantholytic dyskeratosis v., 794
  differential diagnosis of, 135
  histologic features of, 792
  histopathology of, 86, 86*f,* 103, 113, 134–135, 134*f,* 793–794
  hypertrophic actinic keratosis and, 809
  isolated epidermolytic acanthoma with, 793
  linear epidermal nevus with, 791–792
  nevus comedonicus v., 793
  pathogenesis of, 135
Epidermolytic keratosis palmaris et plantaris, 137
  epidermolytic hyperkeratosis in, 793
Epidermophyton floccosum, 593, 595
Epidermophyton infections, 592
Epidermotropic metastatic melanoma, histopathology of, 123, 775
Epidermotropism, 912–913
  with adnexotropic mycosis fungoides, 939
  psoriasiform mycosis fungoides and, 941
Epilepsy
  with nevus sebaceus, 871
  palmar fibromatosis and, 992
Epiligrin. *See also* Laminin
  cicatricial pemphigoid and, 260
Epineurium, anatomic relationships with, 1107
Epithelial hyperplasia
  of giant condyloma acuminata of Buschke and Loewenstein, 656
  perforating folliculitis and, 393
Epithelial membrane antigen (EMA)
  anaplastic large cell lymphoma, 952–953
  antibodies against, 76–77, 76*t*
  chondroid syringoma and, 894
  in epithelioid sarcoma, 996
  granuloma annulare and, 364
  lipofibromatosis, 1070
  neuromas, 1138
  in nodular hidradenoma, 892
  nodular melanoma and, 752
  pacinian perineural cell fibroma, 1134–1135
  storiform perineural cell fibroma, 1132
Epithelial nevus, histopathology of, 106

Epithelioid angiosarcoma, 1043
  cutaneous epithelioid angiomatous nodule v., 1025
  histopathology of, 125–126, 1043, 1043*f*
Epithelioid blue nevi, pigmented epithelioid melanocytoma and, 757
Epithelioid cell histiocytoma
  factor XIIIa and, 78
  histopathology of, 124
Epithelioid cell nevus. *See also* Spitz nevus
  deep penetrating nevus v., 730
Epithelioid cells
  in necrobiosis lipoidica, 366
  Spitz nevus and, 721
Epithelioid fibrous histiocytoma (EFH), 970–971, 973*f*
  neurothekeoma v., 1130
Epithelioid hemangioendothelioma, 1039–1040
  composite hemangioendothelioma and, 1037
  differential diagnosis of, 1040
  histopathology of, 126, 1039–1040, 1039*f*–1040*f*
Epithelioid hemangioma, 1022–1025
  clinical features of, 1022
  cutaneous epithelioid angiomatous nodule v., 1025
  differential diagnosis of, 1024–1025
  epithelioid hemangioendothelioma v., 1040
  histogenesis of, 1024
  histopathology of, 126, 1023–1024, 1023*f*–1024*f*
  lesions of subcutaneous and deeper tissues, 1023
  superficial lesions of, 1022–1023, 1023*f*
Epithelioid histiocytes, cheilitis granulomatosa and, 380
Epithelioid histiocytomas, Spitz nevus v., 723
Epithelioid leiomyosarcoma, 1081
Epithelioid malignant schwannoma, histopathology of, 125
Epithelioid patterns, in malignant peripheral nerve sheath tumor, 1124
Epithelioid pilar leiomyoma, neurothekeoma v., 1130
Epithelioid sarcoma, 995–997, 996*f*
  differential diagnosis of, 997
  granuloma annulare v., 364
  histogenesis of, 996
  histopathology of, 97, 97*f*, 118–119, 124–125, 995–996, 996*f*
  rheumatoid nodules v., 368
Epithelioid schwannoma, 1119–1120, 1120*f*–1121*f*
  histopathology of, 125
Epithelioma adenoides cysticum. *See* Trichoepithelioma
Epithelioma cuniculatum, 822
Epithelioma, definition of, 853
Epitheliotropism, T-cell lymphomatoid hyperplasias and, 935
Epithelium, discoid lupus erythematosus and, 280
EPS. *See* Elastosis perforans serpiginosa
Epstein-Barr virus (EBV), 644–645, 646*f*
  Behçet's syndrome and, 414
  erythema multiforme and, 268
  erythema nodosum with, 514
  Gianotti-Crosti syndrome and, 184
  histopathology of, 645
  in HIV, 659
Erdheim-Chester disease, 672
Erector pilae muscle tumors, histopathology of, 123
Ergot, drug-induced scleroderma with, 316
Erosive adenomatosis of the nipple, 881
  differential diagnosis of, 881
  histopathology of, 123, 881, 881*f*
Eruption of lymphocyte recovery, histopathology of, 112
Eruptive histiocytomas, histopathology of, 124
Eruptive keratoacanthoma, 837
Eruptive normolipemic xanthoma
  diffuse normolipemic plane xanthoma with, 684
  histopathology of, 124
Eruptive psoriasis, 174, 178
Eruptive vellus hair cysts, 806
  histopathology of, 127, 806
  pathogenesis of, 806
Eruptive xanthomas, 680–682, 681*f*
Erysipelas, 541
  histopathology of, 89, 89*f*, 115, 541
  lipomembranous panniculitis with, 531
  sclerema neonatorum v., 529
Erythema
  burns and, 343
  fibroblastic rheumatism and, 307
  radiation dermatitis and, 348
Erythema ab igne, 347–348, 347*f*
  differential diagnosis of, 348
  histopathology of, 120, 347*f*, 348
Erythema annulare centrifugum
  chilblains v., 355
  differential diagnosis of, 171
  erythema chronicum migrans v., 586
  histopathology of, 115, 171, 171*f*–172*f*
  lymphocytoma cutis v., 588
  pathogenesis of, 171
Erythema chronicum migrans, 586, 586*f*
  with borrelial lymphocytoma cutis, 588
  differential diagnosis of, 586
  histopathology of, 93, 93*f*, 115–116, 129, 586, 586*f*
Erythema chronicum perstans, erythema ab igne v., 348
Erythema dyschromicum perstans, 172–173, 172*f*
  differential diagnosis of, 173
  histopathology of, 104, 112, 172
  pathogenesis of, 172–173
Erythema elevatum diutinum (EED), 221–222
  granuloma faciale v., 222
  histopathology of, 111, 116–117, 221–222
  pathogenesis of, 222
  relapsing polychondritis with, 494
Erythema gyratum repens, 171–172
  histopathology of, 108, 172
  pathogenesis of, 172
Erythema induratum, 519–521, 519*f*–520*f*, 553
  clinical presentation of, 519, 519*f*
  differential diagnosis of, 521
  erythema nodosum v., 515
  histopathology of, 130–131, 131, 519–521, 519*f*–520*f*
  lupus erythematosus panniculitis v., 523
  pancreatic disease v., 529
  pathogenesis of, 521
Erythema infectiosum, 662, 662*f*
Erythema multiforme (EM), 268–270, 269*f*–270*f*, 312, 312*f*
  acute generalized exanthematous pustulosis v., 314–315
  chilblains v., 355
  coccidioidomycosis with, 608
  Crohn's disease with, 415
  differential diagnosis of, 270
  fixed drug eruptions v., 314
  granuloma annulare and, 362
  hepatitis and, 419
  hepatitis C with, 661
  herpes simplex associated with, 639
  histopathology of, 91, 91*f*, 110, 112, 114, 129, 269, 270*f*, 312, 312*f*
  human recombinant proteins with, 322–323
  immunofluorescence testing for, 270
  with nail unit, 506
  parvovirus B19 in, 662
  pathogenesis of, 270
  postinflammatory pigmentary alteration with, 690
  SJS and TEN v., 268–269, 269*f*
  ultrastructural study of, 270
Erythema nodosum, 511–515, 550
  Behçet's syndrome and, 413
  celiac disease and, 417
  clinical presentation of, 511, 511*f*
  Crohn's disease with, 415
  differential diagnosis of, 515
  eosinophilic panniculitis and, 515
  erythema induratum v., 519, 521
  hepatitis C with, 661
  histopathology of, 100, 100*f*, 130, 511–514, 512*f*–514*f*
  lipomembranous panniculitis with, 531
  mycobacterial panniculitis v., 534
  pancreatic disease v., 529
  pathogenesis of, 514–515
  sarcoidosis with, 370
  Takayasu's arteritis v., 208
  tattoo reactions and, 378
  Weber-Christian disease v., 524
Erythema nodosum leprosum (ENL), 564–567, 565*f*
  histopathology of, 116, 119, 129–131, 130, 131
Erythema nodosum migrans, 511, 514
Erythema toxicum neonatorum, 267
  differential diagnosis of, 267
  eosinophilic pustular folliculitis and, 467
  histopathology of, 92, 92*f*, 107–108, 113, 128, 267
  pathogenesis of, 267
  transient neonatal pustular melanosis v., 267
Erythematous macules, microscopic polyarteritis and, 212
Erythematous papule
  of endemic syphilis, 585
  of pinta, 584
  of yaws, 583
Erythematous plaque, of chronic cutaneous leishmaniasis, 623
Erythematous pustules, of acquired perforating dermatosis, 396
Erythrasma, histopathology of, 103
Erythrocytes
  in balanitis circumscripta plasmacellularis, 816
  eosinophilic fasciitis and, 303
  extramedullary hematopoiesis and, 956
  pityriasis lichenoides chronica and, 196
Erythroderma
  chronic actinic dermatitis and, 338
  histopathology of, 108, 113, 244
  with mycosis fungoides, 936
  with spongiotic dermatitis, 244
Erythrodermic psoriasis, 178
Erythrokeratodermia variabilis, 136
Erythroplakia of oral mucosa, 812
  histopathology of, 104
  oral leukoplakia v., 812
Erythroplasia of Queyrat, 815
  balanitis circumscripta plasmacellularis v., 815
  differential diagnosis of, 815
  histopathology of, 104, 107, 110–111, 815
Erythropoietic porphyria, 431, 432*t*
  histopathology of, 433–434, 434*f*
  pathogenesis of, 434–435
Erythropoietic protoporphyria, 432, 432*t*
  histopathology of, 433–434, 434*f*
  pathogenesis of, 434–435
Eschars, of human cowpox infection, 647
Escherichia coli
  bowel-associated dermatosis-arthritis syndrome with, 412
  malakoplakia with, 549
ESCNs. *See* Extraneural sporadic cutaneous neurofibromas
Esophageal cancer, human papillomavirus in, 650
Esophagus
  cicatricial pemphigoid and, 259
  oral white sponge nevus in, 794
Essential MC, 661

Esthiomene, 571
Estrogens
  erythema nodosum with, 515
  hyperlipidemia from, 680
Etanercept
  cutaneous eruptions with, 322–323
  lichenoid drug eruption and, 313
Ethionamide, pellagra and, 408
Ethosuxamide, drug-induced pseudolymphoma syndrome with, 320
ETs. *See* Exfoliative toxins
Eumelanin melanosomes, in hair, 31
Eumycetoma, 600*t,* 601–602, 614, 615*f*
  histopathology of, 120, 614, 615*f*
EV. *See* Epidermodysplasia verruciformis
Ewing's sarcoma (EWS), 1140–1141
  differential diagnosis of, 1141
  histogenesis of, 1141
  histopathology of, 122, 1140–1141
  mesenchymal chondrosarcoma v., 1099
EWS. *See* Ewing's sarcoma
Exanthem subitum, 645, 646
Exanthema, of HIV infection, 660
Exanthematous type of generalized pustular psoriasis, 175
Exanthemic drug eruptions, 311–312, 312*f*
  differential diagnosis of, 312
  histopathology of, 311–312
Exanthemic pustular drug eruptions, histopathology of, 113
Exfoliative dermatitis
  histopathology of, 109, 112–113, 244
  with spongiotic dermatitis, 244
Exfoliative toxins (ETs), of *Staphylococcus aureus,* 540
Exogen, of hair follicle, 472
Exogenous ochronosis, 440
Exogenous plasmacytoma, 922
  clinical features of, 922
  differential diagnosis of, 922
  histogenesis of, 922, 923*f*
  histopathology of, 922, 923*f*
Exophiala (Fonsecaea, Wangiella) dermatitidis, 603
Exophiala infection, 601
Exophiala (Fonsecaea, Wangiella) jeanselmei, 607
Exophiala spinifera, 607
Exophthalmos, pretibial myxedema and, 441
External ear canal, apocrine glands of, 35, 35*f*
Extracellular matrix, of dermis, 46–50, 47*f*–48*f*
  collagen fibers, 46–49, 47*f*–48*f*
  elastic fibers, 49
  ground substance, 49–50
Extracellular matrix protein 1 gene (ECM1), lipoid proteinosis and, 431
Extracutaneous melanomas, in central nervous system, 725
Extramammary Paget's disease, 832, 839–840
  differential diagnosis of, 840
  histopathology of, 839–840
  pathogenesis of, 840
  solitary pagetoid reticulosis and, 941
Extramedullary hematopoiesis, 956–957
  clinical features of, 956
  differential diagnosis of, 956–957
  histogenesis of, 956
  histopathology of, 117, 956
Extramedullary myeloid tumor, myeloid sarcoma v., 957
Extraneural neurofibromas, 1113–1114, 1114*f*
Extraneural neuromas, 1135
  acquired, 1135
  histopathology of, 125
  rudimentary, 1135
Extraneural sporadic cutaneous neurofibromas (ESCNs), 1109–1110, 1109*f*
  differential diagnosis of, 1110
  histogenesis of, 1110
  histopathology of, 1109–1110, 1109*f*–1110*f*
Extranodal NK-/T-cell lymphoma, 948–949
  clinical features of, 948–949
  cutaneous γ/δ T-cell lymphoma v., 951
  differential diagnosis of, 949
  histogenesis of, 949
  histopathology of, 949
Extraskeletal chondroma, 1094, 1095*f*
  soft tissue chondromas v., 1096
Extraskeletal Ewing's sarcoma, 1158
Extraskeletal myxoid chondrosarcoma, 1097–1098, 1098*f*
  in chondroid lipoma, 1067
  differential diagnosis of, 1098
  histopathology of, 1098, 1098*f*
  pathogenesis of, 1098
Extraskeletal osteochondroma, 1094
Extraskeletal osteosarcoma, 1093–1094, 1093*f*
  differential diagnosis of, 1094
Extravascular granuloma formation, Churg-Strauss syndrome and, 213
Eyelids
  apocrine glands of, 35, 35*f*
  epidermis of, 57, 58*f*
  mammary carcinoma of, 1152–1153
  plaques on, 681–682, 683*f*
  sebaceous carcinoma of, 875–876
Eyes
  acute febrile neutrophilic dermatosis and, 223
  Onchocerca volvulus in, 630

Fabry disease. *See* Angiokeratoma corporis diffusum
Face
  angiosarcoma of, 1040, 1041*f*
  hyperpigmentations of, 690
  lupus erythematosus profundus/panniculitis and, 283
  sebaceous hyperplasia in, 872
  striated muscle of, 46, 57
Facial hemiatrophy, histopathology of, 120
Facial hemiatrophy of Perry-Romberg, with Lyme disease, 587–588
Facial paralysis, cheilitis granulomatosa and, 380
Factitial panniculitis, histopathology of, 131
Factitious panniculitis, histopathology of, 130
Factor VIII-related antigen, antibodies against, 76*t,* 78
Factor XIIIa, 667
  antibodies against, 76*t,* 78
Faintness, with solar urticaria, 340
Familial acro-osteolysis, 401
Familial benign pemphigus, 148–149, 149*f*
  acantholysis in, 151
  desmosomes and, 151
  differential diagnosis of, 149
  histopathology of, 92, 92*f,* 113–114, 148–149, 149*f*
Familial Leiner's disease, 245
Familial multiple lipomatosis, 1062
Family history, melanoma risk and, 760
Fascia
  eosinophilic fasciitis and, 303
  morphea and, 297*f*–298*f,* 298
  nephrogenic systemic fibrosis and, 301
Fascicular cellular blue nevus, 704
Fat
  lipocytic tumors and, 1057–1058, 1059*f*
  tumors
    angiolipoma, 1064–1066
    benign lipoblastoma, 1070–1071, 1071*f*
    chondroid lipoma, 1067–1068, 1068*f*
    folded skin with lipomatous nevi, 1058–1060
    hibernoma, 1068–1070, 1069*f*
    lipofibromatosis, 1070
    lipomas, 1060–1064, 1061*f*–1064*f,* 1065*t*
    liposarcoma, 1071–1075, 1073*f*–1074*f*
    nevus lipomatosus superficialis, 1058, 1059*f*
    piezogenic papules, 1060
    pleomorphic lipoma, 1066–1067, 1067*f*
    spindle cell lipoma, 1066, 1066*f*
Fat necrosis
  of Buruli ulcer, 556–557, 557*f*
  lupus erythematosus profundus/panniculitis and, 283
  of the newborn, 529–530, 530*f*
    clinical features of, 529
    differential diagnosis of, 530
    histopathology of, 529–530, 530*f*
    pathogenesis of, 530
  in pancreatic disease, 528–529
  panniculitis with, 526, 526*f*
Fat vacuoles, in benign lipoblastoma, 1071
Favre-Racouchot syndrome, 390–391
  actinic comedonal plaques v., 391
  histopathology of, 127, 390–391
Favus, 592–595
  histopathology of, 128
FCC. *See* Follicle center cells
FD. *See* Folliculitis decalvans
FDEs. *See* Fixed drug eruptions
Fecal deposits, of scabies, 627
Feet
  eccrine poroma on, 885
  Meissner corpuscles on, 55
Female-pattern hair loss, 479
Ferric hydrate, tattoo reactions and, 377
Festooning, 434
Fetal-type rhabdomyoma, 1083–1084
  histopathology of, 1084
Fetus, varicella of, 642
Fever
  acute generalized exanthematous pustulosis with, 314–315
  with angioimmunoblastic T-cell lymphoma, 952
  bowel-associated dermatosis-arthritis syndrome and, 412
  Churg-Strauss syndrome and, 213
  drug-induced lupus erythematosus with, 318
  with erythema nodosum, 511
  erythema nodosum with, 514
  microscopic polyarteritis and, 212
  with minocycline pigmentation, 324
  peripheral T-cell lymphoma with, 951
  polyarteritis nodosa and, 209
  with self-healing juvenile cutaneous mucinoses, 445
Fibrillin-1, papillary dermal elastolysis and, 399
Fibrin deposition
  in erythema nodosum, 511, 512*f*
  in lupus erythematosus panniculitis, 522
  lupus erythematosus profundus/panniculitis and, 283
  palisaded granulomatous panniculitis with, 525
Fibrinogen, lichen nitidus and, 193
Fibrinoid degeneration, 216
Fibrinoid deposits
  neonatal lupus erythematosus and, 285
  systemic lupus erythematosus with, 287
Fibrinoid necrosis, Takayasu's arteritis and, 208
Fibroblastic rheumatism, 307
Fibroblastic tumors
  benign, 979–992
    acral fibrokeratoma, 989–990, 990*f*
    angiofibroblastoma of the skin, 991
    angiofibromas, 987–988, 988*f*
    angiomyofibroblastoma of the vulva, 990–991
    collagenous fibroma, 983, 983*f*
    dermatomyofibroma, 980–981, 981*f*

elastofibroma dorsi, 987, 987*f*
fibroma of tendon sheath, 982, 983*f*
fibromatosis colli, 991
fibrous hamartoma of infancy, 986, 986*f*
hypertrophic scar and keloid, 979–980, 980*f*
infantile digital fibromatosis, 986–987, 987*f*
ischemic fasciitis, 984, 985*f*
juvenile hyaline fibromatosis, 986
myofibroma/myofibromatosis, 984–986, 985*f*
nodular fasciitis, 983–984, 984*f*
nuchal-type fibroma, 990
pleomorphic fibroma, 981, 982*f*
sclerotic fibroma, 981–982, 982*f*
soft fibroma, 981
superficial acral fibromyxoma, 990, 991*f*
tuberous sclerosis, 988–989, 989*f*
intermediate biological potential (locally aggressive), 992–993
desmoid-type fibromatosis, 992, 992*f*
knuckle pads, 992–993
palmar fibromatosis, 992, 993*f*
intermediate biological potential (rarely metastasizing), 993–994
inflammatory pseudotumor, 993–994
solitary fibrous tumor, 993, 993*f*
Fibroblasts
aging of, 56
CHILD syndrome and, 136
compound nevus and, 713
dermal, 38, 39*f*
dermal muscle cells, 46
emigrant inflammatory cells, 42–46, 42*f*–43*f,* 45*f*
lymphocytes, 42*f*–43*f,* 45*f*
neutrophilic granulocytes, 42*f*–43*f*
plasma cells, 42*f*
mast cells, 41–42, 41*f*
perivascular and interstitial dendritic cells, 39–40, 39*f*
phagocytic macrophages, 40–41, 40*f*
Ehlers-Danlos syndrome and, 156
eosinophilic fasciitis and, 303
giant cell fibroblastoma v., 977
of juvenile hyaline fibromatosis, 986
keloids and, 980
lipoid proteinosis and, 431
in mucous cyst of the oral mucosa, 998
in multiple trichoepithelioma, 858, 858*f*
nerve sheath myxoma and, 1127
in nodular fasciitis, 983
osteoblastic cells and, 1089
pachydermoperiostosis and, 158
photodistributed hyperpigmentation and, 320
pretibial myxedema and, 442
reticular erythematous mucinoses and, 445
scleredema and, 446
in scleromyxedema, 444
scurvy and, 407
systemic scleroderma and, 300–301
Winchester syndrome and, 155
Fibrocystic breast disease, Cowden's disease with, 869
Fibrocytes, nephrogenic systemic fibrosis and, 301
Fibrodysplasia ossificans progressiva (FOP), 1086–1087
Fibroelastolytic papulosis of the neck, 399
Fibroepithelial polyp. *See* Soft fibroma
Fibroepithelioma, 825
Fibroepithelioma of Pinkus, 829*f,* 831
Fibrofolliculoma, 856–857
additional studies of, 857
histopathology of, 123, 856–857, 856*f*–857*f*
Fibrohistiocytic tumors
benign, 969–974
aneurysmal fibrous histiocytoma, 970, 972*f*
atypical fibrous histiocytoma, 970, 973*f*
cellular fibrous histiocytoma, 969, 972*f*
deep fibrous histiocytoma, 971–972
dermatofibroma, 969, 971*f*
epithelioid fibrous histiocytoma, 970–971, 973*f*
giant cell tumor of tendon sheath, 974, 974*f*
neoplasm *versus* reactive process, 972
intermediate biological potential (locally aggressive), 974–977
dermatofibrosarcoma protuberans, 974–976, 975*f*–976*f*
giant cell fibroblastoma, 976–977, 977*f*
intermediate biological potential (rarely metastasizing), 977–979
atypical fibroxanthoma, 978–979, 978*f*–979*f*
plexiform fibrohistiocytic tumor, 977, 977*f*
malignant, 979
malignant fibrous histiocytoma, 979
Fibrolamellar nerve sheath tumor, histopathology of, 125
Fibrolipomas, histopathology of, 1062, 1063*f*
Fibroma of tendon sheath, 125, 982
histogenesis of, 982
histopathology of, 982, 983*f*
Fibromas, of acrodermatitis chronica atrophicans, 586–587
Fibromatosis. *See also* Juvenile hyaline fibromatosis
in fibrous hamartoma of infancy, 986
plexiform fibrohistiocytic tumor v., 977
soft tissue chondromas v., 1096
Fibromatosis colli, 991
histopathology of, 991
Fibronectin
acquired perforating dermatosis and, 396
with nevus flammeus, 1011
in synovial sarcoma, 995
systemic scleroderma and, 300–301
Fibro-osseus pseudotumor, 1094
Fibroplasia, androgenetic alopecia and, 481
Fibrosarcoma
Kaposi's sarcoma v., 1035
malignant peripheral nerve sheath tumor v., 1125
mesenchymal chondrosarcoma v., 1099
radiation-induced, 351
synovial sarcoma v., 995
xeroderma pigmentosum with, 141
Fibrosing basal cell carcinoma, 825, 825*f*
syringoma v., 885
Fibrosing rheumatism, histopathology of, 120
Fibrosis
cheilitis glandularis and, 381
with chemical burns, 346
with mycosis fungoides, 937, 937*f*
with Spitz nevus, 722
Fibrotic nodules, fibroblastic rheumatism and, 307
Fibrous hamartoma
giant cell fibroblastoma v., 977
plexiform fibrohistiocytic tumor v., 977
rhabdomyomatous mesenchymal hamartoma v., 1083
Fibrous hamartoma of infancy, 986
histopathology of, 986, 986*f*
Fibrous histiocytoma. *See also* Dermatofibroma
dermatomyofibroma v., 981
storiform perineural cell fibroma v., 1133
Fibrous papule
factor XIIIa and, 78
histopathology of, 125
Fibrous papule of the face, 988
histogenesis of, 988
histopathology of, 988, 988*f*
Fibrous streamers, 473, 473*f*
Fibrous stroma, in syringoma, 885
Fibrous tissue
classification of, 969, 970*t*
fibroblastic/myofibroblastic tumors-benign, 979–992
acral fibrokeratoma, 989–990, 990*f*
angiofibroblastoma of the skin, 991
angiofibromas, 987–988, 988*f*
angiomyofibroblastoma of the vulva, 990–991
collagenous fibroma, 983, 983*f*
dermatomyofibroma, 980–981, 981*f*
elastofibroma dorsi, 987, 987*f*
fibroma of tendon sheath, 982, 983*f*
fibromatosis colli, 991
fibrous hamartoma of infancy, 986, 986*f*
hypertrophic scar and keloid, 979–980, 980*f*
infantile digital fibromatosis, 986–987, 987*f*
ischemic fasciitis, 984, 985*f*
juvenile hyaline fibromatosis, 986
myofibroma/myofibromatosis, 984–986, 985*f*
nodular fasciitis, 983–984, 984*f*
nuchal-type fibroma, 990
pleomorphic fibroma, 981, 982*f*
sclerotic fibroma, 981–982, 982*f*
soft fibroma, 981
superficial acral fibromyxoma, 990, 991*f*
tuberous sclerosis, 988–989, 989*f*
fibroblastic/myofibroblastic tumors-intermediate biological potential (locally aggressive), 992–993
desmoid-type fibromatosis, 992, 992*f*
knuckle pads, 992–993
palmar fibromatosis, 992, 993*f*
fibroblastic/myofibroblastic tumors-intermediate biological potential (rarely metastasizing), 993–994
inflammatory pseudotumor, 993–994
solitary fibrous tumor, 993, 993*f*
fibrohistiocytic tumors-benign, 969–974
aneurysmal fibrous histiocytoma, 970, 972*f*
atypical fibrous histiocytoma, 970, 973*f*
cellular fibrous histiocytoma, 969, 972*f*
deep fibrous histiocytoma, 971–972
dermatofibroma, 969, 971*f*
epithelioid fibrous histiocytoma, 970–971, 973*f*
giant cell tumor of tendon sheath, 974, 974*f*
neoplasm *versus* reactive process, 972
fibrohistiocytic tumors-intermediate biological potential (locally aggressive), 974–977
dermatofibrosarcoma protuberans, 974–976, 975*f*–976*f*
giant cell fibroblastoma, 976–977, 977*f*
fibrohistiocytic tumors-intermediate biological potential (rarely metastasizing), 977–979
atypical fibroxanthoma, 978–979, 978*f*–979*f*
plexiform fibrohistiocytic tumor, 977, 977*f*
fibrohistiocytic tumors-malignant, 979
malignant fibrous histiocytoma, 979
miscellaneous lesions, 997–998
cutaneous myxoma, 997, 997*f*
digital mucous cyst, 997, 998*f*
mucous cyst of the oral mucosa, 997–998, 998*f*
tumors of uncertain differentiation-benign, 994
multinucleated cell angiohistiocytoma, 994
tumors of uncertain differentiation-intermediate biological potential (rarely metastasizing), 994
angiomatoid fibrous histiocytoma, 994, 995*f*
tumors of uncertain differentiation-malignant, 994–997
epithelioid sarcoma, 995–997, 996*f*
synovial sarcoma, 994–995, 995*f*
Fibrous tumors, desmoplastic melanoma v., 756
Field cells, acral-lentiginous melanoma and, 748–749
Fifth disease. *See* Erythema infectiosum
Filaggrin
formation of, 11–12
mutations in, 133
Filarial nematode, *Onchocerca volvulus,* 629–631, 631*f*

Filariform larvae, of *Strongyloides,* 628
Filiform lesions, of condyloma acuminatum, 655*f*
Filiform verruca, cutaneous horn and, 811, 811*f*
Filiform warts, 650, 651*f*
First-degree burns, 274, 343, 345
FISH. *See* Fluorescence in situ hybridization
Fissured tongue, cheilitis granulomatosa and, 380
Fite methods, *Mycobacterium leprae* staining with, 559
Fixation artifact, 681
Fixation, of specimen, 67
Fixative, for biopsies, 6
Fixed cutaneous sporotrichosis, 613
Fixed drug eruptions (FDEs), 314, 314*f*
  erythema dyschromicum perstans and, 173
  histopathology of, 112, 114, 314, 314*f*
  pathogenesis of, 314
  subacute radiation dermatitis v., 352
Flame fingers, in Well's syndrome, 515
Flaviviridae, 637
Flea, as tungiasis vector, 633
Flegel's disease. *See also* Hyperkeratosis lenticularis perstans
  histopathology of, 103
Flexural sites, nevi of, 715–716, 718
Fli-1, epithelioid angiosarcoma, 1043
Flies, as myiasis vector, 632–633
Floret-type giant cells, in pleomorphic lipoma, 1067
Florid keratosis. *See* Hypertrophic actinic keratosis
Florid papillomatosis, histopathology of, 123
Flukes, schistosomiasis, 631–632, 632*f*
Fluorescence in situ hybridization (FISH), for Spitz nevus, 722
Fluoroderma, 326
5-Fluorouracil
  erythema multiforme with, 312
  pellagra and, 451
  toxic acral erythema with, 315
Fluorouracil, drug-induced pigmentary alterations of, 692
Foamy cells
  of diffuse normolipemic plane xanthoma, 684–685, 685*f*
  of eruptive xanthomas, 682, 682*f*
  of indeterminate cell histiocytosis, 678
  of papular xanthoma, 673, 674*f*
  of verruciform xanthomas, 685–686
  in xanthelasma, 683*f*
  of xanthoma disseminatum, 675, 675*f*
Focal acantholytic dyskeratosis, 59–60, 59*f*
  histopathology of, 92, 92*f,* 113–114
  transient acantholytic dermatosis with, 273
Focal acral hyperkeratosis, acrokeratoelastoidosis v., 138
Focal dermal hypoplasia syndrome, 142–143, 143*f*
  differential diagnosis of, 142–143
  histopathology of, 120, 142, 143*f*
  pathogenesis of, 142
Focal dermal mucinosis, histopathology of, 96, 96*f,* 121
Focal leukocytoclastic vasculitis, eosinophilic ulcer of the tongue and, 813
Focal mucinosis
  cutaneous myxoma v., 997
  digital mucous cyst v., 997
Focal parakeratosis
  erythema annulare centrifugum and, 171
  lichen planus and, 190
  lichen striatus and, 193, 193*f*
Fogo selvagem, pemphigus foliaceus and, 250
Folded skin with lipomatous nevi, 1058–1060
  differential diagnosis of, 1060
  histopathology of, 1060
Follicle center cells (FCC), nodal follicular lymphoma and, 926, 928
Follicular canal, of hair follicles, 26, 26*f*–27*f*
Follicular centers, of lupus erythematosus panniculitis, 521
Follicular degeneration syndrome, 486–487
  histopathology of, 128
  tufted hair folliculitis with, 487
Follicular dyskeratosis, graft-*versus*-host disease and, 272
Follicular fibroma, histopathology of, 125
Follicular germ cells, in trichoblastoma, 860
Follicular hyperkeratosis
  of follicular occlusion triad (hidradenitis suppurativa, acne conglobata, perifolliculitis capitis abscedens et suffodiens), 545
  scurvy and, 407
Follicular infundibular neoplasms, histopathology of, 123
Follicular infundibular tumor, histopathology of, 123
Follicular isthmus, 27*f,* 30
Follicular lymphoma, primary cutaneous marginal zone lymphoma v., 921
Follicular mucinosis, 467–469, 468*f*
  epithelioid hemangioma and, 1024
  histopathology of, 128, 468–469, 469*f*
  pathogenesis of, 469
  with syringolymphoid hyperplasia, 490
Follicular occlusion disorder, histopathology of, 120
Follicular occlusion triad (hidradenitis suppurativa, acne conglobata, perifolliculitis capitis abscedens et suffodiens), 544–545, 545*f*
  histopathology of, 545
  pathogenesis of, 545
Follicular plugging
  generalized myxedema and, 441
  lichen planopilaris and, 188
Follicular poroma, irritated seborrheic keratosis v., 795
Follicular stem cells, graft-*versus*-host disease and, 272
Folliculin gene, Birt-Hogg-Dubé syndrome, 857
Folliculitis. *See also* Acute bacterial folliculitis; Eosinophilic pustular folliculitis; Fungal folliculitis
  acne vulgaris, 459–461, 460*f*
  acute deep, 543, 544*f*
  acute superficial, 542–543, 543*f*
    impetigo Bockhart, 542
  chronic deep, 544
  chronic, histopathology of, 128
  chronic superficial, 543
  demodicidosis, 464–465, 465*f*
  eosinophilic pustular folliculitis, 466–467, 467*f*
  follicular mucinosis and alopecia mucinosa, 467–469, 468*f*–469*f*
  fungal, 594–595
  graft-*versus*-host disease and, 271
  herpetic, 638–639, 641
  histopathology of, 119
  hookworm, 628
  keratosis pilaris, 469–470, 469*f*
  lupus miliaris disseminatus faciei, 465–466, 466*f*
  Malassezia (Pityrosporum), 596–597, 596*f,* 598*t*
  microorganisms and, 60
  perioral dermatitis, 462–463, 462*f*
  rosacea, 463–464, 463*f*
  steroid acne, 461–462, 461*f*
  trichostasis spinulosa, 470, 470*f*
Folliculitis barbae, 544
  histopathology of, 128
Folliculitis decalvans (FD), 486*f*–487*f,* 487, 544
  histopathology of, 128, 487
  pathogenesis of, 487
  tufted hair folliculitis with, 487
Folliculitis keloidalis nuchae, 544
Folliculosebaceous cystic hamartoma, sebaceous trichofolliculoma v., 855
Folliculotropic mycosis fungoides, histopathology of, 128
Folliculotropism, 912
Fonsecaea compactum, 607
Fonsecaea pedrosoi, 607–608
Fontana-Masson method, for melanocytes, 16
FOP. *See* Fibrodysplasia ossificans progressiva
Fordyce's condition, 31
  histopathology of, 124
Fordyce's spots, 872–873
  histopathology of, 872–873, 873*f*
Foreign-body giant cells
  in necrobiosis lipoidica, 366
  of necrobiotic xanthogranuloma with paraproteinemia, 683, 684*f*
  with rheumatoid nodules, 368
  subepidermal calcified nodule and, 438
  of xanthoma disseminatum, 675
Foreign-body granuloma
  annular elastolytic giant cell granuloma v., 365
  histopathology of, 118
  sarcoidosis v., 373
Foreign-body reactions, 373–380
  aluminum reactions, 122, 376–377, 377*f*
  berylliosis, 377
  bovine collagen implants, 378–379
  cactus granuloma, 374–375
  corticosteroid deposits, 380
  histopathology of, 121, 373–374, 373*f*–374*f*
  paraffinoma, 117, 374–375
  pilonidal sinus, 120, 128, 375
  polariscopic examination for, 70
  sarcoidosis v., 371
  sea urchin granuloma, 374–376
  silica granuloma, 70, 374, 376, 376*f*
  silicone granuloma, 117, 121, 374–375, 375*f*
  starch granuloma, 117, 121, 375
  talc granuloma, 70, 70*f,* 117, 121, 375
  tattoo reactions, 121, 377–378, 378*f*
  titanium granuloma, 377
  zinc-induced granuloma, 377
  zirconium granuloma, 376
Formalin
  for biopsy fixative, 6, 67
  with stratum corneum, 9*f,* 12
Fowler's solution, arsenical keratosis and, 816
Fox-Fordyce disease, 492, 492*f*
  histopathology of, 128, 492
  pathogenesis of, 492
Frambesia tropica. *See* Yaws
Francisella tularensis
  histopathology of, 120
  tularemia from, 568
Freckles, 704–705, 710*t*
  histogenesis of, 705
  histopathology of, 705
  solar lentigines v., 706–707
Free radicals, from pheomelanin melanosomes, 738
Freshwater snail, as *Schistosoma* vector, 631
Friction blisters, 274, 355–356, 356*f*
  differential diagnosis of, 356
  histopathology of, 113, 274, 274*f,* 355–356, 356*f*
  pathogenesis of, 274
  ultrastructural study of, 274
"Fried-egg" pattern, in dysplastic nevus, 735
Fröhlich's syndrome, 1062
Frostbite, 352
  histopathology of, 119
Fulminant sepsis, calciphylaxis and, 230
Functional melanonychia. *See* Hyperpigmentations
Fungal folliculitis, histopathology of, 128
Fungal infection, 591–616
  aspergillosis, 599, 600*t,* 601*f*
  candidiasis, 597–599, 597*f,* 598*t*

acute mucocutaneous candidiasis, 597–598, 597*f,* 598*t*
Candida onychomycosis, 599
chronic mucocutaneous candidiasis, 598
disseminated candidiasis, 598–599
chromomycosis, 600*t,* 607–608, 607*f*
coccidioidomycosis, 600*t,* 608–609, 608*f*
cryptococcosis, 600*t,* 609–611, 610*f*
cutaneous alternariosis, 600*t,* 603, 603*f*
cutaneous protothecosis, 615–616, 616*f*
deep, histopathology of, 95, 95*f,* 102, 102*f,* 104, 106, 110, 117–120, 132
dermatophytosis, 591–595, 593*t,* 594*f*–595*f,* 598*t*
erythema nodosum with, 514
eumycetoma, 600*t,* 614, 615*f*
histoplasmosis, 600*t,* 611–612, 612*f*
African histoplasmosis, 612
in HIV, 593, 598
lobomycosis, 600*t,* 606–607, 606*f*
Malassezia furfur, 596–597, 596*f,* 598*t*
Malassezia (Pityrosporum) folliculitis, 596–597, 596*f,* 598*t*
of the nail, 506–507, 507*f*
North American blastomycosis, 600*t,* 603–605, 605*f*
paracoccidioidomycosis, 600*t,* 605–606, 606*f*
rhinosporidiosis, 600*t,* 615, 616*f*
sporotrichosis, 600*t,* 612–614, 614*f*
subcutaneous phaeohyphomycosis, 600*t,* 601–603, 602*f*
zygomycosis, 599–601, 600*t,* 602*f*
Fungal mycetoma. *See* Eumycetoma
Fungi, PAS stain and, 68
Furocoumarin-containing psoralen, pigment alterations from, 691–692
Furocoumarins, hyperpigmentation from contact with, 691
Furosemide
drug-associated bullous pemphigoid and, 259
drug-induced pseudoporphyria with, 320
pseudoporphyria cutanea tarda with, 435
Furuncle. *See also* Acute deep folliculitis
histopathology of, 128
Furuncular myiasis, 632–633, 633*f*
Fusarium sp., 593
nail unit and, 506–507
Fusiform macrophages, 673

Gadolinium, nephrogenic systemic fibrosis and, 316
Galli-Galli disease, 689–690
Ganglia, VZV in, 643
Ganglion cells
anatomic relationships with, 1107
ganglioneuroma, 1140
Ganglion cyst of nerve, 1144
Ganglioneuroma
histogenesis of, 1140
histopathology of, 125–126, 1140
malignant peripheral nerve sheath tumor and, 1122
malignant peripheral nerve sheath tumor v., 1126
Gangliosides, mucopolysaccharidosis and, 447
Gangosa, of yaws, 584
Gangrenous ischemic necrosis, histopathology of, 118–119
Gardner's fibroma, nuchal-type fibroma v., 990
Gardner's syndrome
epidermal cysts of, 801
pilomatricoma and, 865
Gargoylism, mucopolysaccharidosis and, 447
Gasterophilus species, 633
Gastric bleeding, pseudoxanthoma elasticum with, 154
Gastric carcinoma, 1156
Gastroenteritis, Churg-Strauss syndrome and, 213
Gastrointestinal carcinoma, 1100
metastatic carcinoma of skin, 1155–1156
histopathology of, 1155–1156, 1155*f*
immunoperoxidase study, 1156, 1156*f*
Gastrointestinal metastatic adenocarcinomas, 1155
Gastrointestinal stromal tumor, schwannoma v., 1119
Gastrointestinal tract
Crohn's disease of, 415
mantle cell lymphoma, 930
nodal follicular lymphoma of, 927
strongyloidiasis symptoms of, 628
systemic scleroderma and, 300
GCC. *See* Germinal center cells
GCF. *See* Giant cell fibroblastoma
GCRH. *See* Giant cell reticulohistiocytoma
Gelatinous lesions, of cryptococcosis, 610
Gemcitabine, drug-induced pseudolymphoma syndrome with, 320
Gender, melanoma prognosis and, 769
Generalized acute mucocutaneous herpes simplex, 639
Generalized cutaneous melanosis. *See* Congenital diffuse melanosis
Generalized eruptive histiocytosis, 678
benign cephalic histiocytosis v., 678
differential diagnosis of, 678
histopathology of, 678
JXG v., 672
pathogenesis of, 678
Generalized essential telangiectasia, 1011
histopathology of, 1011
Generalized granuloma annulare, 361
macular atrophy and, 400
Generalized hair follicle hamartoma, 863
additional studies of, 863
differential diagnosis of, 863
histopathology of, 863
Generalized morphea. *See* Morphea
Generalized myxedema, 441
histopathology of, 121, 441
Generalized papular xanthomas, diffuse normolipemic plane xanthoma with, 684
Generalized pustular psoriasis
clinical features of, 174–175
histopathology of, 178, 178*f*
of pregnancy, 175
Generalized vaccinia, 647
Genital herpes. *See* HSV-2
Genital leiomyoma, 1076
Genital lentiginosis, of mucosal melanotic macules, 705
Genital skin, nevi of, 715–716, 715–718, 718*f*
Genital warts. *See* Bowenoid papulosis of genitalia
Genitalia, Bowenoid papulosis of, 656–657, 657*f*
Genital-type rhabdomyoma, 1084
histopathology of, 1084
Genitoanal region, verrucous carcinoma in, 822
Genitourinary neoplasms, transient acantholytic dermatosis with, 273
Genodermatoses, with poikiloderma atrophicans vasculare, 295
Geographic tongue, histopathology of, 109
German measles. *See* Rubella
Germinal center cells (GCC), diffuse large B-cell lymphoma, 931
Gestalt method, 83
GF. *See* Granuloma faciale
GFAP. *See* Glial fibrillary acidic protein
Gianotti-Crosti syndrome, 184, 645, 661, 661*f*
hepatitis and, 419
histopathology of, 108, 115, 184, 418–419
parvovirus B19 in, 662
pathogenesis of, 184
Giant cell(s)
in Bowen's disease, 815
of indeterminate cell histiocytosis, 678
of juvenile xanthogranuloma, 672, 673*f*
necrobiosis lipoidica and, 366
of necrobiotic xanthogranuloma with paraproteinemia, 683, 684*f*
neurothekeoma and, 1128
in plexiform fibrohistiocytic tumor, 977
of reticulohistiocytosis, 675, 676*f*
sarcoidosis and, 370, 372
in sclerotic fibroma, 981–982
Spitz nevus and, 721
in xanthomas associated with lipid abnormalities, 681
Giant cell angioblastoma, 1038–1039
differential diagnosis of, 1039
histopathology of, 1039
Giant cell angiofibroma, 988
Giant cell arteritis, 207–208, 208*f*
differential diagnosis of, 208
histopathology of, 111, 116, 208, 208*f*
Giant cell fibroblastoma (GCF), 976–977
giant cell angioblastoma v., 1039
histogenesis of, 977
histopathology of, 125, 977, 977*f*
Giant cell reticulohistiocytosis (GCRH), 675–676, 676*f*
histopathology of, 124
Giant cell tumors
histopathology of, 125
soft tissue chondromas v., 1096
of tendon sheath, 974, 974*f*
histogenesis of, 974
histopathology of, 125, 974, 974*f*
Giant condyloma acuminata of Buschke and Loewenstein, 655*f,* 656
histogenesis of, 656
histopathology of, 655*f,* 656
Giant condylomata acuminatum of Buschke and Loewenstein, 822
Giant congenital melanocytic nevi, 725, 726*f*
histopathology of, 727*f,* 728
melanoma and, 728
Giant molluscum contagiosum, in HIV, 659
Giant solitary trichoepithelioma, 858
Giardia infection, erythema nodosum with, 514
Giardia intestinalis, vitamin A deficiency and, 407
Giemsa stain, for mast cells, 69, 69*t,* 70*f*
Glabrous skin, tinea of, 594
Glandular schwannoma, histopathology of, 125
Glans penis
eccrine glands of, 35
mucocutaneous end-organs in, 54
Reiter's disease and, 181
Gliadin, dermatitis herpetiformis and, 265
Glial fibrillary acidic protein (GFAP)
chondroid syringoma and, 894
intradermal nevus and, 714
Globi, 561
Globoside, 661
Glomangioma, histopathology of, 126, 1047
Glomangiomyoma, histopathology of, 126, 1047
Glomangiopericytomas, 1051
Glomangiosarcoma, histopathology of, 126, 1047
Glomeruloid hemangioma, 1010
histogenesis of, 1010
histopathology of, 126, 1010, 1010*f*
Glomerulonephritis
localized lipodystrophy with, 527
Wegener's granulomatosis and, 214
Glomus cells, of dermal microvascular unit, 52–53, 53*f,* 56
Glomus tumors, 1047–1049, 1047*f,* 1182*f*
differential diagnosis of, 1049
histogenesis of, 1049

Glomus tumors (*continued*)
histopathology of, 126, 1047–1049, 1048*f*
myopericytoma v., 1050
pacinian perineural cell fibroma v., 1135
Glossitis, necrolytic migratory erythema, 409
Glucagonoma syndrome. *See* Necrolytic migratory erythema
Gluconeogenesis, necrolytic migratory erythema and, 409
β-Glucuronidase, in syringoma, 885
Glutaraldehyde, with stratum corneum, 12
Gluten, celiac disease and, 417
Glycocalyx, of stratum spinosum, 10
Glycogen
in clear cell acanthoma, 800
from clear cells, 32
in eccrine poroma, 886
in eccrine spiradenoma, 889
in nodular hidradenoma, 892
PAS and, 68
Glycosaminoglycans
of ground substance, 48*f,* 49–50
of stratum spinosum, 10
Gnathostomum spinigerum, 627
Gnats, as myiasis vector, 632
Goiter, Cowden's disease with, 869
Gold
drug-induced pigmentary alterations of, 692
drug-induced pseudolymphoma syndrome with, 320
lichenoid drug eruption and, 313
Goltz syndrome. *See* Focal dermal hypoplasia syndrome
Gonococcemia. *See also* Chronic gonococcemia
histopathology of, 111
Goodpasture's syndrome, with follicular mucinosis, 468
Gottron's papules, with dermatomyositis, 293–294
Gottron's sign, with dermatomyositis, 293
Gougerot-Blum disease, 226–227
Goundou, 584
Gout, 438–439, 438*f*–439*f*
calciphylaxis and, 230
foreign-body reactions and, 373
histogenesis of, 439
histopathology of, 96, 96*f,* 121, 131, 438–439, 439*f*
polariscopic examination for, 70
reticulohistiocytosis v., 676
Graft-*versus*-host disease (GVHD), 270–273, 271*f*–272*f*
differential diagnosis of, 272–273
histopathology of, 110, 112, 114, 120, 271, 272*f*
human herpesvirus in, 646
immunofluorescence testing for, 271–272
necrolytic migratory erythema v., 409
nephrogenic systemic fibrosis and, 301
scleroderma and, 296
subacute radiation dermatitis v., 352
ultrastructural study for, 272
vitamin A deficiency and, 408
Graham-Little syndrome, 185–186
Grains, 592*t*
of eumycetoma, 614
Granular cell epulis of infancy, 1131
Granular cell nerve sheath tumor (GCNST), 1130–1131, 1130*f*
differential diagnosis of, 1131
histogenesis of, 1131
histopathology of, 124, 1130–1131, 1131*f*
Granular cell tumor, 1130–1132, 1184*f*
granular cell epulis of infancy, 1131
granular cell nerve sheath tumor, 1130–1131, 1130*f*–1131*f*
hibernoma v., 1070
histopathology of, 106, 110, 124
malignant, 1131–1132
pseudocarcinomatous hyperplasia and, 822
rhabdomyoma v., 1084
Granular cell variant of atypical fibroxanthoma, 979
Granular degeneration. *See also* Epidermolytic hyperkeratosis
linear epidermal nevus with, 791–792
Granular layer
ILVEN and, 194
of keratinocytes, 8, 8*f*–11*f,* 11
lichen planus and, 186
psoriasis vulgaris and, 176
Granules, of eumycetoma, 614, 615*f*
Granulocyte colony-stimulating factor, cutaneous eruptions with, 323, 323*t*
Granulocytes, LCA and, 78–79
Granulocytic sarcoma, myeloid sarcoma v., 957
Granuloma. *See also* Actinic granuloma; Cactus granuloma; Zinc granuloma
of Buruli ulcer, 558
of leprosy, 562–564, 563*f*–564*f,* 566
with silica, 70
of tuberculosis, 550–553, 551*f*–552*f,* 554, 554*f,* 556
of tularemia, 568
Granuloma annulare, 361–364, 362*f*–363*f*
annular elastolytic giant cell granuloma v., 364–365
differential diagnosis of, 363–364
epithelioid sarcoma v., 997
histopathology of, 95, 95*f,* 118, 121, 124, 361–362, 362*f*–363*f*
interstitial granulomatous drug reaction v., 381
middermal elastolysis and, 399
necrobiosis lipoidica v., 366–367
palisaded neutrophilic and granulomatosis v., 369
pathogenesis of, 362–363
sarcoidosis and, 370
Granuloma faciale (GF), 222
differential diagnosis of, 222
eosinophils and, 44
erythema elevatum diutinum v., 221–222
histopathology of, 111, 116–117, 222, 222*f*
pathogenesis of, 222
Granuloma fissuratum. *See* Acanthoma fissuratum
Granuloma gluteale infantum, 381
histopathology of, 117, 118, 381
pathogenesis of, 381
Granuloma inguinale, 570, 570*f*
differential diagnosis, 570
histopathology of, 110, 117–118, 120, 570, 570*f*
histoplasmosis v., 312
leishmaniasis v., 622
plasma cells and, 46
pseudocarcinomatous hyperplasia and, 822
rhinoscleroma v., 571
Granuloma multiforme. *See* Annular elastolytic giant cell granuloma
Granuloma pyogenicum
cherry hemangioma v., 1015
clear cell acanthoma v., 799
Granulomas
of chronic cutaneous leishmaniasis, 624
of tertiary syphilis, 583
Granulomatous amebic encephalitis, 625
Granulomatous disease. *See also* Chronic granulomatous disease
mercury pigmentation and, 328, 328*f*
Granulomatous granuloma annulare, histopathology of, 118
Granulomatous infiltrate, of juvenile xanthogranuloma, 672
Granulomatous inflammation, of syphilis, 583
Granulomatous leishmaniasis, leprosy v., 566
Granulomatous lesions, of cryptococcosis, 610–611
Granulomatous mycosis fungoides, 941
Granulomatous necrotizing mucocutaneous leishmaniasis, 624
Granulomatous panniculitis, histopathology of, 131
Granulomatous processes, characterization of, 2
Granulomatous proliferative mucocutaneous leishmaniasis, 624
Granulomatous reactions, in LCD, 669–671
Granulomatous rosacea
childhood granulomatous periorificial dermatitis v., 462
histopathology of, 118, 463–464, 463*f*
pathogenesis of, 464
Granulomatous slack skin, 941
histopathology of, 111
Granulomatous vascular reactions, 212–213, 213*t*
Granulomatous vasculitis, 212–213, 212*f*
Behçet's syndrome with, 414
Granulomatous vasculopathy, Crohn's disease and, 416
Granzyme B, anaplastic large cell lymphoma, 953
Graphite, tattoo reactions and, 378, 379*f*
Grave's disease, macular atrophy and, 400
Griscelli syndrome, 693
Griseofulvin
photoallergic drug eruption and, 318
SJS and TEN with, 313
Grossing, of specimen, 67, 68*f*
Ground substance, of dermis, 49–50
Group A beta-hemolytic *Streptococcus,* toxic shock syndrome from, 546
Group A streptococci
ecthyma from, 541
in impetigo contagiosa, 539
Grover's disease. *See also* Transient acantholytic dermatosis
histopathology of, 114
Growth factors, of keratinocytes, 13
Guarnieri bodies, 647
Gumma, pseudocarcinomatous hyperplasia and, 822
Gummatous lesions, of endemic syphilis, 585
Gummatous tertiary syphilis, histopathology of, 131
Guttate lesions, morphea and, 296
Guttate morphea. *See* Morphea
Guttate parapsoriasis, acute spongiotic dermatitis and, 243
Guttate psoriasis, 178
GVHD. *See* Graft-*versus*-host disease
Gyrate erythema. *See also* Erythema annulare centrifugum
chronic lymphocytic lymphoma/small lymphocytic lymphoma and, 926
deep, histopathology of, 115
Haarscheiben, Merkel cells and, 18–19
HAART. *See* Highly active antiretroviral therapy
Haemophilus ducreyi
chancroid from, 569–570, 569*f*
histopathology of, 120
Haemophilus influenzae, necrotizing fasciitis from, 541
Hailey-Hailey disease. *See also* Familial benign pemphigus
transient acantholytic dermatosis v., 273
Haim-Munk syndrome, acro-osteolysis and, 401
Hair
color of, 31
ectodermal dysplasia and, 142
growth cycles of, 26–27, 26*f,* 28*f*–29*f,* 31
of hair follicles, 25
inflammatory processes of, 85
keratin of, 26
Hair bulb
anatomy of, 26*f*–27*f,* 28–30
in hair growth cycle, 31
Hair canal, formation of, 25

Hair cone, formation of, 25
Hair cortex, keratin of, 28–29
Hair cuticle
  anatomy of, 27*f,* 29
  of hair follicles, 25
Hair follicle(s), 24–31
  acantholytic actinic keratosis and, 810
  aging of, 56
  alopecia diseases of, 470–490
    diagnosis of, 470–473, 471*f*–473*f*
    miscellaneous, 489–490
    nonscarring, 473–481
    scarring, 481–489, 482*f*–483*f*
  apocrine glands from, 32
  basal cell carcinomas of, 829*f,* 830
  in dermoid cyst, 804
  embryology of, 24–25, 24*f*–25*f*
  erythema toxicum neonatorum and, 267
  generalized myxedema and, 441
  histopathology of, 99, 99*f,* 127–128
  inflammatory diseases of, 459–470
    acne vulgaris, 459–461, 460*f*
    demodicidosis, 464–465, 465*f*
    eosinophilic pustular folliculitis, 466–467, 467*f*
    follicular mucinosis and alopecia mucinosa, 467–469, 468*f*–469*f*
    keratosis pilaris, 469–470, 469*f*
    lupus miliaris disseminatus faciei, 465–466, 466*f*
    perioral dermatitis, 462–463, 462*f*
    rosacea, 463–464, 463*f*
    steroid acne, 461–462, 461*f*
    trichostasis spinulosa, 470, 470*f*
  intradermal nevus and, 714
  lichen planopilaris and, 188
  lichen striatus and, 193*f,* 194
  melanocytes in, 25, 27–28, 30–31
  Merkel cells in, 18
  in microcystic adnexal carcinoma, 897
  middermal elastolysis and, 399
  necrosis in coma, 317
  normal microanatomy of, 25–30
    bulb and lowermost portion, 26*f*–27*f,* 28–30
    cycles of hair growth, 26–27, 26*f,* 28*f*–29*f,* 31
    follicular isthmus and infundibulum, 27*f,* 30
    general anatomic features, 25–26, 25*f*–29*f*
  in pigmented follicular cyst, 804
  porokeratotic eccrine ostial and dermal duct nevus of, 793
  regional variation of, 30–31
  sebaceous glands, 28*f,* 30
  sensory nerves to, 53
  specialized structure and function of, 31
    follicular immunity, 31
    hair color, 31
    hair cycle, 31
  in steatocystoma multiplex, 804
  striae distensae and, 398
  tumors with differentiation toward, 853–870
    desmoplastic trichoepithelioma, 859–860, 860*f*
    dilated pore and pilar sheath acanthomas, 855–856, 855*f*–856*f*
    fibrofolliculoma and trichodiscoma, 856–857, 856*f*–857*f*
    generalized hair follicle hamartoma and basaloid follicular hamartoma, 863, 863*f*–864*f*
    hair follicle nevus, 853–854, 853*f*
    malignant proliferating trichilemmal tumor, 867
    pilomatricoma, 864–865, 864*f*–865*f*
    pilomatrix carcinoma, 865–866, 866*f*
    proliferating trichilemmal cyst, 866–867, 867*f*
    sebaceous trichofolliculoma, 855
    trichilemmal carcinoma, 870
    trichilemmal horn; trichilemmomal horn, 870
    trichilemmoma, 867–869, 868*f*
    trichoadenoma, 862–863, 862*f*–863*f*
    trichoblastoma, 860–862, 861*f*–862*f*
    trichoepithelioma, 857–859, 858*f*
    trichofolliculoma, 854–855, 854*f*
    tumor of the follicular infundibulum, 869–870, 869*f*–870*f*
  in warty dyskeratoma, 807
Hair follicle hamartoma
  hair follicle nevus v., 854
  histopathology of, 123
Hair follicle nevus, 853–854
  differential diagnosis of, 854
  histopathology of, 123, 853, 853*f*
Hair loss
  Sézary syndrome with, 944
  systemic lupus erythematosus with, 285
Hair matrix
  of hair follicles, 25
  pluripotential cells of, 28
Hair medulla, identification of, 28
Hair shaft, of hair follicles, 26
Hajdu-Cheney syndrome, acro-osteolysis and, 401
Hallopeau type, of pemphigus vegetans, 250
Hallopeau-Siemens, with nail unit, 506
Halo dermatitis around a melanocytic nevus, 730
Halo nevus, 730–732, 731*f*
  differential diagnosis of, 732
  histogenesis of, 732
  histopathology of, 110, 122, 730–732, 731*f*
Halo nevus phenomenon, 730
Halo nevus without halo. *See* Halo nevus phenomenon
Halogenodermas, 326–327, 326*f*
  histopathology of, 104, 106, 110, 118, 326, 326*f*
  North American blastomycosis v., 604
  pathogenesis of, 327
  pemphigus vegetans v., 250
Hamartomas. *See also* Hair follicle hamartoma
  definition of, 853
  mongolian spot, 699–700
  nevi of Ota, Ito, and Hori; dermal melanocyte hamartoma, 700–701
Hand(s)
  eccrine poroma on, 885
  Meissner corpuscles on, 55
Hand-foot syndrome. *See* Toxic acral erythema
Hand-foot-and-mouth disease, 658, 658*f*
  histogenesis and diagnosis of, 658
  histopathology of, 114, 658, 658*f*
Hand-Schüller-Christian disease, 669–671
  histopathology of, 111
Hanging groins, 630
Harlequin ichthyosis, 136
  histopathology of, 136
  pathogenesis of, 136
Hartnup's disease, 408–409, 451
  histogenesis of, 451
  histopathology of, 103, 110, 409, 451
  pathogenesis of, 409
Hashimoto thyroiditis, mucosa-associated lymphoid tissue lymphoma and, 920–921
Hashimoto-Pritzker disease. *See* Congenital self-healing reticulohistiocytosis
Hashimoto's disease
  middermal elastolysis and, 399
  scleroderma and, 296
HAV. *See* Hepatitis A virus
HBV. *See* Hepatitis B virus
HCV. *See* Hepatitis C virus
Headache, with solar urticaria, 340
Heart
  systemic scleroderma and, 300
  tuberous sclerosis in, 989
Heat-associated injuries, 343–348
  burns, 343–347, 344*f*–346*f*
  erythema ab igne, 347–348, 347*f*
Heavy metals, drug-induced pigmentary alterations of, 692
HEB. *See* Hereditary epidermolysis bullosa
Heck's disease. *See* Oral focal epithelial hyperplasia
Hedgehog-Patched pathway, basal cell carcinoma and, 833
Helicobacter pylori
  mucosa-associated lymphoid tissue lymphoma and, 920–921
  rosacea and, 464
Heliotrope rash, with dermatomyositis, 293
Helminths. *See* Worms
Hemangioendotheliomas
  histopathology of, 126
  spindle cell hemangioma with, 1027
Hemangiomas. *See* Cavernous hemangioma; Congenital hemangiomas; Epithelioid hemangioma; Glomeruloid hemangioma; Hobnail hemangioma; Microvenular hemangioma; Spindle cell hemangioma
Hemangiopericytoma
  histopathology of, 126
  myopericytoma and, 1049–1050
Hemapoietic cells, tumors of, 96, 96*f,* 121–122
Hematopoietic infiltrates, 911–915
  abnormal trafficking, 913–915, 914*f*
  cell lineage, 911, 912*f*
  T- and B-cell infiltration patterns, 911–913, 913*f,* 913*t*
Hematoxylin-eosin
  for nail psoriasis, 504
  for specimen staining, 68
Hemidesmosomes
  anatomy of, 22–23, 22*f*–23*f*
  epidermolysis bullosa and, 147
  keratinocytes and, 7–10
  melanocytes and, 17
Hemochromatosis, 449–450
  histogenesis of, 450
  histopathology of, 104, 121, 450
Hemodialysis, with pseudoporphyria cutanea tarda, 435
Hemophagocytic syndrome
  with cutaneous γ/δ T-cell lymphoma, 951
  intravascular large B-cell lymphoma with, 932
  subcutaneous panniculitis-like T-cell lymphoma and, 948
  subcutaneous T-cell lymphoma with, 532–534, 532*f*–533*f*
Hemorrhage, 206
Hemorrhagic pustules, of human cowpox infection, 647
Hemorrhagic type smallpox, 647
Hemosiderin
  dermal dendrocytes and, 40
  hemochromatosis and, 450
  Kaposi-like infantile hemangioendothelioma and, 1038
  lymphangiomatosis, 1046
  progressive lymphangioma, 1045
Henle layer
  of hair follicles, 25–26, 26*f*–27*f,* 29
  keratinization of, 28
Henna, tattoo reactions and, 378
Henoch-Schönlein purpura (H-SP), 218–219, 218*f*
  bowel-associated dermatosis-arthritis syndrome v., 412
  direct immunofluorescence for, 71–73
  hepatitis C with, 661
  histopathology of, 111, 219
  parvovirus B19 in, 662
Hepadnaviridae, 637

Heparan sulfate, mucopolysaccharidosis and, 447
Heparin
for acute meningococcemia, 547
PAS and, 69, 69*t*
Hepatic cirrhosis
hereditary hemochromatosis and, 449
necrolytic migratory erythema and, 409
porphyria cutanea tarda with, 433
Hepatitis, 418–419
histopathology of, 418–419
pathogenesis of, 419
subcutaneous polyarteritis nodosa and, 518
Hepatitis A virus (HAV), 659
Hepatitis B vaccine
granuloma annulare and, 362
lichenoid drug eruption and, 313
Hepatitis B virus (HBV), 660–661, 661*f*
Gianotti-Crosti syndrome and, 184
necrolytic migratory erythema and, 409
papular acrodermatitis with, 418
Hepatitis C virus (HCV), 661
leukocytoclastic vasculitis and, 216, 218
primary cutaneous marginal zone lymphoma and, 921
sarcoidosis and, 370
Hepatocytes, protoporphyrin in, 435
Hepatomegaly, drug-induced lupus erythematosus with, 318
Hepatopathies, pyoderma gangrenosum with, 411
Hepatosplenomegaly
with angioimmunoblastic T-cell lymphoma, 952
with common variable immunodeficiency, 381
with histiocytic cytophagic panniculitis, 533
mucopolysaccharidosis and, 447
peripheral T-cell lymphoma with, 951
Herbal medications, interstitial granulomatous drug reaction and, 381
Hereditary coproporphyria, 433
histopathology of, 433–434, 434*f*
pathogenesis of, 434–435
Hereditary epidermolysis bullosa (HEB), indirect immunofluorescence testing for, 74, 74*t*
Hereditary hemochromatosis. *See* Hemochromatosis
Hereditary hemorrhagic telangiectasia, 1012
histogenesis of, 1012
histopathology of, 126, 1012
Hereditary progressive mucinous histiocytosis, histopathology of, 121
Hermansky-Pudlak syndrome, 693
Herpes genitalis. *See* HSV-2
Herpes gestationis, 260–261, 261*f,* 1172*f*
histopathology of, 115, 260, 261*f*
immunofluorescence testing, 260–261
ultrastructural study of, 261
vesicular pemphigoid v., 259
Herpes labialis, 638
Herpes simplex virus (HSV), 638–639, 638*f*
Behçet's syndrome and, 414
chancroid v., 570
in compromised hosts, 639
congenital, 639
differential diagnosis of, 641
erythema multiforme with, 268, 270, 639
erythema nodosum with, 514
histogenesis and viral identification of, 641
histopathology of, 92, 92*f,* 107, 114, 639–641, 639*f*–640*f*
nail unit and, 508, 508*f*
recurrent infection of, 639
Tzanck smear of, 641
Herpes viral infection, 85
hydroa vacciniforme v., 338
Herpes zoster infection, 640*f,* 642–644, 643*f*
in compromised hosts, 643–644
granuloma annulare and, 361–362
herpes simplex v., 641
histogenesis and viral identification of, 643–644
histopathology of, 643
in HIV, 659
sarcoidosis and, 370
Tzanck smear of, 643
zoster-related granulomas after, 381
Herpes zoster vasculitis, 643
Herpesviridae, 637–646, 638*f*–640*f,* 642*f*–643*f,* 645*f*–646*f*
herpes simplex, 638–639, 638*f*
in compromised hosts, 639
congenital, 639
erythema multiforme with, 639
herpes zoster infection, 640*f,* 642–644, 643*f*
in compromised hosts, 643–644
Kaposi's varicelliform eruption, 638, 638*f,* 641–642
varicella, 640*f,* 642–643, 642*f*
in compromised hosts, 643
Herpesvirus, leukocytoclastic vasculitis and, 218
Herpetic folliculitis, 638–639, 641
Herpetic infections, in HIV, 659
Herpetic whitlow, 638–639
Heterotopias, 1141
differential diagnosis of, 1141
histopathology of, 1141, 1141*f*
HHV-6. *See* Human herpesvirus 6
HHV-7. *See* Human herpesvirus 7
HHV-8. *See* Human herpesvirus 8
Hibernoma, 1068–1070, 1069*f*
differential diagnosis of, 1070
histopathology of, 127, 1069–1070, 1069*f*
pathogenesis of, 1070
rhabdomyoma v., 1084
ultrastructure of, 1070
Hidradenitis suppurativa
Crohn's disease with, 415
in follicular occlusion triad, 544
histopathology of, 99, 99*f,* 120, 128, 131
Hidradenoma papilliferum, 878
additional studies of, 878
erosive adenomatosis of the nipple v., 881
histopathology of, 97, 97*f,* 123, 127, 878, 878*f*
tubular apocrine adenoma v., 880
Hidroacanthoma simplex, 886, 886*f*
histopathology of, 104
Hidrotic ectodermal dysplasia, eccrine syringofibroadenoma with, 888
Highly active antiretroviral therapy (HAART), Kaposi's sarcoma and, 1029
Hirsutism, mucopolysaccharidosis and, 447
Histamine, anaphylactic reaction and, 41–42
Histiocytes. *See also* Epithelioid histiocytes; Macrophages
in androgenetic alopecia, 481
cheilitis glandularis and, 381
chronic actinic dermatitis and, 339
cicatricial pemphigoid and, 259–260
classification of, 668*t*
dermatofibroma and, 969
of eosinophilic ulcer of the tongue, 813
granuloma annulare and, 361–362
granuloma gluteale infantum and, 381
in halogenodermas, 326
hydroa vacciniforme and, 337
Jessner's lymphocytic infiltration of the skin and, 291
with lichen planus of the nail, 505
of lupus miliaris disseminatus faciei, 466
in lymphomatoid granulomatosis, 933
markers for, 668*t*
with nail psoriasis, 504
necrobiosis lipoidica and, 366
perforating folliculitis and, 393
with rheumatoid nodules, 367
S100 protein in, 77
tattoo reactions and, 378
in titanium granuloma, 377
tumors of, 124
Histiocytic cytophagic panniculitis, 532–534
clinical features of, 532–533, 532*f*
histopathology of, 102, 102*f,* 131, 533–534, 533*f*
pathogenesis of, 534
Weber-Christian disease v., 524
Histiocytic sarcoma, 679–680
Histiocytoid hemangioma, 1022
Histiocytoma, Kaposi's sarcoma v., 1034
Histiocytoses, 667–686
dermal dendrocytoma, 678
histiocytic sarcoma, 679–680
indeterminate cell histiocytosis, 678
Langerhans cell disease, 668–671, 670*f*
miscellaneous xanthomas, 686
normolipemic xanthomas, 683–686, 684*f*–685*f*
diffuse normolipemic plane xanthoma, 684–685, 685*f*
necrobiotic xanthogranuloma with paraproteinemia, 683–684, 684*f*
verruciform xanthomas, 685–686, 685*f*
Rosai-Dorfman disease, 678–679, 679*f*
xanthogranuloma family, 671–678, 672*f*–677*f,* 672*t*
benign cephalic histiocytosis, 677–678, 677*f*
generalized eruptive histiocytosis, 678
juvenile xanthogranuloma, 672–673, 673*f*
papular xanthoma, 673–674, 674*f*
progressive nodular histiocytosis, 676*f,* 677
reticulohistiocytosis, 675–676, 676*f*
scalloped cell xanthogranuloma, 674, 674*f*
spindle cell xanthogranuloma, 676, 676*f*
xanthoma disseminatum, 674*f*–675*f,* 675
xanthomas associated with lipid abnormalities, 680–683, 680*t,* 681*f*–683*f*
Histiocytosis X
eosinophils and, 44
histopathology of, 111, 117
Histochemical staining, 68–69, 69*t,* 70*f*. *See also* Immunohistochemical stains
Histoid leprosy, 561–562, 562*f*
histopathology of, 117
Histologic diagnosis, 1–4
biological relevance of, 4
biopsy for, 5
consistency of, 3
criteria in, 3
difficulties of, 1–3
improvement of, 4
problem solving of, 3
prognostication and, 3–4
ruling out by, 1–2
sensitivity and specificity of, 1–2
Histopathologic differential diagnosis, of leprosy, 566
Histoplasma capsulatum, 600*t,* 604, 611–612, 612*f*
cryptococcosis v., 611
Histoplasma capsulatum var. *duboisii,* 612
Histoplasma, in HIV, 611, 659
Histoplasmosis, 600*t,* 611–612, 612*f*
African histoplasmosis, 612
Crohn's disease v., 416
differential diagnosis, 612
erythema nodosum with, 514
histopathology of, 117–118, 612, 612*f*
leishmaniasis v., 622
molluscum contagiosum v., 649
pathogenesis of, 612
HIV. *See* Human immunodeficiency virus

HLA types, Behçet's syndrome and, 414
HMB-45
antibodies against, 76*t,* 77
common blue nevus and, 701
for desmoplastic melanoma, 753, 755–756
nodular melanoma and, 752
Spitz nevi and, 722
Hoarseness, with acrodermatitis enteropathica, 410
Hobnail hemangioma, 1021–1022
atypical vascular proliferation after radiotherapy v., 1046
differential diagnosis of, 1022
histopathology of, 126, 1021–1022, 1022*f*
Kaposi's sarcoma v., 1035
pathogenesis of, 1022
retiform hemangioendothelioma v., 1036
Hodgkin's disease
acanthosis nigricans and, 448
cutaneous, histopathology of, 124
eosinophils and, 44
erythema nodosum with, 514
with follicular mucinosis, 468
herpes zoster with, 643
Hodgkin's lymphoma (HL), 933–935
anaplastic large cell lymphoma with, 953
clinical features of, 933
differential diagnosis of, 935
histogenesis of, 934–935
histopathology of, 933–934, 934*f,* 934*t*
peripheral T-cell lymphoma v., 952
Hoffa disease. *See* Lipoma arborescens
Holocrine secretion
with apocrine glands, 36
sebaceous gland and, 30
Homogentisic acid, ochronosis and, 439–440
Hookworm folliculitis, 628
Hookworm-related cutaneous larva migrans, 627–628, 627*f*
histopathology of, 627*f,* 628
pathogenesis of, 628
Hormones
adipose tissue production of, 535
localized lipoatrophy and, 527
perioral dermatitis and, 463
Horn cysts
in acanthotic seborrheic keratosis, 798
in dermatosis papulosa nigra, 799
in desmoplastic trichoepithelioma, 860
in microcystic adnexal carcinoma, 897
soft fibroma and, 981
in solitary trichoepithelioma, 859
in trichoadenoma, 862
Horn pearls, of squamous cell carcinoma, 820
Hornets, reactions to stings of, 634–635, 634*f*
Horny layer, of keratinocytes, 8, 8*f*–11*f,* 10–12
Host resistance, in histopathological diagnosis, 3
Housefly, as myiasis vector, 632
Howship's lacunae, 1087
HPV. *See* Human papillomavirus
HR gene. *See* Human hairless gene
HRAS, for Spitz nevus, 722
H-SP. *See* Henoch-Schönlein purpura
HSV. *See* Herpes simplex virus
HSV keratoconjunctivitis, 639
HSV-1, 638–641, 638*f*
HSV-2 v., 641
HSV-2, 638–641
HSV-1 v., 641
HTLV-1 infection, adult T-cell leukemia/lymphoma, 953–954
Human botfly, as myiasis vector, 632–633
Human cowpox infection, 647
histopathology of, 647
Human demodectic alopecia, 465
Human hairless *(HR)* gene, atrichia with papular lesions and, 490
Human herpesvirus 6 (HHV-6), 645–646
histopathology of, 646
Human herpesvirus 7 (HHV-7), 645–646
histopathology of, 646
Human herpesvirus 8 (HHV-8)
histopathology of, 646
Kaposi's sarcoma and, 1029, 1033, 1034*f*
Human immunodeficiency virus (HIV), 659–660
acanthamoebiasis with, 625
bacillary angiomatosis and, 572, 659
Behçet's syndrome and, 414
botryomycosis and, 573
candidiasis with, 597–598, 659–660
coccidioidomycosis with, 608, 659
cryptococcosis with, 609, 659
cytomegalovirus with, 644, 659
demodicidosis and, 465, 660
eosinophilic pustular folliculitis and, 466, 660
fungal infections with, 593, 598
granuloma annulare and, 361
herpes simplex with, 639
herpes zoster with, 643
histoplasmosis with, 611, 659
Kaposi's syndrome and, 1029–1030, 1030*f,* 1034
leishmaniasis with, 621
leprosy and, 566
localized lipodystrophy and, 527
macular atrophy and, 400
molluscum contagiosum with, 649, 659
neutrophilic eccrine hidradenitis and, 491
nocardiosis and, 574, 659
nontuberculosis mycobacteria infections with, 555
oral hairy leukoplakia with, 644–645, 659–660
paracoccidioidomycosis with, 606
psoriasis and, 175
histopathology of, 179
pathogenesis of, 180–181
seborrheic dermatitis and, 243, 659–660
syphilis with, 579, 582, 659
telogen effluvium and, 478
tuberculosis with, 550
verruca vulgaris with, 650–651
visceral leishmaniasis with, 625
Human papillomavirus (HPV), 649–650
lichen sclerosus et atrophicus and, 306–307
myrmecia warts from, 793
verrucae vulgares from, 793
Human recombinant proteins, cutaneous eruptions from, 322–324, 323*f*–324*f,* 323*t*
histopathology of, 323, 323*f*–324*f*
pathogenesis of, 324
Hunter's syndrome
histopathology of, 121, 447
mucopolysaccharidosis and, 447
Hurler's syndrome, mucopolysaccharidosis and, 447
Hurler-Scheie syndrome, mucopolysaccharidosis and, 447
Hutchinson-Gilford syndrome, acro-osteolysis and, 401
Hutchinson's melanotic freckle. *See* Lentigo maligna melanoma
Hutchinson's sign, acral-lentiginous melanoma and, 747
Huxley layer
of hair follicles, 25–26, 26*f*–27*f,* 29
keratinization of, 28
Hyalin
in chondroid syringoma, 894
cylindroma and, 882–883
in eccrine spiradenoma, 889
with lipoid proteinosis, 431
soft tissue chondromas and, 1094
Hyaline sheath
cylindroma and, 882–883
malignant cylindroma and, 883
Hyalinizing Spitz nevus, 722
Hyalinosis cutis et mucosae. *See also* Lipoid proteinosis
doubly refractile lipids in, 70
histopathology of, 121
Hyaluronic acid
reactions to, 378
scleredema and, 446, 446*f*
in stratum spinosum, 10
Hyaluronidase, for mucin-producing squamous cell carcinoma, 821
Hydralazine, drug-induced lupus erythematosus with, 318
Hydroa vacciniforme (HV), 337–338, 337*f*
differential diagnosis of, 337–338
Hartnup's disease v., 408–409
histology of, 337, 337*f*
histopathology of, 113–114
pathogenesis of, 337
Hydrolytic enzymes, of eosinophils, 43
Hydropic degeneration, ultraviolet recall and, 346
Hydroquinone
chemical depigmentation with, 691
ochronosis and, 439–440
3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, dermatomyositis and, 294
Hydroxychloroquine, acute generalized exanthematous pustulosis with, 314
L-5 Hydroxytryptophan, scleroderma and, 296
Hydroxyurea
antineoplastic chemotherapeutic drugs and, 321
dermatomyositis and, 294
Hyperacanthosis, of giant condyloma acuminata of Buschke and Loewenstein, 656
Hypercalcemia
with adult T-cell leukemia/lymphoma, 953–954
metastatic calcinosis cutis with, 435
subcutaneous fat necrosis and, 529
Hyperchromasia, malignant eccrine spiradenoma with, 890, 890*f*
Hyperchromatism, symplastic hemangioma and, 1028
Hypereosinophilia
Churg-Strauss syndrome and, 213
eosinophilic panniculitis and, 515
Hypergammaglobulinemia
with chilblains, 353
eosinophilic fasciitis and, 303
Hypergranulosis
graft-*versus*-host disease and, 271
lichen planopilaris and, 188
lichen planus and, 186
with lichen planus of the nail, 505
oculocutaneous tyrosinosis and, 452
Hyperimmunoglobulin E syndrome, 245
Hyperimmunoglobulinemia, acro-osteolysis and, 401
Hyperkeratosis. *See also* Follicular hyperkeratosis; Incidental epidermolytic hyperkeratosis
of acanthosis nigricans, 448
of acanthotic seborrheic keratosis, 798
of acral fibrokeratoma, 989
of actinic keratosis, 807
of arsenical keratosis, 817
confluent and reticulated papillomatosis, 449
Darier's disease and, 151, 151*f*
of deep palmoplantar warts, 652, 652*f*
of folliculitis decalvans, 487
Fox-Fordyce disease and, 492
of giant condyloma acuminata of Buschke and Loewenstein, 656
of graft-*versus*-host disease, 271
of hyperkeratotic seborrheic keratosis, 798

Hyperkeratosis (*continued*)
of hypertrophic actinic keratosis, 808
with hypogranulosis, 86, 86*f,* 103
of ichthyosis vulgaris, 133, 134*f*
incontinentia pigmenti and, 161
with lichen planus of the nail, 505
of lichen sclerosus et atrophicus, 305
of lichen simplex chronicus, 242
of linear epidermal nevus, 791
with nail psoriasis, 504–505
neonatal lupus erythematosus and, 285
with normal or hypergranulosis, 86, 86*f,* 103
with parakeratosis, 86, 86*f,* 103
seborrheic keratosis and, 795
Sézary syndrome with, 944
smooth muscle hamartoma and, 1075
soft fibroma and, 981
of verruca plana, 653, 653*f*
of verruca vulgaris, 650, 651*f*
of verruciform xanthomas, 685*f*
X-linked ichthyosis with, 133
Hyperkeratosis lenticularis perstans, 397–398
histogenesis of, 398
histopathology of, 103, 397–398, 398*f*
Hyperkeratotic follicular papules, lichen planopilaris and, 188
Hyperkeratotic scale, in verrucous lupus erythematosus, 283
Hyperkeratotic seborrheic keratosis, 798
stucco keratosis v., 799
Hyperlipidemia, xanthomas associated with, 680–683, 680*t,* 681*f*–683*f*
Hyperlipoproteinemia, polariscopic examination for, 70
Hyperparathyroidism, 435–436
acquired perforating dermatosis with, 396
calcifying panniculitis with, 530–531, 531*f*
Hyperphosphatemia, metastatic calcinosis cutis with, 435
Hyperpigmentation, 704–706
acanthosis nigricans and, 448
of acral-lentiginous melanoma, 748
with Addison's disease, 690
with antineoplastic chemotherapeutic drugs, 321, 321*f*
Becker's melanosis, 706
with Berloque dermatitis and phytophotodermatitis, 691
with chemical burns, 346
with congenital diffuse melanosis, 689
with cutaneous and systemic diseases, 692–693
drug-induced, 692
with erythema ab igne, 348
of face, 690
with furocoumarins contact, 691
with hereditary hemochromatosis, 449
kwashiorkor and, 410
with lichen planus of the nail, 505
with linear and whorled nevoid hypermelanosis, 690
localized or diffuse, 87, 87*f,* 104
with melanonychia striata, 717
of ochronosis, 439
in perforating calcific elastosis, 396
with pinta, 585
of pityriasis (tinea) versicolor, 596
postinflammatory, 690–691, 691*f*
with psoralen and ultraviolet A-induced pigment alterations, 691–692
reticulate pigmentary anomalies, 689–690
of smooth muscle hamartoma, 1075
Hyperpigmented mycosis fungoides, 942
Hyperplasia
chondrodermatitis nodularis helicis and, 494
dermatofibroma and, 969
of granuloma inguinale, 570
linear melorheostotic scleroderma and, 155
of rhinoscleroma, 571
Hypersensitivity
mast cells and, 41–42
T cells and, 45
Hypersensitivity syndrome, human herpesvirus in, 646
Hypertension, subcutaneous polyarteritis nodosa and, 518
Hypertrichosis
Becker's melanosis, 706
porphyria cutanea tarda with, 433
Hypertrophic actinic keratosis, 808–809, 808*f*
Hypertrophic dermatitis, histopathology of, 90, 90*f,* 109–110
Hypertrophic lichen planus, 185, 187, 187*f*
histopathology of, 111
lichen amyloidosis and macular amyloidosis v., 427
Hypertrophic scar, 979–980
histogenesis of, 980
histopathology of, 125, 980, 980*f*
Hyperuricemia, gout and, 439
Hyphae, of fungi, 591, 592*t*
Hypocomplementemic urticarial vasculitis, direct immunofluorescence and, 72–73
Hypoderma species, 633
Hypomelanosis of Ito, 161–162, 161*f,* 690
Hyponychium
anatomy of, 36–38, 36*f*–37*f*
bullous disease of, 506
fungal infection of, 507
lichen planus of, 505
psoriasis of, 504
Hypopigmentation
in Chediak-Higashi syndrome, 695
with cryotherapy-induced injury, 355
with cutaneous and systemic diseases, 692–693
discoid lupus erythematosus and, 280
kwashiorkor and, 410
localized or diffuse, 87, 87*f,* 104
perifollicular elastolysis and, 401
with pinta, 584
of pityriasis (tinea) versicolor, 596
postinflammatory, 690–691, 691*f*
progressive macular, 691
in tuberous sclerosis, 989
Hypopigmented macules, of post-kala-azar dermal leishmaniasis, 624
Hypopigmented mycosis fungoides, 942
Hypopituitarism, with sarcoidosis, 372
Hypothalamus, leptin and, 535
Hypothyroidism
acquired perforating dermatosis with, 396
generalized myxedema and, 441
telogen effluvium and, 478

IAMPUS. *See* Intraepidermal atypical melanocytic proliferation of uncertain significance
Iatrogenic immunosuppression, Kaposi's sarcoma and, 1030
IBIDS syndrome, 136
ICH. *See* Indeterminate cell histiocytosis
Ichthyosiform mycosis fungoides, 942
Ichthyosiform sarcoidosis, 370
Ichthyosis, 133–137
autosomal recessive, 135
CHILD syndrome, 135–136, 135*f*
epidermolytic hyperkeratosis, 134–135, 134*f*
erythrokeratodermia variabilis, 136
harlequin, 136
syndromes associated with, 136–137
X-linked, 133
Ichthyosis hystrix, 791
Ichthyosis linearis circumflexa, 136
Ichthyosis vulgaris
differential diagnosis of, 133
histogenesis of, 133
histopathology of, 86, 86*f,* 103, 133
Kaposi's varicelliform eruption with, 641
with keratosis pilaris, 470
scurvy v., 407
Id reaction, 241
histopathology of, 241
pathogenesis of, 241
IDC. *See* Interdigitating dendritic cell
Idiopathic acro-osteolysis, 401
Idiopathic calcification of the scrotum, histopathology of, 121
Idiopathic calcinosis cutis, 437
histopathology of, 437
pathogenesis of, 437
of the scrotum, 437
Idiopathic cutaneous verruciform xanthomas, 685
Idiopathic diseases, histiocytoses, 668
Idiopathic guttate hypomelanosis, 691
histogenesis of, 691
histopathology of, 104, 691
Idiopathic pustular vasculitis, bowel-associated dermatosis-arthritis syndrome v., 412–413
Idiopathic thrombocytopenia purpura, alopecia areata and, 475
IFEMS. *See* Infiltrating and fascicular epithelioid malignant schwannoma
IFs. *See* Intermediate filaments
IFSCT. *See* Infiltrating fascicular schwannoma
IgA
with dermatitis herpetiformis, 264–265
linear IgA dermatosis and, 265–266
subcorneal pustular dermatosis and, 268
IgA antibodies, celiac disease and, 417
IgA pemphigus, 253–254, 253*f*
differential diagnosis of, 254
histopathology of, 253–254, 253*f*
immunofluorescence testing of, 254
subcorneal pustular dermatosis v., 267
IgG antibodies
celiac disease and, 417
neonatal lupus erythematosus and, 285
IgG deposition
with mixed connective tissue disease, 293
systemic scleroderma and, 301
IgG paraprotein, in scleromyxedema, 444
ILs. *See* Interleukins
ILVEN. *See* Inflammatory linear verrucous epidermal nevus
Imatinib, lichenoid drug eruption and, 313
Imipramine, photodistributed hyperpigmentation and, 319, 319*f*–320*f*
Immature trichoepithelioma, histopathology of, 123
Immune functions, of keratinocytes, 13
Immune response, to *Mycobacterium leprae,* 559, 559*f*
Immunity, of hair follicles, 31
Immunizations, erythema nodosum with, 515
Immunoblastic, histopathology of, 122
Immunoblasts
in B-cell lymphomatoid hyperplasia, 916
in lymphomatoid granulomatosis, 933
Immunoblotting, 74
Immunocompromised hosts
herpes simplex in, 639
herpes zoster in, 643–644
varicella in, 643
Immunocytoma, histopathology of, 121
Immunodepression, strongyloidiasis with, 628
Immunofluorescence testing, 70–74
direct, 71–73, 71*t,* 72*f*
for anti-p200 pemphigoid, 263

biopsy technique, 71
for bullous pemphigoid, 71, 257–258, 257*f,* 257*t*
for cicatricial pemphigoid, 260
for dermatitis herpetiformis, 264–265, 264*f*
for diabetic bullae, 273
for drug-induced pemphigus, 253
for herpes gestationis, 260
for IgA pemphigus, 254
interpretation, 72–73
for linear IgA dermatosis, 265, 267
for mixed connective tissue disease, 293
for PAMS, 254
for pemphigus erythematosus, 252
for pemphigus foliaceus, 251, 251*f*
for pemphigus herpetiformis, 252
for pemphigus vulgaris, 248–249, 248*f*
for subcorneal pustular dermatosis, 268
for systemic lupus erythematosus, 290–291, 291*t*
transport and processing of specimen, 71–72
for edema blisters, 273
for EM, SJS, and TEN, 270
indirect, 73–74, 73*f,* 74*t*
for anti-p200 pemphigoid, 263
for bullous systemic lupus erythematosus, 263
for cicatricial pemphigoid, 258*t,* 260
for circulating antiepithelial antibodies, 73–74, 73*f*
for dermatitis herpetiformis, 265
for epidermolysis bullosa acquisita (EBA), 261, 262*f*
for hereditary epidermolysis bullosa, 74, 74*t*
for herpes gestationis, 260–261
for IgA pemphigus, 254
for mixed connective tissue disease, 293
for PAMS, 254
for pemphigus erythematosus, 252
for pemphigus foliaceus, 251–252
for pemphigus herpetiformis, 252–253
for pemphigus vegetans, 250
for pemphigus vulgaris, 249
for systemic lupus erythematosus, 290, 290*t*
for lichen planus, 189–190
Immunoglobulin(s)
lichen amyloidosis and macular amyloidosis and, 429
lupus erythematosus panniculitis and, 522
plasma cells and, 46
in precursor B-cell lymphoblastic lymphoma, 924
pseudoporphyria cutanea tarda with, 435
rosacea and, 464
Immunoglobulin A dermatosis, linear, histopathology of, 115
Immunoglobulin A pemphigus, histopathology of, 112–114
Immunoglobulin deposits, systemic scleroderma and, 301
Immunohistochemical stains, for eccrine and apocrine glands, 34*f*–35*f,* 36
Immunohistochemical techniques, for melanocytes, 16–17, 16*t*
Immunohistochemistry, 74–75
for chondroid syringoma, 894
of eccrine glands, 34*f*
for epithelioid fibrous histiocytoma, 970
of extramammary Paget's disease, 840
of keratinocytes, 11*f,* 13–14, 13*f*
for lichen planus, 190
of melanocytes and sun exposure, 17
of Merkel cells, 18
of neural tissue, 1108–1109, 1109*f*
for neurothekeoma, 1129
of nodular melanoma, 752–753
of Paget's disease, 838–839
for pilomatricoma, 865
for Sézary syndrome, 944
of Spitz nevus, 722
for squamous cell carcinoma, 820
techniques for, 74–75
of tonofilaments, 11, 11*f*
Immunohistopathology, applications of, 75–80
electron microscopy, 79–80
lymphoma diagnosis, 79
tumor diagnosis, 75–79, 76*t,* 77*f*–79*f,* 79*t*
Immunomapping, 71
Immunopathologic spectrum, of leprosy, 559, 559*f*
Immunoprecipitation, 74
Immunosuppressed hosts
epidermal tumors in, 835, 835*f*
solitary keratoacanthoma in, 836
Immunosuppressive therapy
for actinic prurigo, 335
alternariosis with, 603
for chronic actinic dermatitis, 338
coccidioidomycosis with, 608
for fibroblastic rheumatism, 307
malakoplakia with, 549
nontuberculosis mycobacteria infections with, 555
squamous cell carcinoma and, 818
for staphylococcal scalded-skin syndrome, 540
verruca vulgaris with, 650–651
Impetiginized dermatitis, histopathology of, 112–113
Impetigo, 85, 539–541, 540*f*
acropustulosis of infancy v., 267
bullous impetigo, 539–541
erythema toxicum neonatorum v., 267
impetigo contagiosa, 539, 540*f*
pemphigus foliaceus v., 252
psoriasis vulgaris v., 181
staphylococcal scalded skin syndrome, 539–541
subcorneal pustular dermatosis v., 268
Impetigo Bockhart, 542
histopathology of, 128, 542
Impetigo contagiosa, 539, 540*f*
differential diagnosis of, 539
histopathology of, 90, 90*f,* 92, 92*f,* 110, 112–113, 539, 540*f*
pathogenesis of, 539
Impetigo herpetiformis, 175
Impingement neurofasciitis, 1143
histopathology of, 126
Inapparent vasculitis, histopathology of, 130, 131
Incidental epidermolytic hyperkeratosis, 58–59, 59*f*
hypertrophic actinic keratosis and, 809
Incipient pyoderma gangrenosum, bowel-associated dermatosis-arthritis syndrome v., 412
Incisional biopsy
for alopecia, 470–472, 471*f*
of melanoma, 762
Inclusion bodies. *See also* Eosinophilic inclusion bodies
of deep palmoplantar warts, 652, 652*f*
in herpes simplex infection, 640, 640*f*
of herpes zoster, 643
of human cowpox infection, 647
of molluscum contagiosum, 649, 649*f*
Inclusion body fibromatosis. *See* Infantile digital fibromatosis
Inclusion warts, 652
Incontinentia pigmenti (IP), 160–161, 161*f,* 690, 1167*f*
histopathology of, 108–110, 113, 161, 161*f*
pathogenesis of, 161
stages of, 160–161
Incontinentia pigmenti achromians. *See* Hypomelanosis of Ito
Indeloxazine hydrochloride, eosinophilic pustular folliculitis and, 466
Indeterminate cell histiocytosis (ICH), 667, 678
histopathology of, 124, 678
pathogenesis of, 678
Indeterminate leprosy, 559–560, 560*f,* 566
histopathology of, 560, 560*f*
Infant myofibromatosis, 984–985
Infantile digital fibromatosis, 986–987
histogenesis of, 987
histopathology of, 987, 987*f*
Infantile hemangioma, 1014–1015
differential diagnosis of, 1015
histopathology of, 1014, 1014*f*–1015*f*
pathogenesis of, 1015
Infantile lipofibromatosis, 1070
Infantile myofibromatosis, histopathology of, 126
Infantile pustular psoriasis, 175
Infantile systemic hyalinosis, 986
Infarcts, histopathology of, 118–119, 131
Infection
bacterial, 539–575
actinomycosis, 574, 574*f*–575*f*
acute deep folliculitis, 543, 544*f*
acute septicemia, 546–548, 547*f*
acute superficial folliculitis, 542–543, 543*f*
anthrax, 567, 567*f*
bacillary angiomatosis, 572–573, 572*f*
blastomycosis-like pyoderma, 546
botryomycosis, 573, 573*f*
cat-scratch disease, 571–572
chancroid, 569–570, 569*f*
chronic deep folliculitis, 544
chronic septicemia, 548–549, 548*f*
ecthyma, 541
erysipelas, 541
follicular occlusion triad (hidradenitis suppurativa, acne conglobata, perifolliculitis capitis abscedens et suffodiens), 544–545, 545*f*
granuloma inguinale, 570, 570*f*
impetigo, 539–541, 540*f*
injection abscess, 567–568, 568*f*
leprosy, 558–567, 559*f*–565*f*
lymphogranuloma venereum, 571
malakoplakia, 549, 549*f*
methicillin-resistant *Staphylococcus aureus* skin infections, 542
mycobacterial infections, 549–550
necrotizing fasciitis, 541–542, 541*f*–542*f*
nocardiosis, 574, 574*f*
nontuberculosis mycobacteria infections, 555–558, 555*f*–558*f*
pseudofolliculitis of beard, 544
rhinoscleroma, 570–571, 571*f*
rickettsial infections, 568–569, 568*f*–569*f*
toxic shock syndrome, 546
tuberculosis, 550–555, 551*f*–554*f*
tularemia, 568
fungal, 591–616
aspergillosis, 599, 600*t,* 601*f*
candidiasis, 597–599, 597*f,* 598*t*
chromomycosis, 600*t,* 607–608, 607*f*
coccidioidomycosis, 600*t,* 608–609, 608*f*
cryptococcosis, 600*t,* 609–611, 610*f*
cutaneous alternariosis, 600*t,* 603, 603*f*
cutaneous protothecosis, 615–616, 616*f*
dermatophytosis, 591–595, 593*t,* 594*f*–595*f,* 598*t*
erythema nodosum with, 514
eumycetoma, 600*t,* 614, 615*f*
histoplasmosis, 600*t,* 611–612, 612*f*
lobomycosis, 600*t,* 606–607, 606*f*
Malassezia furfur, 596–597, 596*f,* 598*t*
of the nail, 506–507, 507*f*
North American blastomycosis, 600*t,* 603–605, 605*f*
paracoccidioidomycosis, 600*t,* 605–606, 606*f*
rhinosporidiosis, 600*t,* 615, 616*f*

Infection (*continued*)
sporotrichosis, 600*t,* 612–614, 614*f*
subcutaneous phaeohyphomycosis, 600*t,* 601–603, 602*f*
zygomycosis, 599–601, 600*t,* 602*f*
histiocytoses v., 668
histopathology of, 101, 101*f*
of the nail, 506–508, 507*f*–508*f,* 593–595, 599
parasitic, 626–635
arthropod assault reactions, 634–635, 634*f*
hookworm-related cutaneous larva migrans, 627–628, 627*f*
myiasis, 632–633, 633*f*
onchocerciasis, 629–631, 631*f*
scabies, 626–627, 626*f*
schistosomiasis, 631–632, 632*f*
strongyloidiasis, 628, 629*f*
subcutaneous cysticercosis, 632, 632*f*
subcutaneous dirofilariasis, 628–629, 629*f*
tungiasis, 633–634, 633*f*
protozoan, 621–625
acanthamoebiasis, 625, 625*f*
leishmaniasis, 621–625, 622*t,* 623*f*–624*f*
spirochetal. *See* Treponemal diseases
viral, 637–662
Bowenoid papulosis of genitalia, 656–657, 657*f*
cytomegalovirus, 644–646, 645*f*–646*f*
hepatitis B, 660–661, 661*f*
hepatitis C, 661
Herpesviridae, 637–646, 638*f*–640*f,* 642*f*–643*f,* 645*f*–646*f*
measles, 662
oral focal epithelial hyperplasia, 657, 657*f*
Papillomaviridae, 649–656, 651*f*–655*f*
parvovirus B19, 661–662, 662*f*
Picornaviridae, 637, 658–659, 658*f*
Poxviridae, 637, 646–649, 648*f*–649*f*
Retroviridae, 659–660
rubella, 662
Infectious mononucleosis, 644–645
Infiltrating and fascicular epithelioid malignant schwannoma (IFEMS), 1121
Infiltrating angiolipoma, 1065
Infiltrating fascicular schwannoma, 1121
histogenesis of, 1121
histopathology of, 125, 1121
of infancy, 1125
prognosis of, 1121
Infiltrating glomus tumor, histopathology of, 126
Infiltrating lipoma of the face, 1062
Infiltrative-nodular leprosy, 560–561
Inflammation
of actinomycosis, 574, 574*f*–575*f*
of acute deep folliculitis, 543, 544*f*
of acute septicemia, 546–548, 547*f*
acute meningococcemia, 546–547
Pseudomonas septicemia, 547–548, 547*f*
Vibrio vulnificus septicemia, 548
of acute superficial folliculitis, 542–543, 543*f*
impetigo Bockhart, 542
Pseudomonas folliculitis, 542–543
of anthrax, 567, 567*f*
of bacillary angiomatosis, 572–573, 572*f*
of blastomycosis-like pyoderma, 546
of botryomycosis, 573, 573*f*
of cat-scratch disease, 571–572
of chancroid, 569–570, 569*f*
of chronic deep folliculitis, 544
of chronic septicemia, 548–549, 548*f*
chronic gonococcemia, 548–549
chronic meningococcemia, 548, 548*f*
of chronic superficial folliculitis, 543
of ecthyma, 541
of erysipelas, 541
of follicular occlusion triad (hidradenitis suppurativa, acne conglobata, perifolliculitis capitis abscedens et suffodiens), 544–545, 545*f*
of granuloma inguinale, 570, 570*f*
of impetigo, 539–541, 540*f*
bullous impetigo, 539–541
impetigo contagiosa, 539, 540*f*
staphylococcal scalded skin syndrome, 539–541
of injection abscess, 567–568, 568*f*
of leprosy, 558–567, 559*f*–565*f*
borderline lepromatous leprosy, 559, 559*f,* 562
borderline tuberculoid leprosy, 559, 559*f,* 562–563, 563*f*–564*f*
histoid, 561–562, 562*f*
indeterminate, 559–560, 560*f*
lepromatous leprosy, 559–562, 559*f,* 561*f*–562*f,* 566–567
leprosy reactions, 564–567, 564*f*–565*f*
midborderline leprosy, 559, 559*f,* 562
tuberculoid leprosy, 559, 559*f,* 563, 566
of lymphogranuloma venereum, 571
of malakoplakia, 549, 549*f*
of methicillin-resistant *Staphylococcus aureus* skin infections, 542
of mycobacterial infections, 549–550
of necrotizing fasciitis, 541–542, 541*f*–542*f*
of nocardiosis, 574, 574*f*
of nontuberculosis mycobacteria infections, 555–558, 555*f*–558*f*
Buruli ulcer, 556–558, 557*f*
Mycobacterium avium-intracellulare, 555, 555*f*–556*f*
Mycobacterium kansasii, 555, 555*f*
Mycobacterium marinum, 555–556, 556*f*
other, 558, 558*f*
of pinta, 585
of pseudofolliculitis of beard, 544
of rhinoscleroma, 570–571, 571*f*
of rickettsial infections, 568–569, 568*f*–569*f*
of schistosomiasis, 631
T- and B-cell trafficking v., 913–915, 914*f*
of toxic shock syndrome, 546
of tuberculosis, 550–555, 551*f*–554*f*
erythema nodosum, 550
lichen scrofulosorum, 550
lupus vulgaris, 550, 551–552, 552*f*
papulonecrotic tuberculid, 550
primary, 550–551, 551*f*
scrofuloderma, 550, 552
tuberculids, 553–555, 554*f*
tuberculosis cutis orificialis, 553
tuberculosis verrucosa cutis, 550, 551, 551*f*
tuberculous gumma, 552, 553*f*
of tularemia, 568
of venereal syphilis, 579–583, 580*f*–582*f*
Inflammatory bowel disease
erythema elevatum diutinum v., 222
palisaded neutrophilic and granulomatosis with, 369
pyoderma gangrenosum with, 224, 411
ulcerative colitis, 416
Inflammatory breast carcinoma, 1152
Inflammatory carcinoma, 1152–1153
Inflammatory dermatoses
angioimmunoblastic T-cell lymphoma v., 952
histopathologic features of, 1–2
punch biopsy for, 5
Inflammatory diseases
of apocrine glands, 492
Fox-Fordyce disease, 492, 492*f*
of cartilage, 492–494
chondrodermatitis nodularis helicis, 492–493, 493*f*
pseudocyst of the auricle, 494, 494*f*
relapsing polychondritis, 493–494
of eccrine glands, 490–492
neutrophilic eccrine hidradenitis, 491–492, 491*f*
syringolymphoid hyperplasia with alopecia, 490–491, 490*f*
of hair follicles, 459–470
acne vulgaris, 459–461, 460*f*
demodicidosis, 464–465, 465*f*
eosinophilic pustular folliculitis, 466–467, 467*f*
follicular mucinosis and alopecia mucinosa, 467–469, 468*f*–469*f*
keratosis pilaris, 469–470, 469*f*
lupus miliaris disseminatus faciei, 465–466, 466*f*
perioral dermatitis, 462–463, 462*f*
rosacea, 463–464, 463*f*
steroid acne, 461–462, 461*f*
trichostasis spinulosa, 470, 470*f*
of the nail, 503–508
bullous diseases, 506
connective tissue disease, 506
eczematous dermatitis, 503–504
infection, 506–508, 507*f*–508*f*
lichen planus, 505–506, 505*f*
psoriasis, 504–505, 540*f*
of subcutaneous fat, 509–536
alpha-1 antitrypsin deficiency panniculitis, 516–517, 516*f*–517*f*
calcifying panniculitis, 530–531, 531*f*
eosinophilic panniculitis and fasciitis, 515–516, 515*f*
erythema induratum, 519–521, 519*f*–520*f*
erythema nodosum, 511–515, 511*f*–514*f*
histiocytic cytophagic panniculitis, 532–534, 532*f*–533*f*
lipedema, 527
lipomembranous panniculitis, 531–532, 532*f*
localized lipoatrophy and lipodystrophy, 526–527
lupus erythematosus panniculitis, 521–523, 522*f*
miscellaneous panniculitis, 534–535, 534*f*
palisaded granulomatous panniculitis, 524–525, 524*f*
panniculitis classification, 509–511, 510*t*
panniculitis due to physical or chemical agents, 525–526, 526*f*
panniculitis Rothmann-Makai, 524
sclerema neonatorum, 529
subcutaneous fat necrosis of the newborn, 529–530, 530*f*
subcutaneous nodular fat necrosis in pancreatic disease, 528–529, 528*f*
subcutaneous polyarteritis nodosa, 517–518, 518*f*
superficial migratory thrombophlebitis, 517, 517*f*
Weber-Christian disease, 523–524, 523*f*
Inflammatory lesions, of acne vulgaris, 459
Inflammatory linear verrucous epidermal nevus (ILVEN), 194–195, 194*f*
differential diagnosis of, 194–195
histopathology of, 109–110, 194, 194*f*
linear epidermal nevus v., 791
pathogenesis of, 194
Inflammatory pseudotumor, 993–994
differential diagnosis of, 994
histogenesis of, 994
histopathology of, 993–994
Inflammatory responses
to fungi, 591–592, 594–595
neutrophilic granulocytes and, 43
of onchocerciasis, 631
to pityriasis (tinea) versicolor, 596
Infliximab (Remicade)
for histoplasmosis, 611
lichenoid drug eruption and, 313
Inframammary crease, carcinoma of, 1152–1153
Infundibular acanthosis, Fox-Fordyce disease and, 492

Infundibular cysts, 800–802, 801*f*
  histopathology of, 801–802, 801*f*
  pathogenesis of, 802
Infundibular epidermis, in pigmented follicular cyst, 804
Infundibular folliculitis, histopathology of, 128
Infundibulocystic basal cell carcinoma, in basaloid follicular hamartoma, 863
Infundibulum
  anatomy of, 27*f,* 30
  Demodex folliculorum in, 60
  immunity function of, 31
Injection abscess, 558, 558*f,* 567–568, 568*f*
Injection granuloma, histopathology of, 130
Ink spot lentigo, 706
Insect bite reactions, 634–635, 634*f*
  actinic prurigo v., 336
  epithelioid hemangioma v., 1024–1025
  granuloma annulare and, 362
  histopathology of, 99, 99*f,* 116–117, 129
Insulin resistance, acanthosis nigricans and, 448
Insulin, zinc granuloma and, 377
Integrin α6β4
  cicatricial pemphigoid and, 260
  functions of, 24
  of hemidesmosomes, 23
Intercellular bridges, of stratum basalis, 9–10
Interdigitating dendritic cell (IDC), in histiocytoses, 667
Interface dermatitis, 91, 91*f,* 112
  alopecia areata and, 475
  with chemical burns, 345
  chilblains and, 353
Interferon-α 2b, radiation recall dermatitis and, 352
Interferon-α, pyoderma gangrenosum with, 411
Interferon-γ, eosinophilic pustular folliculitis and, 467
Interfollicular fibroplasia, tufted hair folliculitis with, 488
Interleukins (ILs)
  allergic contact dermatitis and, 239
  atopic dermatitis and, 242
  eosinophilic pustular folliculitis and, 467
  of keratinocytes, 13
  with pustular mycosis fungoides, 942
  pyoderma gangrenosum with, 412
Intermediate filaments (IFs)
  antibodies against, 75
  of basement membrane zone, 256, 256*f*
Intermediate malignancy, 1029
Interstitial granulomatous dermatitis with plaques. *See* palisaded neutrophilic and granulomatosis
Interstitial granulomatous drug reaction, 381
  differential diagnosis of, 381
  histopathology of, 381
Interstitial pattern, of granuloma annulare, 361–363
Intertriginous plane xanthomas, 680
Intestinal polyposis, Cowden's disease with, 869
Intestines, argyria of, 327
Intracellular edema, pityriasis rosea and, 183
Intracytoplasmic desmosomes, Bowen's disease and, 815
Intracytoplasmic tubuloreticular structures, systemic lupus erythematosus and, 291
Intradermal apocrine duct, 33, 35*f*
Intradermal duct, of eccrine glands, 33*f*
Intradermal eccrine duct, 32, 33*f*
Intradermal nevus, 1185*f*
  glomus tumor v., 1049
  histopathology of, 712*f*–713*f,* 714
  nodular melanoma and, 751
Intraductal carcinoma, erosive adenomatosis of the nipple v., 881
Intraepidermal apocrine duct, 33, 35*f*
Intraepidermal atypical melanocytic proliferation of uncertain significance (IAMPUS), 749
Intraepidermal duct, 33, 35*f*
  of eccrine glands, 33*f*
Intraepidermal eccrine duct, 32, 33*f*
Intraepidermal epithelioma of Borst-Jadassohn, Bowen's disease v., 814
Intraepidermal junction nevus, 832
Intraepidermal malignant eccrine poroma, 832
Intraepidermal neutrophilic dermatosis (EIN), IgA pemphigus, 253–254
Intraepidermal poroma, 832
Intraepidermal spongiotic vesicles, pityriasis rosea and, 183
Intraepithelial epithelioma, histopathology of, 105
Intralesional steroids, histopathology of, 121
Intramuscular angiolipoma, 1065
Intramuscular lipoma, 1060
  histopathology of, 1062, 1062*f*
Intramuscular myxoma, extraskeletal myxoid chondrosarcoma v., 1098
Intraneural granuloma, of leprosy, 566
Intraneural neurofibroma, schwannomas v., 1118
Intraneural neuromas, 1135–1136
  histopathology of, 125
  palisaded and encapsulated, 1135–1136, 1136*f*–1137*f*
Intraneural perineurioma, 1133–1134
  differential diagnosis of, 1134, 1134*f*
  histogenesis of, 1133
  histopathology of, 1133, 1133*f*
Intraneural plexiform neuroma, 1136–1137
  histopathology of, 125, 1137
Intravascular fasciitis, 984
Intravascular large B-cell lymphoma, 932–933
  clinical features of, 932
  differential diagnosis of, 933
  histogenesis of, 932, 932*f*
  histopathology of, 932, 932*f*
Intravascular lymphoma, histopathology of, 126
Intravascular lymphomatosis, 1007
Intravascular papillary endothelial hyperplasia, 1007
  angiosarcoma v., 1043
  differential diagnosis of, 1007
  histopathology of, 126, 1007, 1009*f*
Inverted follicular keratosis
  histopathology of, 106, 123
  irritated seborrheic keratosis v., 795
  tumor of the follicular infundibulum v., 870
Involucrin, 12
  ILVEN and, 194
Iodides
  erythema nodosum with, 515
  panniculitis with, 534
Iododerma, 326
IP. *See* Incontinentia pigmenti
Iridocyclitis, with onchocerciasis, 630
Iris, melanoma of, 700
Iron deposition
  with erythema ab igne, 348
  in hereditary hemochromatosis, 449–450
Iron oxide, tattoo reactions and, 377
Irregular papillomatosis, incontinentia pigmenti and, 161
Irritant contact dermatitis, 240, 240*f*
  histopathology of, 108, 113, 240, 240*f*
  pathogenesis of, 240
Irritated seborrheic keratosis, 795, 796*f*–797*f*
  pathogenesis of, 795
Ischemic fasciitis, 984
  histopathology of, 984, 985*f*
Ischemic liposclerosis, histopathology of, 130
Ischemic panniculitis, lipomembranous panniculitis v., 532
Isolated acantholytic acanthoma, 794
Isolated epidermolytic acanthoma, 793
  differential diagnosis of, 793
  histopathology of, 793
Isoniazid
  dermatomyositis and, 294
  drug-induced lupus erythematosus with, 318
  pellagra and, 408
Itching, Sézary syndrome with, 944
Itraconazole, for aspergillosis, 599
Ixodes dammini, Lyme disease from, 585
Ixodes ricinus, Lyme disease from, 587–588

Jadassohn phenomenon, 832
Jadassohn-Pellizzari anetoderma, 399–400
Jejunal adenocarcinoma, necrolytic migratory erythema and, 409
Jentigo, of lentigines, 709
Jessner's lymphocytic infiltrate of skin, 291–292, 292*f*
  with borrelial lymphocytoma cutis, 588
  chilblains v., 355
  discoid lupus erythematosus v., 282–283
  histopathology of, 107, 115, 117, 291–292, 292*f*
  pathogenesis of, 292
  polymorphic light eruption v., 335
  reticular erythematous mucinoses v., 445
Job's syndrome. *See* Hyperimmunoglobulin E syndrome
Joint synovium, lipoma of, 1060
Junctional epidermolysis bullosa, 146–147, 146*f*
Junctional nevi, 738
  histopathology of, 105, 711–712, 711*f*
  superficial spreading melanoma v., 744
Juvenile aponeurotic fibroma, soft tissue chondromas v., 1096, 1097*f*
Juvenile colloid milium, 429
  histopathology of, 429–430, 430*f*
  pathogenesis of, 430
Juvenile cutaneous mucinosis, histopathology of, 121
Juvenile hemangioendothelioma. *See also* Infantile hemangioma
  histopathology of, 126
Juvenile hemangioma. *See* Infantile hemangioma
Juvenile hyaline fibromatosis, 986
  histogenesis of, 986
  histopathology of, 125, 986
Juvenile lipofibromatosis, 1070
Juvenile pustular psoriasis, 175
Juvenile rhabdomyoma, rhabdomyomatous mesenchymal hamartoma v., 1083
Juvenile xanthogranuloma (JXG), 672–673, 673*f*
  benign cephalic histiocytosis v., 678
  differential diagnosis of, 673
  histopathology of, 124–125, 672–673, 673*f*
  macular atrophy and, 400
  pathogenesis of, 673
  reticulohistiocytosis v., 676
  Spitz nevus v., 723
Juxta-articular myxoma, extraskeletal myxoid chondrosarcoma v., 1098
JXG. *See* Juvenile xanthogranuloma

Kala-azar, 624–625
Kalinin. *See* Laminin
Kamino bodies
  with pigmented spindle cell nevus, 724, 725*f*
  Spitz nevus and, 719*f*–720*f,* 721, 973–974
Kaposiform hemangioendothelioma
  Kaposi's sarcoma v., 1035
  lymphangiomatosis with, 1045–1046
  tufted angioma v., 1016
Kaposi-like infantile hemangioendothelioma, 1038
  histopathology of, 1038, 1038*f*

Kaposi's sarcoma, 1029–1035
angiosarcoma v., 1043
atypical vascular proliferation after radiotherapy v., 1046
bacillary angiomatosis v., 572–573
CD31 and, 78
clinical features of, 1029–1030, 1030*f*
dermal dendrocytes and, 39
differential diagnosis of, 1034–1035
erythema elevatum diutinum v., 222
histopathology of, 107, 116, 126, 1030–1034, 1031*f*–1034*f*
in HIV, 659–660
hobnail hemangioma v., 1022
human herpesvirus in, 646
iatrogenic immunosuppression and, 1030
in immunosuppressed hosts, 835
intravascular papillary endothelial hyperplasia v., 1007
Leishmania parasitization of, 625
microvenular hemangioma v., 1021
pathogenesis of, 1034
progressive lymphangioma v., 1045
pyogenic granuloma v., 1018
spindle cell hemangioma v., 1028
stages of, 1031–1033, 1031*f*–1033*f*
tufted angioma v., 1016
Kaposi's varicelliform eruption, 638, 638*f,* 641–642
differential diagnosis of, 642
histopathology of, 642
Kasabach-Merritt syndrome
capillary hemangiomas and, 1014
Kaposi-like infantile hemangioendothelioma and, 1038
Katayama's syndrome, 631
Kawasaki's disease. *See* Mucocutaneous lymph node syndrome
Keloid, 979–980
collagenous fibroma, 983
histogenesis of, 980
histopathology of, 980, 980*f*
Kenogen, of hair follicle, 472, 481
Keratin
antibodies against, 75, 76*t*
families of, 11*f,* 13
granuloma annulare and, 364
of hair, 26
in nodular hidradenoma, 892
nodular melanoma and, 752
in pilomatrix carcinoma, 866
signet cell melanoma and, 757
soft v. hard, 11
of trichoadenoma, 863
Keratin genes, defects in, 135
Keratin granuloma
with epidermal cysts, 801, 801*f*
histopathology of, 95, 95*f,* 119
Keratinocytes, 85. *See also* Basilar keratinocytes; Dyskeratotic keratinocytes; Necrotic keratinocytes
acantholysis and, 235
aging of, 56
in alopecia areata, 474
blisters and, 235–237, 236*t*–238*t*
with cryotherapy-induced injury, 355, 355*f*
cytolysis and, 235
degeneration of, 686
dermatitis herpetiformis and, 264
embryology of, 7–8, 8*f*
of epidermis, 8*f*–11*f,* 13*f*
of epidermodysplasia verruciformis, 654, 654*f*
erythema toxicum neonatorum v., 267
in freckles, 704
friction blisters and, 357
graft-*versus*-host disease and, 271
herpes gestationis and, 261
herpes simplex degeneration of, 639–640, 639*f*–640*f*
in hyperpigmentation, 704
with hyperpigmented mycosis fungoides, 942
with hypopigmented mycosis fungoides, 942
incontinentia pigmenti and, 161
in large cell acanthoma, 799
lichen planus and, 187, 187*f*
lichen sclerosus et atrophicus and, 307
of measles, 662
melanin transfer to, 15
necrolytic migratory erythema and, 409
nevus comedonicus and, 793
in nodular melanoma, 751
normal microanatomy of, 8–12, 9*f*–11*f*
mucosal epithelium, 10*f,* 12
stratum basalis, 8–10, 8*f*–11*f*
stratum corneum, 8, 8*f*–11*f,* 10–12
stratum granulosum, 8, 8*f*–11*f,* 11
stratum spinosum, 8, 8*f*–11*f,* 10–11
in Paget's disease, 838
PAMS and, 254
pemphigus and, 245
pemphigus foliaceus and, 251
pemphigus vulgaris and, 247–249
in pigmented actinic keratosis, 810
psoriasis vulgaris and, 177
reticular degeneration and, 235
specialized structure and function of, 12–14
barrier function, 12
enzyme activity, 12–13
immune functions, 13
immunohistochemistry, 11*f,* 13–14, 13*f*
superficial cellular cohesion, 12
terminal differentiation, 12
spongiosis and, 235
in verrucous carcinoma, 822
in verrucous melanoma, 756
Keratinocytic atypia, lichen planus-like keratosis and, 191
Keratinocytic hyperplasia, with mucosal lentigines, 706
Keratinosomes, function of, 12
Keratitis
with onchocerciasis, 630
rosacea and, 463
Keratoacanthoma
histopathology of, 106, 110, 123
with Muir-Torre syndrome, 875
multiple, 837–838
histopathology of, 838
pathogenesis of, 838
North American blastomycosis v., 605
prurigo nodularis v., 174
solitary, 835–837, 835*f*
differential diagnosis of, 837
histopathology of, 836–837, 836*f*–837*f*
pathogenesis of, 837
solitary, variants of, 836
squamous cell carcinoma v., 820–821
verrucous lupus erythematosus v., 283
Keratoderma, histopathology of, 109
Keratoderma punctatum, of secondary syphilis, 582
Keratoelastoidosis marginalis. *See* Collagenous and elastotic marginal plaques of the hands
Keratohyaline granules, 650, 654, 654*f*
cellular cohesion with, 12
epidermolytic hyperkeratosis and, 135
with ichthyosis vulgaris, 133
nails and, 37–38
of squamous cell carcinoma, 820
of stratum granulosum, 9*f,* 11
Keratomalacia, vitamin A deficiency and, 407
Keratosis follicularis
histopathology of, 114
isolated, histopathology of, 113
Keratosis lichenoides chronica, 191–192
differential diagnosis of, 192
histopathology of, 111, 192
Keratosis palmaris et plantaris, 137, 137*f*
forms of, 137, 137*f*
histopathology of, 137
pachyonychia congenita with, 138
Keratosis palmaris et plantaris of the Meleda type, 137
Keratosis palmaris et plantaris of Unna-Thost, 137
Keratosis palmoplantaris punctata, 137
Keratosis pilaris, 469–470
histopathology of, 127, 469, 469*f*
with ichthyosis vulgaris, 133
pathogenesis of, 470
scurvy v., 407
Keratotic basal cell carcinomas, 830–831
desmoplastic trichoepithelioma v., 860
trichoepithelioma v., 859
Kerion Celsi, 593, 594
Ketobemidone, drug-induced scleroderma with, 316
Ki-67
acne vulgaris and, 459
diffuse large B-cell lymphoma, 931
melanoma prognosis and, 769
for melanomas, 753
KID syndrome, 136
Kidneys
with minocycline pigmentation, 324
nephrogenic systemic fibrosis and, 301
perforating calcific elastosis and, 396
systemic scleroderma and, 300
tuberous sclerosis in, 989
Kimura's disease
epithelioid hemangioma v., 1025
histopathology of, 107, 119
Kinetoplasts, of localized (acute) cutaneous leishmaniasis, 622, 623*f*
KIT gene, 694
KIT oncogene, acral-lentiginous melanoma and, 749
Klebsiella rhinoscleromatis, 570–571, 571*f*
histopathology of, 117, 119
leishmaniasis v., 622
Klippel-Trenaunay syndrome
nevus flammeus with, 1010–1011
spindle cell hemangioma with, 1027
Knees, dermatitis herpetiformis and, 263
Knuckle pads, 992–993
histopathology of, 993
Koebnerization, acquired perforating dermatosis and, 396
Koebner's phenomenon, 650
lichen nitidus and, 192
lichen planus and, 185
Koilocytotic cells, 650
Kraurosis vulvae. *See* Lichen sclerosus et atrophicus
Kupffer cells, protoporphyrin in, 435
Kviem test, for sarcoidosis, 372
Kwashiorkor, 410
histopathology of, 109, 410
pathogenesis of, 410
Kynurenic acid, pellagra and, 408
Kyrle-like lesions. *See* Acquired perforating dermatosis
Kyrle's disease, 392, 392*f*
acquired perforating dermatosis v., 396
clinical features of, 392
differential diagnosis of, 393*t*
elastosis perforans serpiginosa v., 395
histogenesis of, 392
histopathology of, 120, 392, 392*f*
perforating folliculitis v., 392

Labia majora, hidradenoma papilliferum on, 878
Labia minora
  eccrine glands of, 35
  mucocutaneous end-organs in, 54
Labial edema, cheilitis granulomatosa and, 380
Labial lentigo, 705
Labial melanosis, 705
Labial melanotic macule, 705
Laboratory methods, 67–80
  histochemical staining, 68–69, 69*t*
  immunofluorescence testing, 70–74
    direct, 71–73, 71*t,* 72*f*
    indirect, 73–74, 73*f,* 74*t*
  immunohistochemistry, 74–75
  immunohistopathology applications, 75–80
    electron microscopy, 79–80
    lymphoma diagnosis, 79
    tumor diagnosis, 75–79, 76*t,* 77*f*–79*f,* 79*t*
  polariscopic examination, 69–70, 70*f*
  specimen preparation
    enzyme activity demonstration, 67
    fixation, 67
    grossing, 67, 68*f*
    processing, 68
    staining, 68
LAD. *See* Linear IgA dermatosis
Ladinin, 23
LAMB syndrome, 709
Lamellar fibroplasia
  with central centrifugal cicatricial alopecia, 486
  dysplastic nevus and, 735
Lamellar fibrosis
  cicatricial pemphigoid and, 260
  pseudopelade of Brocq and, 485
Lamellar granules, function of, 12
Lamellar ichthyosis, 135
  histopathology of, 86, 86*f,* 103
Lamina densa
  anatomy of, 22–24, 22*f*–23*f*
  of basement membrane zone, 256, 256*f*
Lamina elastica, giant cell arteritis and, 208
Lamina lucida
  anatomy of, 22–23, 22*f*–23*f*
  of basement membrane zone, 256, 256*f*
  linear IgA dermatosis and, 265–266
  suction blister and, 275
Laminin
  cicatricial pemphigoid and, 260
  dermatitis herpetiformis and, 265
  granular cell epulis of infancy, 1131
  in lamina lucida, 23
  in synovial sarcoma, 995
Lamotrigine, drug-induced pseudolymphoma syndrome with, 320
Langerhans cell(s), 19–21, 20*f,* 673, 1163*f*
  aging of, 56
  allergic contact dermatitis and, 238
  chronic actinic dermatitis and, 339
  embryology of, 19–20, 20*f*
  graft-*versus*-host disease and, 272
  in histiocytoses, 667
  with hyperpigmented mycosis fungoides, 942
  LCA and, 78–79
  lichen planus and, 190
  lichen planus-like keratosis and, 191
  lichen striatus and, 194
  normal microanatomy of, 20–21, 20*f*
  prurigo nodularis and, 174
  regional variation of, 21
  S100 protein in, 77
  specialized structure and function of, 21
  T cells and, 45
Langerhans cell disease (LCD), 668–671, 670*f*
  benign cephalic histiocytosis v., 678
  differential diagnosis of, 671
  histopathology of, 669–671, 670if
  pathogenesis of, 671
  visceral lesions of, 671
Langerhans cell granules, 20–21, 20*f,* 669, 1163*f*
Langerhans cell histiocytosis, histopathology of, 107, 124
Langerhans cell microgranules, mycosis fungoides and, 944
Langerhans cell sarcoma, 671
Langerin, 669
Langhans giant cells
  in necrobiosis lipoidica, 366
  in sarcoidosis, 371
  silica granuloma and, 376
Lanreotide, radiation recall dermatitis and, 352
Large cell acanthoma, 799
  histopathology of, 103–104, 799, 799*f*
  pathogenesis of, 799
  solar lentigines v., 707
Large cell lung carcinoma, EMA antibodies and, 76
Large-plaque parapsoriasis, 182
Larva currens, 627–628
Larvae
  of scabies, 627
  of *Taenia solium,* 632
Larynx
  cicatricial pemphigoid and, 259
  eruptive keratoacanthoma in, 837
Late-onset focal dermal elastosis, 397
  histogenesis of, 397
  histopathology of, 397
LATS. *See* Long-acting thyroid stimulator
Laugier-Hunziker syndrome, melanonychia striata of, 717
LCA. *See* Leukocyte common antigen
LCD. *See* Langerhans cell disease
LCV. *See* Leukocytoclastic vasculitis
LDHL. *See* Lymphocyte depleted Hodgkin's lymphoma
Leder's method. *See* Naphthol AS-D chloroacetate esterase activity
Leiomyoma, 1076–1080
  differential diagnosis of, 1079
  histopathology of, 98, 98*f,* 126, 1076–1079, 1077*f*–1079*f*
  pathogenesis of, 1079–1080
  schwannoma v., 1119
  types of, 1076
Leiomyosarcoma, 1080–1083, 1081*f*–1082*f*
  atypical fibroxanthoma v., 979
  differential diagnosis of, 1083
  histopathology of, 1080–1082, 1081*f*
  Kaposi's sarcoma v., 1035
  malignant peripheral nerve sheath tumor v., 1125
  pathogenesis of, 1082–1083
  schwannoma v., 1119
Leishman-Donovan bodies, 622, 624
Leishmania infections, 621–625, 622*t,* 623*f*–624*f*
Leishmania tropica, 625
Leishmanial cutaneous spindle cell pseudotumor, 625
Leishmaniasis, 621–625, 622*t,* 623*f*–624*f*
  chronic cutaneous leishmaniasis, 621, 623–624
  classification of, 621, 622*t*
  diffuse (acute) cutaneous leishmaniasis, 621–623, 622*t,* 624*f*
  localized (acute) cutaneous leishmaniasis, 621–622, 622*t,* 623*f*
  mucocutaneous leishmaniasis, 621, 622*t,* 624
  post-kala-azar dermal leishmaniasis, 621, 622*t,* 624
  visceral leishmaniasis, 621, 622*t,* 624–625
  viscerotropic leishmaniasis, 621, 622*t,* 625
Leishmaniasis recidivans, 621, 622*t,* 623–624
Leishmanioma, 625
Lennert's lymphoma, 951
  histopathology of, 122
Lentigines, 706–709, 710*t*. *See also* Mucosal lentigines; Solar lentigo
  freckles and hyperpigmentation v., 704
  freckles v., 705
  histopathology of, 709
  lentigo simplex and related lesions, 708–709, 708*f,* 710*t*
Lentiginosis profusa, 708, 710*t*
  histopathology of, 709
Lentiginous junctional nevus, 711, 790
  histopathology of, 88, 88*f,* 105
Lentiginous nevi, 738
Lentiginous pattern
  of mycosis fungoides, 937
  of nontumorigenic melanoma, 743
Lentigo maligna, histopathology of, 123
Lentigo maligna melanoma (LMM), 711, 745–747
  classification of, 738, 739*f*
  cytologic features of, 747
  differential diagnosis of, 747
  histopathology of, 123, 746–747, 746*f*
  pathogenesis of, 747
  pigmented actinic keratosis v., 811
  pigmented spindle cell nevus v., 724
  prognosis of, 768
  solar lentigines v., 708
  superficial spreading melanoma v., 744
Lentigo simplex, 708–709, 708*f,* 710*t*
  histopathology of, 105, 709, 711, 711*f*
  solar lentigines v., 708
LEOPARD syndrome, 708–709
Lepra cells, 561
Lepromatous leprosy, 559–562, 559*f,* 561*f*–562*f,* 566–567
  histopathology of, 94, 94*f,* 117, 124, 561–562, 561*f*–562*f*
  leukocytoclastic vasculitis and, 218
  reticulohistiocytosis v., 676
Lepromin skin test, 566
Lepromin, T lymphocytes reaction to, 566
Leprosy, 558–567, 559*f*–565*f*. *See also* Borderline tuberculoid leprosy; Histoid leprosy; Lepromatous leprosy; Lucio leprosy; Macular leprosy; Midborderline leprosy
  borderline lepromatous leprosy, 559, 559*f,* 562
  borderline tuberculoid leprosy, 559, 559*f,* 562–563, 563*f*–564*f*
  clinical pathology of, 560
  differential diagnosis of, 566
  electron microscopy of, 565
  with follicular mucinosis, 468
  histoid, 561–562, 562*f*
  histopathology of, 99, 99*f,* 115, 129
  HIV and, 566
  immunopathologic spectrum of, 559, 559*f*
  indeterminate, 559–560, 560*f*
  lepromatous leprosy, 559–562, 559*f,* 561*f*–562*f,* 566–567
  macular atrophy and, 400
  midborderline leprosy, 559, 559*f,* 562
  pathogenesis of, 566
  peripheral nerve involvement in, 564
  reactions, 564–567, 564*f*–565*f*
    Lucio, 565–566, 565*f*
    type 1, 564, 564*f*–565*f,* 566
    type 2, 564–565, 565*f*
  sarcoidosis and, 371, 373
  staining of *Mycobacterium leprae,* 559–560
  tuberculoid leprosy, 559, 559*f,* 563, 566
Leprosy reactions, 564–567, 564*f*–565*f*
  Lucio, 565–566, 565*f*

Leprosy reactions (*continued*)
type 1, 564, 564*f*–565*f,* 566
type 2, 564–565, 565*f*
Leptin, subcutaneous fat production of, 535
Leptomeningeal melanocytosis, 729
Leptospirosis, erythema nodosum with, 514
Leser-Trélat sign, 799
histopathology of, 799
Lesions. *See also* Bacterial lesions
with adult T-cell leukemia/lymphoma, 954
benign pigmented, 699–738
blue nevi, 701–704
dermal melanocytoses and hamartomas, 699–701
freckles and hyperpigmentations, 704–706
lentigines, 706–709, 710*t*
melanocytic nevi, 710–738
of borrelial lymphocytoma cutis, 588–589
of endemic syphilis, 585
of erythema chronicum migrans, 586
fungal, 591–616
of acute mucocutaneous candidiasis, 597–598, 597*f,* 598*t*
of aspergillosis, 599, 600*t,* 601*f*
of *Candida* onychomycosis, 599
of chromomycosis, 600*t,* 607–608, 607*f*
of chronic mucocutaneous candidiasis, 598
of coccidioidomycosis, 600*t,* 608–609, 608*f*
of cryptococcosis, 600*t,* 609–611, 610*f*
of cutaneous alternariosis, 600*t,* 603, 603*f*
of cutaneous protothecosis, 615–616, 616*f*
of dermatophytosis, 591–595, 593*t,* 594*f*–595*f,* 598*t*
of disseminated candidiasis, 598–599
of eumycetoma, 600*t,* 614, 615*f*
of histoplasmosis, 600*t,* 611–612, 612*f*
of lobomycosis, 600*t,* 606–607, 606*f*
of Malassezia furfur, 596–597, 596*f,* 598*t*
of North American blastomycosis, 600*t,* 603–605, 605*f*
of paracoccidioidomycosis, 600*t,* 605–606, 606*f*
of rhinosporidiosis, 600*t,* 615, 616*f*
of sporotrichosis, 600*t,* 612–614, 614*f*
of subcutaneous phaeohyphomycosis, 600*t,* 601–603, 602*f*
of zygomycosis, 599–601, 600*t,* 602*f*
of histiocytoses, 667–686
dermal dendrocytoma, 678
histiocytic sarcoma, 679–680
indeterminate cell histiocytosis, 678
Langerhans cell disease, 668–671, 670*f*
miscellaneous xanthomas, 686
normolipemic xanthomas, 683–686, 684*f*–685*f*
Rosai-Dorfman disease, 678–679, 679*f*
xanthogranuloma family, 671–678, 672*f*–677*f,* 672*t*
xanthomas associated with lipid abnormalities, 680–683, 680*t,* 681*f*–683*f*
of Lyme disease, 586–587, 587–588, 587*f*
parasitic, 626–635
of arthropod assault reactions, 634–635, 634*f*
of hookworm-related cutaneous larva migrans, 627–628, 627*f*
of myiasis, 632–633, 633*f*
of onchocerciasis, 629–631, 631*f*
of scabies, 626–627, 626*f*
of schistosomiasis, 631–632, 632*f*
of strongyloidiasis, 628, 629*f*
of subcutaneous cysticercosis, 632, 632*f*
of subcutaneous dirofilariasis, 628–629, 629*f*
of tungiasis, 633–634, 633*f*
of pinta, 584–585
protozoan, 621–625
of acanthamoebiasis, 625, 625*f*
of leishmaniasis, 621–625, 622*t,* 623*f*–624*f*
of venereal syphilis, 579–583, 580*f*–582*f*
primary, 579–581, 580*f*–581*f*
secondary, 579, 581–583, 581*f*–582*f*
tertiary, 580, 583
viral, 637–662
of Bowenoid papulosis of genitalia, 656–657, 657*f*
of cytomegalovirus, 644–646, 645*f*–646*f*
of hepatitis B, 660–661, 661*f*
of hepatitis C, 661
of Herpesviridae, 637–646, 638*f*–640*f,* 642*f*–643*f,* 645*f*–646*f*
of measles, 662
of oral focal epithelial hyperplasia, 657, 657*f*
of Papillomaviridae, 649–656, 651*f*–655*f*
of parvovirus B19, 661–662, 662*f*
of Picornaviridae, 637, 658–659, 658*f*
of Poxviridae, 637, 646–649, 648*f*–649*f*
of Retroviridae, 659–660
of rubella, 662
of vitiligo, 694, 695*f*
of yaws, 583–584, 584*f*
Letterer-Siwe disease
histopathology of, 111
urticaria pigmentosa v., 160
Leucine aminopeptidase, in syringoma, 885
Leukemia(s), 1158. *See also* Acute myeloid leukemia; Chronic lymphocytic leukemia; Chronic myeloid leukemia; Lymphoproliferative disease; T-cell leukemia; T-cell prolymphocytic leukemia; T-lymphoblastic leukemia
erythema nodosum with, 514
histopathology of, 122
Leser-Trélat sign with, 799
Leukemia cutis
diffuse large B-cell lymphoma v., 931
extramedullary hematopoiesis v., 957
histopathology of, 117, 122, 124
Leukocyte(s)
in skin, 911
subcutaneous fat necrosis and, 509
Leukocyte common antigen (LCA)
antibodies against, 76*t,* 78–79
lymphomas and, 752
Leukocytoclasis, palisaded neutrophilic and granulomatosis with, 369
Leukocytoclastic vasculitis (LCV), 215–222, 215*f,* 216*t*. *See also* Palisaded neutrophilic and granulomatosis
of acanthamoebiasis, 625
acute generalized exanthematous pustulosis v., 315
ANCA-associated vasculitis, 221
autoimmune diseases, 221
Behçet's syndrome, 221
bowel-associated dermatosis-arthritis syndrome v., 412
Churg-Strauss syndrome and, 213–214
connective tissue disease, 220–221
Crohn's disease and, 416
cryoglobulinemias, 219–220, 220*f*
diagnostic approach to, 216–217
drug-induced vasculitis, 221
erythema elevatum diutinum, 221–222
granuloma faciale, 222
Henoch-Schönlein purpura, 218–219, 218*f*
hepatitis and, 419
histopathology of, 94, 94*f,* 129, 215*f,* 216, 217*f*
infectious, 217–218, 218*f*
neutrophilic dermatoses, 223
paraneoplastic vasculitis, 221
pathogenesis of, 216, 216*t*
pyoderma gangrenosum v., 412
relapsing polychondritis with, 493
serum sickness, 220
with strongyloidiasis, 628
Leukocytosis
acute generalized exanthematous pustulosis with, 314–315
eosinophilic pustular folliculitis with, 466
with erythema nodosum, 511
Leukoedema of oral mucosa, 794–795
histopathology of, 104, 795
Leukokeratosis, 811
Leukonychia, nail psoriasis and, 504
Leukoplakia, description of, 811
Lhermitte-Duclos disease, Cowden's disease with, 869
Libman-Sacks endocarditis, 288
Lichen amyloidosis, 427–429, 427*f*–428*f*
histogenesis of, 428–429
histopathology of, 103–104, 428, 428*f*
Lichen aureus, pigmented purpuric dermatosis in, 227
Lichen myxedematosus, 442–444, 443*f*
histopathology of, 121, 443, 443*f*
scleromyxedema, 444
Lichen nitidus, 192–193, 192*f*
histopathology of, 91, 91*f,* 111, 192, 192*f*
lichen planus and, 186, 192–193
Lichen planopilaris, 185–186, 187–188, 188*f*
histopathology of, 128
immunofluorescence for, 189
postmenopausal frontal fibrosing alopecia and, 488
pseudopelade of Brocq v., 483–484
scarring in, 482, 486*f*
scurvy v., 407
tufted hair folliculitis with, 487
Lichen planus, 185–191, 185*f,* 1173*f*. *See also* Acrosyringeal lichen planus
alopecia areata and, 475
differential diagnosis for, 190–191
direct immunofluorescence for, 71, 73
discoid lupus erythematosus v., 282
erythema dyschromicum perstans v., 172
graft-*versus*-host disease v., 271, 273
hepatitis and, 419
hepatitis C and, 661
histopathology of, 91, 91*f,* 110, 129, 186–187, 186*f*–187*f*
hypertrophic actinic keratosis v., 809
keratosis lichenoides chronica v., 192
lichen nitidus and, 186, 192–193
lichen planus-like keratosis v., 191
lichen sclerosus et atrophicus v., 307
lichenoid drug eruption v., 313–314
of the nail, 505–506, 505*f*
oral, 187, 188*f*
overlap syndrome of, 186, 189
pathogenesis of, 189
electron microscopy for, 189
immunofluorescence for, 189–190
immunohistochemistry, 190
postinflammatory pigmentary alteration with, 690
postmenopausal frontal fibrosing alopecia and, 488
primary biliary cirrhosis with, 417
secondary syphilis v., 583
twenty-nail dystrophy, 186, 189
ulcerative, 186, 188
verruciform xanthomas with, 685
verrucous lupus erythematosus v., 283
Lichen planus actinicus, 186, 188
Lichen planus pemphigoides, 185, 189
immunofluorescence for, 189
Lichen planus pigmentosus, 186
erythema dyschromicum perstans v., 173
Lichen planus-like keratosis (LPLK), 191, 191*f*
histopathology of, 191, 191*f*
pathogenesis of, 191

Lichen sclerosis
chronic radiation dermatitis v., 352
vulvar intraepithelial neoplasia v., 816
Lichen sclerosus et atrophicus, 303–307, 305*f*–306*f*
differential diagnosis of, 307
histopathology of, 90, 90*f,* 105, 108, 114, 305, 305*f*–306*f*
with Lyme disease, 587–588
morphea v., 296, 299, 299*t*
nevus of genital skin and, 717
pathogenesis of, 305–307
Lichen scrofulosorum, 550, 553–555, 554*f*
differential diagnosis of, 554
histopathology of, 118, 130, 554, 554*f*
pathogenesis of, 554–555
Lichen simplex chronicus, 242–243
acanthoma fissuratum v., 357
histopathology of, 105–106, 109–110, 240*f,* 242–243
lichen amyloidosis and macular amyloidosis v., 427
prurigo nodularis v., 174
psoriasis vulgaris v., 181
with strongyloidiasis, 628
Lichen spinulosus
histopathology of, 127
keratosis pilaris v., 470
scurvy v., 407
Lichen striatus, 193–194, 193*f*
differential diagnosis of, 194
with follicular mucinosis, 468
histopathology of, 108, 110–111, 128, 193–194, 193*f*
pathogenesis of, 194
Lichen urticatus. *See* Papular urticaria
Lichenification
actinic prurigo and, 335, 336*f*
chronic actinic dermatitis and, 338
lichen simplex chronicus, 242
Lichenoid actinic keratosis, 808–809
histopathology of, 111
lichen planus-like keratosis v., 191
Lichenoid dermatitis
histopathology of, 91, 91*f,* 110–111
human recombinant proteins with, 322–323
T-cell lymphomatoid hyperplasias and, 935
Lichenoid drug eruptions, 313–314, 313*f*
histopathology of, 91, 91*f,* 111, 313–314, 313*f*
lichen planus and, 190
Lichenoid hypersensitivity reaction, secondary syphilis v., 583
Lichenoid inflammation, with pinta, 585
Lichenoid keratosis
histopathology of, 111
hypertrophic actinic keratosis v., 809
Lichenoid pattern, of benign cephalic histiocytosis, 677–678
Lichenoid tattoo reaction, histopathology of, 110
Light-chain disease, histopathology of, 131
Linear and whorled nevoid hypermelanosis, 690
histogenesis of, 690
histopathology of, 690
Linear cutaneous neuroma, histopathology of, 125, 1137
Linear epidermal nevus, 791–792, 792*f*
differential diagnosis of, 792
epidermolytic hyperkeratosis in, 793
histopathology of, 791–792, 792*f*
hypertrophic actinic keratosis and, 809
nevus comedonicus v., 793
types of, 791, 792*f*
Linear focal elastosis, 398–399
histogenesis of, 398–399
histopathology of, 398
Linear IgA dermatosis (LAD), 265–267, 266*f*
adult type, 265–266, 266*f*
histopathology of, 265, 266*f*
immunofluorescence testing for, 265, 266*f*
pathogenesis of, 265–266
ultrastructural study of, 266
childhood type, 266–267, 266*f*
histopathology of, 266
immunofluorescence testing for, 267
drug-associated, 266
vesicular pemphigoid v., 259
Linear melorheostotic scleroderma, 155
Linear morphea. *See* Morphea
Linear porokeratosis, 139
Linear unilateral basal cell nevus, 826, 832
in basaloid follicular hamartoma, 863
Lingua geographica, 795
histopathology of, 109, 795
pathogenesis of, 795
Lingua plicata, cheilitis granulomatosa and, 380
Lip(s)
cheilitis glandularis of, 380
discoid lupus erythematosus and, 280
eccrine glands of, 35
lichen planus and, 190
mucocutaneous end-organs in, 54
mucosal lentigines of, 705
Lipase, in pancreatic disease, 528
Lipedema, 527
clinical features of, 527
differential diagnosis of, 527
histopathology of, 527
pathogenesis of, 527
Lipedematous alopecia, 489
histopathology of, 489
pathogenesis of, 489
Lipedematous scalp, 1062
Lipid abnormalities, xanthomas associated with, 680–683, 680*t,* 681*f*–683*f*
histopathology of, 681–682, 681*f*–683*f*
pathogenesis of, 682–683
Lipids
with lipoid proteinosis, 431
polariscopic examination for, 70
Lipoatrophy
histopathology of, 101, 101*f,* 131
localized, 526–527
clinical features of, 526–527
histopathology of, 527
pathogenesis of, 527
Lipoblasts
in chondroid lipoma, 1067
melanoma in congenital nevi and, 728–729
Lipocytic tumors, fat and, 1057–1058, 1059*f*
Lipodermatosclerosis
histopathology of, 131
lipomembranes of, 531–532
nephrogenic systemic fibrosis and, 301
Lipodystrophy, localized, 526–527
clinical features of, 526–527
histopathology of, 527
pathogenesis of, 527
Lipodystrophy syndrome, histopathology of, 131, 324
Lipofibromatosis, 1070
Lipogranulomatosis of Rothmann-Makai, histopathology of, 131
Lipoid proteinosis, 430–431, 431*f*
differential diagnosis of, 431
doubly refractile lipids in, 70
histopathology of, 121, 430, 431*f*
pathogenesis of, 431
systemic lesions of, 430–431
Lipoleiomyoma, 1078, 1079*f*
Lipoma arborescens, 1060
Lipoma of joint synovium, 1060
Lipoma of tendon sheath, 1060
Lipomas, 1060–1064, 1061*f*
differential diagnosis of, 1064
hibernoma v., 1068–1069
histopathology of, 127, 1062–1064, 1062*f*–1064*f,* 1065*t*
types of, 1060–1062
Lipomatous nevi, folded skin with, 1058–1060
Lipomembrane, lipomembranous panniculitis with, 531–532, 532*f*
Lipomembranous panniculitis, 531–532, 532*f*
clinical features of, 531
differential diagnosis of, 532
histopathology of, 101, 101*f,* 131, 531–532, 532*f*
Liposarcomas, 1071–1075. *See also* Spindle cell liposarcoma
classification of, 1071–1072
differential diagnosis of, 1075
histopathology of, 127, 1072–1075, 1073*f*–1074*f*
pleomorphic lipoma v., 1067
radiation-induced, 351
Liquefication degeneration, discoid lupus erythematosus and, 280
Livedo reticularis, 231
microscopic polyarteritis and, 212
polyarteritis nodosa and, 210
relapsing polychondritis with, 494
subcutaneous polyarteritis nodosa, 518
systemic lupus erythematosus and, 288
Liver
argyria of, 327
hereditary hemochromatosis and, 449
in porphyrias, 435
with pseudoporphyria cutanea tarda, 435
Liver spots, 707
LMM. *See* Lentigo maligna melanoma
Lobomycosis, 600*t,* 606–607, 606*f*
histopathology of, 119, 606–607, 606*f*
pathogenesis of, 607
Lobular capillary hemangioma. *See* Pyogenic granuloma
Lobular panniculitis
of acanthamoebiasis, 625
relapsing polychondritis with, 494
septal mixed with, 102, 102*f*
without vasculitis, 101, 101*f*
Localized acquired pseudoxanthoma elasticum. *See* Perforating calcific elastosis
Localized (acute) cutaneous leishmaniasis, 621–622, 622*t,* 623*f*
differential diagnosis of, 622
histopathology of, 621–622, 623*f*
Localized pustular psoriasis
clinical features of, 175, 175*f*
histopathology of, 178–179
pathogenesis of, 180
Localized urticarial reaction, to arthropod assault, 634
9p Locus, dysplastic nevus and, 738
Löffler's syndrome, polyarteritis nodosa and, 210
Long-acting thyroid stimulator (LATS), pretibial myxedema and, 442
Longitudinal melanonychia. *See* Melanonychia striata
Loxosceles reclusa, reaction to bites of, 634–635
LPLK. *See* Lichen planus-like keratosis
LRCHL. *See* Lymphocyte rich Hodgkin's lymphoma
Lucio leprosy, 560, 562, 565–566, 565*f*
histopathology of, 116, 565, 565*f*
Lucio reaction, histopathology of, 116
Lucio's phenomenon, leukocytoclastic vasculitis and, 218
Lues. *See* Syphilis
Lues maligna, 579
of secondary syphilis, 582
Lumbosacral lipoma, 1060

Lumina
in acantholytic squamous cell carcinoma, 821
syringocystadenoma papilliferum in, 879
Luna stain, for elastic tissues, 69, 69*t*
Lung carcinoma
human papillomavirus in, 650
metastatic carcinoma of skin, 1154–1155
histopathology of, 1154–1155
immunoperoxidase studies, 1155
Lungs, systemic scleroderma and, 300
Lupoid leishmaniasis. *See* Leishmaniasis recidivans
Lupus anticardiolipin syndrome, histopathology of, 112
Lupus anticoagulant syndrome, histopathology of, 112
Lupus band test, 72
dermatomyositis and, 294–295
drug-induced lupus erythematosus and, 318
Lupus erythematosus, 279–292. *See also* Systemic lupus erythematosus
acanthosis nigricans and, 448
actinic prurigo v., 336
acute, histopathology of, 107
alopecia areata and, 475
atrophic actinic keratosis v., 811
bullous systemic lupus erythematosus and, 263
chilblains v., 355
chronic cutaneous, 280–283, 281*f*–282*f,* 284*f*
discoid lupus erythematosus, 280–283, 281*f*–282*f*
lupus erythematosus profundus/panniculitis, 283, 284*f*
tumid lupus erythematosus, 283, 284*f*
verrucous lupus erythematosus, 282*f,* 283
chronic lymphocytic lymphoma/small lymphocytic lymphoma and, 926
direct immunofluorescence for, 71–72, 72*f*
drug-induced, 318, 318*f*
dystrophic calcinosis cutis and, 437
histopathology of, 91, 91*f,* 99, 99*f,* 108, 110–112, 115–116, 121, 128, 129
hydroa vacciniforme v., 337
Jessner's lymphocytic infiltration of skin, 291–292, 292*f*
leukocytoclastic vasculitis and, 220
lichen planus and, 186, 189–190
lymphocytoma cutis v., 588
macular atrophy and, 400
malignant atrophic papulosis and, 232
middermal elastolysis and, 399
neonatal, 283–285, 285*f*
overview of, 279
palisaded neutrophilic and granulomatosis with, 369
pemphigus erythematosus v., 252
perioral dermatitis v., 462
polymorphic light eruption v., 335
pseudopelade of Brocq v., 483
pyoderma gangrenosum with, 411
reticular erythematous mucinoses v., 445
scurvy v., 407
solar urticaria v., 340
subacute cutaneous, 283, 285*f*
subacute, histopathology of, 107
subcutaneous polyarteritis nodosa v., 518
systemic, 285–291, 286*t,* 287*f*–289*f,* 289*t*–291*t*
Lupus erythematosus panniculitis, 283, 284*f,* 521–523
clinical features of, 521
differential diagnosis of, 522–523
histopathology of, 521–522, 522*f*
lipomembranous panniculitis with, 531
pathogenesis of, 522
subcutaneous panniculitis-like T-cell lymphoma v., 948
Lupus erythematosus profundus, 283, 284*f*
Lupus miliaris disseminatus faciei, 465–466
histopathology of, 118, 466, 466*f*
Lupus panniculitis, histopathology of, 101, 101*f,* 130–131
Lupus pernio. *See also* Chilblains
histopathology of, 95, 95*f,* 118
sarcoidosis and, 370
Lupus profundus, 521
histopathology of, 130
Lupus vulgaris, 550, 551–552, 552*f*
chronic cutaneous leishmaniasis v., 624
histopathology of, 95, 95*f,* 118, 552
Mycobacterium marinum infection v., 556
pathogenesis of, 552
pseudocarcinomatous hyperplasia and, 822
sarcoidosis v., 372–373
Lutzomia, as leishmaniasis vector, 621
Luxol-fast blue stain, for neuromas, 1138
Lyell's syndrome. *See also* Toxic epidermal necrolysis
histopathology of, 112
LYG. *See* Lymphomatoid granulomatosis
Lyme disease, 585–589, 586*f*–587*f*
acrodermatitis chronica atrophicans, 586–587, 587*f*
background of, 585–586
borrelial lymphocytoma cutis, 588–589
discoid lupus erythematosus v., 282–283
erythema chronicum migrans, 586, 586*f*
erythema multiforme and, 268
histopathology of, 116
Jessner's lymphocytic infiltration of the skin v., 291
middermal elastolysis and, 399
other atrophying and sclerosing disorders of, 587–588, 587*f*
histopathology of, 588
Lymph nodes
dissection of, 770–771
epithelioid hemangioma of, 1023
Langerhans cells in, 21
metastatic melanoma of, 774
Lymphadenopathy
with adult T-cell leukemia/lymphoma, 953–954
with angioimmunoblastic T-cell lymphoma, 952
with common variable immunodeficiency, 381
peripheral T-cell lymphoma with, 951
Sézary syndrome with, 944
Lymphangiectasia, 1044
Lymphangioendothelioma, angiosarcoma v., 1043
Lymphangioma circumscriptum, 1044–1045, 1045*f*
atypical vascular proliferation after radiotherapy v., 1046
composite hemangioendothelioma and, 1037
histopathology of, 126, 1044–1045, 1045*f*
Lymphangiomas, 1043–1046
atypical vascular proliferation after radiotherapy, 1046, 1046*f*–1047*f*
cavernous lymphangioma and cystic hygroma, 1044, 1044*f*
histogenesis of, 1044
Kaposi's sarcoma v., 1034–1035
lymphangioma circumscriptum, 1044–1045, 1045*f*
lymphangiomatosis, 1045–1046
progressive lymphangioma, 1045, 1046*f*
Lymphangiomatosis, 1045–1046
histopathology of, 126, 1046
Kaposi-like infantile hemangioendothelioma and, 1038
Lymphangiosarcoma, angiosarcoma v., 1042
Lymphatic dilation, rosacea and, 463
Lymphatic invasion, melanoma prognosis and, 768, 768*f*
Lymphatic nodules, of sporotrichosis, 613
Lymphatic vessels
D2-40 and, 768
tumors of, 1043–1046
Lymphedema
angiosarcoma following, 1040–1041
chronic, histopathology of, 120
lichen sclerosus et atrophicus and, 305
lipedema v., 527
sclerema neonatorum v., 529
spindle cell hemangioma with, 1027
Lymphoblastic lymphoma, histopathology of, 121
Lymphocutaneous sporotrichosis, 613
Lymphocyte depleted Hodgkin's lymphoma (LDHL), 934, 934*t*
Lymphocyte rich Hodgkin's lymphoma (LRCHL), 934, 934*t*
Lymphocytes, 42*f*–43*f,* 44–46, 45*f*
with adult T-cell leukemia/lymphoma, 954
allergic contact dermatitis and, 238–239
in alopecia areata, 474
in androgenetic alopecia, 481
with angioimmunoblastic T-cell lymphoma, 952
atopic dermatitis and, 242
Behçet's syndrome and, 414
berylliosis and, 377
cheilitis glandularis and, 381
in chronic lymphocytic lymphoma/small lymphocytic lymphoma, 925
cicatricial pemphigoid and, 259–260
dermatitis herpetiformis and, 264
emperipolesis of, 679, 679*f*
with eosinophilic pustular folliculitis, 466
of eosinophilic ulcer of the tongue, 813
epidermolysis bullosa acquisita and, 261
erythema multiforme with, 312
in erythema nodosum, 512
erythema toxicum neonatorum and, 267
generalized pustular psoriasis and, 178
graft-*versus*-host disease and, 271
granuloma annulare and, 361
granuloma gluteale infantum and, 381
herpes gestationis and, 261
histiocytic cytophagic panniculitis and, 533, 533*f*
hydroa vacciniforme and, 337
in inflammatory pseudotumor, 994
LCA and, 78–79
with lichen planus of the nail, 505
in lymphomatoid granulomatosis, 933
macular atrophy and, 400
mantle cell lymphoma, 928
monocytes v., 40
in mucous cyst of the oral mucosa, 998
with nail psoriasis, 504
nevi of acral skin with, 715
perforating folliculitis and, 393
with poikiloderma vasculare atrophicans, 941
of primary cutaneous aggressive CD8-positive T-cell lymphoma, 950
primary cutaneous follicle center lymphoma and, 919–920
psoriasiform mycosis fungoides and, 942
psoriasis vulgaris and, 176
with pustular mycosis fungoides, 942
resting v. activated, 44, 45*f*
with rheumatoid nodules, 367
sarcoidosis and, 370
Sézary syndrome with, 944
solar urticaria and, 340
in squamous cell carcinoma, 820
subcutaneous fat necrosis and, 509
of subcutaneous panniculitis-like T-cell lymphoma, 948
in superficial perivascular dermatitis, 89–91, 89*f*–91*f*
in titanium granuloma, 377
transient acantholytic dermatosis and, 273
tumors of, 96, 96*f,* 121–122
types of, 44–45

Lymphocytic exocytosis, chronic actinic dermatitis with, 338–339
Lymphocytic infiltrate, of superficial spreading melanoma, 744
Lymphocytic leukemia, chronic
  with follicular mucinosis, 468
  histopathology of, 117, 131
  lymphocytoma cutis v., 588
Lymphocytic lymphoma
  discoid lupus erythematosus v., 282
  histopathology of, 117
  lymphocytoma cutis v., 588
Lymphocytic small-vessel vasculitis, 224–225, 226*f,* 226*t*
Lymphocytic vasculitis
  chilblains and, 353, 355
  Dego's syndrome and, 232
  erythema nodosum with, 514–515
  Gianotti-Crosti syndrome and, 184
  histopathology of, 94, 94*f,* 116
Lymphocytoma cutis, 588–589
  differential diagnosis of, 588
  discoid lupus erythematosus v., 282–283
  histogenesis of, 588–589
  histopathology of, 94, 94*f,* 96, 96*f,* 117, 122, 588
  Jessner's lymphocytic infiltration of the skin v., 291
Lymphoepithelioma-like carcinoma, histopathology of, 122
Lymphogranuloma venereum, 571
  erythema nodosum with, 514
  histopathology of, 120, 571
Lymphoid epidermotropism, with mycosis fungoides, 937
Lymphoid exocytosis, mycosis fungoides and, 944
Lymphoid follicles
  in inflammatory pseudotumor, 994
  in necrobiosis lipoidica, 366–367
  with subcutaneous panniculitis-like T-cell lymphoma, 948
Lymphoid neoplasm, parapoxvirus infections v., 648
Lymphoma, 1158. *See also* Anaplastic large cell lymphoma; B-cell lymphoma; Burkitt lymphoma; Cutaneous T-cell lymphoma; Extranodal NK-/T-cell lymphoma; Hodgkin's lymphoma; Intravascular large B-cell lymphoma; Intravascular lymphoma; Lymphoblastic lymphoma; Lymphocyte depleted Hodgkin's lymphoma; Lymphocyte rich Hodgkin's lymphoma; Lymphocytic lymphoma; Malignant lymphoma; Mantle cell lymphoma; Marginal zone lymphoma; Nodal follicular lymphoma; Precursor B-cell lymphoblastic lymphoma; Primary cutaneous anaplastic large cell lymphoma; Primary cutaneous diffuse large B-cell lymphoma; Primary cutaneous follicle center lymphoma; Primary cutaneous marginal zone lymphoma; Primary cutaneous peripheral T-cell lymphoma; Small lymphocytic lymphoma; Subcutaneous panniculitis-like T-cell lymphoma; T-cell lymphoma; T-lymphoblastic lymphoma
  acquired perforating dermatosis with, 396
  actinic prurigo v., 336
  arthropod assault reactions v., 634
  cutaneous small cell undifferentiated carcinoma v., 1139
  diagnosis of, 79
  follicular mucinosis and, 467
  histiocytoses v., 668
  histopathology of, 122
  immunohistochemistry for, 74
  Jessner's lymphocytic infiltration of the skin v., 291
  keratosis lichenoides chronica with, 192
  linear IgA dermatosis and, 265
  malignant extrarenal rhabdoid tumor v., 1086
  paraproteinemia relationship to, 183
Lymphoma cutis, 46
Lymphoma-leukemia, ataxia-telangiectasia with, 145
Lymphomatoid granulomatosis (LYG), 933
  clinical features of, 933
  differential diagnosis of, 933
  histogenesis of, 933
  histopathology of, 116, 933, 933*f*
Lymphomatoid papulosis (LYP), 945–947
  histopathology of, 116
  Hodgkin's lymphoma v., 935
  primary cutaneous aggressive CD8-positive T-cell lymphoma v., 950
Lymphomatoid vascular reaction, 224–225, 226*t*
Lymphomatoid vasculitis, 224–225, 226*t*
Lymphoproliferative disease, 911–960
  classification of, 911, 912*t*
  hematopoietic infiltrates, 911–915
    abnormal trafficking, 913–915, 914*f*
    cell lineage, 911, 912*f*
    T- and B-cell infiltration patterns, 911–913, 913*f,* 913*t*
  primary cutaneous B-cell, 915–922
    B-cell lymphomatoid hyperplasia, 195*f,* 196*t,* 197*f,* 915–916
    exogenous plasmacytoma, 922
    primary cutaneous diffuse large B-cell lymphoma leg type, 921–922
    other, 922
    primary cutaneous follicle center lymphoma, 917–920, 918*f*–919*f,* 919*t*–920*t*
    primary cutaneous marginal zone lymphoma, 920–921, 921*f*
  primary cutaneous myeloid hyperplasia/neoplasia, 956–957
    extramedullary hematopoiesis, 956–957
    myeloid sarcoma, 957
  primary cutaneous T-cell, 935–936
    T-cell lymphomatoid hyperplasias, 935–936, 935*f*
  secondary B-cell, 922–935
    chronic lymphocytic leukemia/small lymphocytic lymphoma, 925–926, 926*f*
    diffuse large B-cell lymphoma, 930–932, 931*f*
    Hodgkin's lymphoma, 933–935, 934*f,* 934*t*
    intravascular large B-cell lymphoma, 932–933, 932*f*
    lymphomatoid granulomatosis, 933, 933*f*
    mantle cell lymphoma, 928–930, 929*f*
    nodal follicular lymphoma, 926–928, 927*f*
    precursor B-cell lymphoblastic lymphoma, 922–925, 924*f*
  secondary myeloid neoplasms, 957–960
    acute and chronic myeloid leukemia, 957–958, 958*f*–959*f,* 958*t*
    precursor plasmacytoid dendritic cell lineage, 959–960
  secondary T-/NK-cell, 951–956
    adult T-cell leukemia/lymphoma, 953–955, 954*f*
    anaplastic large cell lymphomas, 952–953, 953*f*
    angioimmunoblastic T-cell lymphoma, 952
    peripheral T-cell lymphoma, 951–952, 951*f*
    precursor T-lymphoblastic leukemia/lymphoblastic lymphoma, 955
    T-cell prolymphocytic leukemia, 955–956
  T-/NK-cell neoplasms, 936–951
    cutaneous γ/δ T-cell lymphoma, 950–951
    extranodal NK-/T-cell lymphoma, 948–949
    mycosis fungoides, 936–944, 936*f*–941*f,* 939*t,* 943*f*
    primary cutaneous aggressive CD8-positive T-cell lymphoma, 949–950
    primary cutaneous CD4-positive small-/ medium-sized pleomorphic T-cell lymphoma, 950
    primary cutaneous CD30-positive T-cell, 945–947, 945*f*–947*f*
    primary cutaneous peripheral T-cell lymphoma, 949
    Sézary syndrome, 944–945, 945*f*
    subcutaneous panniculitis-like T-cell lymphoma, 948, 948*f*
  xanthomas with, 683
Lymphoproliferative lesions
  human herpesvirus in, 646
  palisaded neutrophilic and granulomatosis with, 369
  pyoderma gangrenosum with, 224
  transient acantholytic dermatosis with, 273
LYP. *See* Lymphomatoid papulosis
Lysosomal enzymes
  of keratinocytes, 12–13
  sebaceous gland and, 30
  of stratum granulosum, 11
Lysosomal granules, histopathology of, 121
Lysosomes
  eosinophils as, 43
  granuloma annulare and, 362
  of keratinocytes, 12–13
  of macrophages, 40–41
  mercury pigmentation and, 328
  mucopolysaccharidosis and, 447
  neutrophils as, 43, 43*f*
  photodistributed hyperpigmentation and, 320
Lysozyme
  antibodies against, 76*t,* 78
  of azurophilic granules, 43
  demonstration of, 67
  granular cell epulis of infancy, 1131
Lysyl hydroxylase, Ehlers-Danlos syndrome and, 156
Lysyl oxidase, Ehlers-Danlos syndrome and, 156

Macroglobulinemia, histopathology of, 112
Macromelanosomes, melanotic macules of Albright's syndrome, 705
Macrophage(s), 667. *See also* Scalloped macrophages; Spindle cell macrophages
  allergic contact dermatitis and, 238
  in aneurysmal fibrous histiocytoma, 970
  in B-cell lymphomatoid hyperplasia, 916
  of benign cephalic histiocytosis, 677*f*
  burns and, 345
  chrysiasis and, 327
  erythema nodosum and, 512–514
  of generalized eruptive histiocytosis, 678
  granuloma annulare and, 362
  hemochromatosis and, 450
  histiocytic cytophagic panniculitis and, 533, 533*f*
  with hyperpigmented mycosis fungoides, 942
  incontinentia pigmenti and, 161
  of juvenile xanthogranuloma, 672
  LCA and, 78–79
  macular atrophy and, 400
  malignant tumors of, 679–680
  middermal elastolysis and, 399
  ochronosis and, 441
  patterns of, 672*t*
  phagocytic, 40–41, 40*f*
  photodistributed hyperpigmentation and, 320
  of Rosai-Dorfman disease, 679, 679*f*
  in skin, 911
  subcutaneous fat necrosis and, 509
  subepidermal calcified nodule and, 438
  in titanium granuloma, 377
  xanthogranuloma cells from, 671
  xanthomatization of, 673–674

Macrophage activation
leishmaniasis disruption of, 621
syndrome, 669, 672
Macrophagic melanoma. *See* Animal-type melanoma
Macular amyloidosis, 427–429, 427*f*–428*f*
histogenesis of, 428–429
histopathology of, 428, 428*f*
Macular atrophy, 399–401
histogenesis of, 400–401
histopathology of, 400, 400*f*
Macular leprosy, 560–561
Macular lesion, microvenular hemangioma v., 1021
Macular stage, of Kaposi's sarcoma, 1031, 1031*f*–1032*f*
Macular telangiectases, systemic scleroderma and, 299
Macules, of generalized eruptive histiocytosis, 678
Maculopapular stages, of parapoxvirus infections, 648
Madelung's disease, 1061–1062
Madura foot, 614
Madurella grisea, 614
Madurella mycetomatis, 614
Maffucci's syndrome, spindle cell hemangioma with, 1027
Maggots, as myiasis vector, 632
Magnesium silicate. *See* Talc granuloma
MAI. *See Mycobacterium avium*-intracellulare
Majocchi's granuloma, 225–226, 593, 595
histopathology of, 128
Majocchi-Schamberg-Gougerot-Bloom, histopathology of, 111
Major basic protein (MBP), eosinophils and, 44
Malaise
bowel-associated dermatosis-arthritis syndrome and, 412
with erythema nodosum, 511
polyarteritis nodosa and, 209
Malakoplakia, 549, 549*f*
histopathology of, 117, 549, 549*f*
pathogenesis of, 549
Malar erythema, systemic lupus erythematosus with, 285
Malassezia (Pityrosporum) folliculitis, 596–597, 596*f,* 598*t*
histogenesis of, 597
Malassezia furfur, 596–597, 596*f,* 598*t*
histogenesis of, 596
histopathology of, 596, 596*f*
Malassezia (Pityrosporum) folliculitis, 596–597, 596*f,* 598*t*
in skin, 60, 60*f*
Malassezia sp., seborrheic dermatitis and, 243
Male-pattern hair loss, 479
Malignant acanthosis nigricans, 448
Malignant acrospiroma, histopathology of, 123
Malignant adnexal neoplasm, 861
Malignant angioendotheliomatosis, reactive angioendotheliomatosis v., 1009
Malignant atrophic papulosis
Dego's syndrome and, 232
histopathology of, 91, 91*f,* 108, 111
Malignant B cells, abnormal trafficking of, 913–915, 914*f*
Malignant blue nevus, 771–772
cellular blue nevus v., 704
differential diagnosis of, 772
histogenesis of, 772
histopathology of, 122, 771–772, 771*f*–772*f*
melanoma in congenital nevi v., 728
Malignant chondroid syringoma, 894–895
histopathology of, 123, 895, 895*f*
Malignant clear cell hidradenoma, histopathology of, 123
Malignant cylindroma, 883
histopathology of, 123, 883
Malignant eccrine poroma, 887–888
histopathology of, 123, 887–888, 887*f*
with nevus sebaceus, 872
Malignant eccrine spiradenoma, 890
histopathology of, 123, 890, 890*f*
Malignant endothelial papillary angioendothelioma. *See* Papillary intralymphatic angioendothelioma
Malignant endovascular papillary angioendothelioma, histopathology of, 126
Malignant extrarenal rhabdoid tumor, 1085–1086
differential diagnosis of, 1086
pathogenesis of, 1086
Malignant fibrous histiocytoma (MFH), 979
extraskeletal osteosarcoma v., 1094
histopathology of, 125
leiomyosarcoma v., 1083
malignant peripheral nerve sheath tumor v., 1125
radiation-induced, 351
Malignant granular cell tumor (MGCT), 1131–1132
histopathology of, 125, 1132
Malignant hemangiopericytoma, mesenchymal chondrosarcoma v., 1099
Malignant histiocytosis, histiocytic cytophagic panniculitis v., 534
Malignant lCD, 671
Malignant lymphoma, 1158
epidermolysis bullosa acquisita and, 261
Malignant melanoma, 738–775, 832, 1100, 1158, 1186*f*. *See also* Melanoma; Melanoma cells
biopsy for, 762
burn scars and, 346
classification of, 738–739, 739*t*
histopathology of, 90, 90*f,* 110
malignant blue nevus, 771–772, 771*f*–772*f*
malignant peripheral nerve sheath tumor v., 1125
melanocytic tumors of uncertain malignant potential, 772–774
metastatic melanoma, 774–775, 774*f*
nontumorigenic, 743–749
acral-lentiginous, 747–748, 748*f*
lentigo maligna melanoma, 745–747, 746*f*
mucosal lentiginous, 749
superficial atypical melanocytic proliferation of uncertain significance, 749
superficial spreading melanoma, 743–745, 745*f*
risk factors for development of, 759–762
in infancy and childhood, 761–762
multiple primary melanomas, 760–761
multivariable prognostic models, 762
preexisting melanocytic nevus, 760, 761*f*
staging of, 762–770
biological markers, 769
Breslow's thickness of tumor, 765, 765*f*
Clark's levels of invasion, 764–765
local excision, 769–770
mitotic rate, 767
other clinicopathologic prognostic factors, 768–769
partial and complete regression, 766–767, 766*f*
pathology of microstaging attributes, 764
satellites, 768
TNM staging system, 762–764, 763*t*–764*t*
tumor-infiltrating lymphocytes, 766*f,* 767
ulceration, 767–768, 767*f*
vascular or lymphatic invasion, 768, 768*f*
vertical growth phase, 764
therapeutic and elective lymph node dissection, 770–771
tumorigenic, 749–759
animal-type, 757
balloon cell, 756–757
common, 749–753, 751*f*
desmoplastic and neurotropic, 753–756, 754*f*–755*f*
minimal deviation, 757–758
myxoid, 757
nevoid, 758, 759*f*
pigmented epithelioid melanocytoma, 757, 758*f*
polypoid, 756
signet cell, 757
verrucous, 756
Malignant mesenchymal tumors, histopathology of, 126
Malignant mesenchymoma, 1100
Malignant mesotheliomas, 1156
Malignant myxoid fibrous histiocytoma, 1116
Malignant neoplasms
acquired perforating dermatosis with, 396
biopsies for, 5
Malignant nodular hidradenoma, 892
histopathology of, 892, 892*f*–893*f*
Malignant peripheral nerve sheath tumor (MPNST), 1122–1126, 1122*f*–1123*f*
cellular schwannoma v., 1118
differential diagnosis of, 1125–1126, 1126*f*
histogenesis of, 1125
histopathology of, 1123–1125, 1123*f*–1125*f*
prognostication and treatment for, 1126
storiform perineural cell fibroma and, 1132
ultrastructure of, 1125
Malignant proliferating trichilemmal tumor, 867
additional studies of, 867
histopathology of, 867
Malignant syringoacanthomas, malignant eccrine poroma and, 888
Malignant T cells, abnormal trafficking of, 913–915, 914*f*
Malignant tumors
description of, 791
immunohistochemistry for, 74
of macrophage, 679–680
MALT lymphoma. *See* Mucosa-associated lymphoid tissue lymphoma
Mammary carcinoma, of the eyelid, 1152–1153
Mammary Paget's disease, 838
Mammary-like glands of the vulva, adenocarcinoma of, 1151
Manganese superoxide dismutase, Behçet's syndrome and, 415
Mantle cell lymphoma (MCL), 928–930
B-cell lymphomatoid hyperplasia v., 919
clinical features of, 928
differential diagnosis of, 919*t,* 930
diffuse large B-cell lymphoma v., 931–932
histogenesis of, 930
histopathology of, 929, 929*f*
nodal follicular lymphoma v., 919*t,* 928
precursor B-cell lymphoblastic lymphoma v., 925
primary cutaneous marginal zone lymphoma v., 921
Marfan's syndrome
elastosis perforans serpiginosa and, 394
histopathology of, 120
Margin of resection, for primary tumors, 769
Marginal band, formation of, 11–12
Marginal zone lymphoma (MZL), nodal follicular lymphoma v., 919*t,* 928
Marjolin's ulcers, squamous cell carcinoma from, 817, 820
MART-1. *See* Melanoma antigen recognized by T cells
Masson trichrome stain
for acquired perforating dermatosis, 396
for reactive perforating collagenosis, 395
Masson's tumor. *See also* Intravascular papillary endothelial hyperplasia
spindle cell hemangioma with, 1027
Mast cell(s), 41–42, 41*f*
aging of, 56
basophils and, 44

bullous pemphigoid and, 258–259
eosinophils and, 43–44
Giemsa stain for, 69, 69*t,* 70*f*
LCA and, 78–79
nerve sheath myxoma and, 1127
in superficial perivascular dermatitis, 89–91, 89*f*–91*f*
tumors of, 97, 97*f,* 124
urticaria pigmentosa and, 158–160
Mast cell disease
congenital self-healing reticulohistiocytosis v., 669
urticaria pigmentosa and, 158
Mast cell leukemia, urticaria pigmentosa and, 158
Mast precursors, of dermis, 38
Mastocytomas, juvenile xanthogranuloma v., 673
Mastocytosis
histopathology of, 97, 97*f,* 111, 124
myeloid leukemias with, 958
Matrix elastin, of elastic fibers, 49
Mature neurothekeoma, histopathology of, 125
Max-Joseph spaces, lichen planus and, 187, 187*f*
MBP. *See* Major basic protein
MC. *See* Mixed cryoglobulinemia
MC1R. *See* Melanocortin-1-receptor
MCHL. *See* Mixed cellularity Hodgkin's lymphoma
MCL. *See* Mantle cell lymphoma
MCTD. *See* Mixed connective tissue disease
Measles, 662
mucocutaneous lymph node syndrome v., 184
Median raphe cyst of the penis, 805–806, 805*f*
apocrine hidrocystoma v., 878
histopathology of, 127, 806
pathogenesis of, 806
Mediterranean spotted fever. *See* Boutonneuse fever
Medullary thyroid carcinoma, 1137, 1158
Megakaryocytes, extramedullary hematopoiesis and, 956
Meibomian glands, 31
Meissner end organs
of dermal microvascular unit, 53
in dermis, 54*f,* 55
Meissner's tactile bodies, intradermal nevus and, 714
Melan-A/MART-1
antibodies against, 76*t,* 77
common blue nevus and, 701
for desmoplastic melanoma, 753, 755–756
halo nevus and, 731
for melanocyte labeling, 16–17, 16*t*
Spitz nevi and, 722
Melanin
in acanthotic seborrheic keratosis, 798
albinism lack of, 693
argyria and, 327
in dermatosis papulosa nigra, 799
drug-induced production of, 692
in epidermal cysts, 801–802
in hair follicles, 27–28
in halo nevus, 730–732
in hemochromatosis, 450
histopathology and, 16
with hyperpigmented mycosis fungoides, 942
incontinentia pigmenti and, 161
in junctional nevus, 711–712
in lentigines, 709
in lentigo maligna melanoma, 745
macrophages and, 40
malignant blue nevus and, 772
melanoma prognosis and, 768
in melanosomes, 17
myxoid melanoma and, 757
nodular melanoma and, 752
pellagra and, 451
in phaeohyphomycetes virulence, 603
photodistributed hyperpigmentation and, 320
in piebaldism, 693–694
in pigmented actinic keratosis, 810
in pigmented basal cell carcinoma, 834
in reticulate pigmentary anomalies, 689–690
solar elastosis and, 390
in Spitz nevus, 721–722
synthesis of, 14
transfer of, 15, 18
Melanin granules, in Chediak-Higashi syndrome, 695
Melanoacanthoma, 798
pathogenesis of, 798
pigmented basal cell carcinoma and, 834
Melanoblasts, of dermis, 38
Melanocortin-1-receptor (MC1R), macular hyperpigmentations and, 705
Melanocytes, 14–18, 1162*f*
with Addison's disease, 690
aging of, 56
in alopecia areata, 474
antibodies to, 694
in cellular blue nevus, 704
with chemical depigmentation, 691
in clear cell acanthoma, 800
in common blue nevus, 701
cryotherapy-induced injury and, 355
cutaneous and systemic disease effects on, 693
in dysplastic nevus, 734–736
embryology of, 14
in epidermal cysts, 801–802
in freckles, 704–705
in hair follicles, 25, 27–28, 30
in halo nevus, 731–732
in hyperpigmentation, 704
with idiopathic guttate hypomelanosis, 691
incontinentia pigmenti and, 161
of lentigo maligna melanoma, 746–747
of leptomeningeal melanocytosis, 729
lesions of, 106
lichen sclerosus et atrophicus and, 307
with linear and whorled nevoid hypermelanosis, 690
in melanoacanthoma, 798
melanocytic tumors of uncertain malignant potential and, 773
melanoma and, 738–739
mucosal lentigines and, 705
neoplastic localized proliferations of, 85, 87–89, 87*f*–89*f*
irregular proliferations, 88, 88*f*
localized irregular thickening, 87, 87*f*
localized lesions with elongated rete ridges, 88, 88*f*
localized lesions with pagetoid epithelial proliferation, 88, 88*f*
localized lesions with thinning, 87, 87*f*
localized papillomatous epithelial lesions, 88, 88*f*
superficial polypoid lesions, 89, 89*f*
in nevi of Ota, Ito, and Hori, 700–701
nevus cells and, 715
of nevus of genital skin, 717
normal microanatomy of, 14–16, 14*f*–15*f*
overview of, 699, 700*t*
photodistributed hyperpigmentation and, 319
in piebaldism, 693–694
in pigmented basal cell carcinoma, 834
pigmented epithelioid melanocytoma and, 757
in recurrent nevus, 732–733
regional and racial variation of, 17
S100 protein in, 77
with solar lentigines, 707, 707*f*
special stains for, 16–17, 16*t*
specialized structure and function of, 17–18
melanin transfer, 18
melanogenesis, 17–18
in Spitz nevus, 722
in sun-exposed areas, 15*f,* 17
tumors of, 97, 97*f*
ultrastructure of, 15*f,* 17
in vitiligo, 694, 695*f*
Melanocyte-stimulating hormone (MSH), in Addison's disease, 690
α-Melanocyte-stimulating hormone (α-MSH), melanin and, 18
Melanocytic dysplasia, diagnosis of, 735–737
Melanocytic matricoma, 865
Melanocytic nevi, 710–738. *See also* Nevus cells
acantholytic dyskeratosis and, 794
acquired, 714–715
balloon cell nevus, 715, 715*f*
common, 710–714
congenital, 725–729, 726*f*
histopathology of, 122
deep penetrating nevus, 729–730, 729*f*
dysplastic nevus, 733–738, 734*f*–735*f,* 736*t,* 737*t*
with follicular mucinosis, 468
halo nevus, 730–732, 731*f*
melanoma risk and, 760
melanonychia striata, 716
nevi of acral skin, 715–716
nevi of flexural sites, 718
nevi of special sites, 715–716
nevus of genital skin, 717–718, 718*f*
pigmented spindle cell nevus, 724–725, 725*f*
preexisting, 760, 761*f*
recurrent nevus, 732–733, 733*f*
Spitz nevus, 718–724, 719*f*–720*f*
Melanocytic schwannoma, malignant, histopathology of, 123
Melanocytic tumors, histopathology of, 122–123
Melanocytic tumors of uncertain malignant potential (MELTUMP), 772–774
differential diagnosis of, 773
histopathology of, 773
management of, 773–774
Melanocytoma, of meninges, 700
Melanogenesis, 17–18
Melanoma(s). *See also* Acral-lentiginous melanoma; Balloon cell melanoma; Common tumorigenic melanoma; Desmoplastic melanoma; Extracutaneous melanomas; Lentigo maligna melanoma; Malignant melanoma; Metastatic malignant melanoma; Metastatic melanoma; Minimal deviation melanoma; Mucosal-lentiginous melanoma; Neurotropic melanoma; Nevoid melanoma; Nodular melanoma; Nontumorigenic melanoma; Prepubertal melanoma; Small cell melanoma; Spindle cell melanoma; Spitzoid melanomas; Tumorigenic melanoma; Variant vertical growth phase melanoma; Vertical growth phase melanoma
atypical fibroxanthoma v., 979
with Becker's melanosis, 706
biopsies for, 5–6, 762
cells of, 699, 700*t*
of choroid, iris, orbit, or brain, 700
common melanocytic nevi v., 710
in congenital nevi, 728–729
curettage of, 6
dysplastic nevus v., 735–738, 736*t,* 737*t,* 749
halo nevus v., 732
histologic diagnosis of, 1–3
histopathology of, 87–88, 87*f*–88*f,* 100, 100*f,* 105
incidence of, 726, 726*f*
junctional nevus and, 711
malignant extrarenal rhabdoid tumor v., 1086
metastatic, histopathology of, 97, 97*f,* 122
molecular pathology of, 743
neutropic, histopathology of, 99, 99*f*

Melanoma(s) (*continued*)
nevi of acral skin v., 715
nevi of flexural sites and, 718
nevus of genital skin v., 717–718
overview of, 699, 700*t*
partial and complete regression of, 766–767, 766*f*
pigmented spindle cell nevus v., 724–725
risk factors for, 737–738
selective lymphadenectomy for, 770–771
Spitz nevus v., 719*f*–720*f,* 720–721, 723–724, 723*t,* 735
Melanoma antigen recognized by T cells (MART-1). *See also* Melan-A/MART-1
antibodies against, 76*t,* 77
for melanomas, 753
Melanoma in situ, classification of, 738–739, 739*t*
Melanonychia striata, 716
histopathology of, 716
Melanophages, 16, 40
with Addison's disease, 690
argyria and, 327
with balloon cell nevus, 715
with Berloque dermatitis and phytophotodermatitis, 691
in cellular blue nevus, 704
in common blue nevus, 701
with compound nevus, 713
with congenital diffuse melanosis, 589
in epidermal cysts, 801–802
in halo nevus, 732
with hyperpigmented mycosis fungoides, 942
incontinentia pigmenti and, 161
of lentigo maligna melanoma, 746–747
lichen planus and, 186–187
with linear and whorled nevoid hypermelanosis, 690
melanocytic tumors of uncertain malignant potential and, 773
with melasma, 690
with mucosal lentigines, 706
nevi of acral skin with, 715
in pigmented actinic keratosis, 810
pityriasis lichenoides chronica and, 196
poikiloderma atrophicans vasculare and, 295
poikiloderma congenitale and, 143–144
with postinflammatory pigmentary alteration, 691, 691*f*
of superficial spreading melanoma, 744
Melanosis circumscripta preblastomatosa of Dubreuilh. *See* Lentigo maligna melanoma
Melanosis diffusa congenita. *See* Congenital diffuse melanosis
Melanosis, in metastatic melanoma, 775
Melanosomes, 1162*f*
in albinism, 693
of balloon cell melanoma, 756
in Chediak-Higashi syndrome, 695
in clear cell acanthoma, 800
with congenital diffuse melanosis, 589
cutaneous and systemic disease effects on, 693
in dysplastic nevus, 738
in freckles, 705
in hair follicles, 31
hypopigmented mycosis fungoides and, 942
in Langerhans cells, 21
lichen sclerosus et atrophicus and, 307
malignant blue nevus and, 772
melanogenesis and, 18
with melasma, 690
myxoid melanoma and, 757
photodistributed hyperpigmentation and, 320
in pigmented basal cell carcinoma, 834
solar lentigines and, 708
in Spitz nevus, 722
of superficial spreading melanoma, 744
in tuberous sclerosis, 989
ultrastructure of, 15*f,* 17
Melanotic freckle of Hutchinson. *See* Lentigo maligna melanoma
Melanotic macules
histopathology of, 104
with melanonychia striata, 717
Melanotic macules of Albright's syndrome, 705, 710*t*
differential diagnosis of, 705
histopathology of, 705
Melanotic neuroectodermal tumor of infancy, 1141
Melanotic neuroepithelial tumor of infancy, histopathology of, 122–123
Melasma, 690
histopathology of, 104, 690
Melena, Behçet's syndrome and, 413
Melkersson-Rosenthal syndrome, Crohn's disease v., 416
MELTUMP. *See* Dermal melanocytic tumors of uncertain malignant potential; Melanocytic tumors of uncertain malignant potential
MEN. *See* Multiple endocrine neoplasia
Meninges, melanocytoma of, 700
Meningitis, with cryptococcosis, 609
Meningoceles, 1142–1143
Meningococcemia. *See also* Acute meningococcemia; Chronic meningococcemia
histopathology of, 111
Meningoencephalitis, Behçet's syndrome and, 413
Meningoencephaloceles, 1142–1143
Meningomyeloceles, 1142–1143
Meningothelial heterotopias, 1141–1143
differential diagnosis of, 1143
histogenesis of, 1142–1143
histopathology of, 1142, 1142*f*
Meningovascular syphilis, 579, 583
Mental retardation, with nevus sebaceus, 871
Meperidine hydrochloride (Demerol), panniculitis with, 525
Mercuric sulfide, tattoo reactions and, 377
Mercury
drug-induced pigmentary alterations of, 692
ochronosis and, 440
Mercury pigmentation, 327–328, 328*f*
histopathology of, 121, 327–328, 328*f*
pathogenesis of, 328
Merkel cell(s), 18–19, 19*f,* 1164*f*
chromogranin and, 77
embryology of, 18
normal microanatomy of, 18–19, 19*f*
NSE and, 77
prurigo nodularis and, 174
regional variation of, 19
specialized structure and function of, 19
synaptophysin and, 77
Merkel cell carcinomas, 1155, 1157–1158
extraskeletal osteosarcoma v., 1094
malignant extrarenal rhabdoid tumor v., 1086
Merkel disk, 18
Merkel granules, 1164*f*
Merkel's cell tumor, histopathology of, 122
Merocrine secretion, with apocrine glands, 36
Mesenchymal cells
of dermis, 38
of extraskeletal osteosarcoma, 1093
Mesenchymal chondrosarcoma, 1098–1099, 1099*f*
differential diagnosis of, 1099
myopericytoma and, 1049
pathogenesis of, 1099
Mesenchymal patterns, in malignant peripheral nerve sheath tumor, 1123–1124
Mesenchymal sarcomas, radiation-induced, 351
Metabolic diseases
histiocytoses v., 667–668
of skin, 425–452
acanthosis nigricans, 447–448, 448*f*–449*f*
amyloidosis, 425–429
calcinosis cutis, 435–438
colloid milium and nodular colloid degeneration, 429–430, 430*f*
gout, 438–439, 438*f*–439*f*
lipoid proteinosis, 430–431, 431*f*
mucinoses, 441–447
mucopolysaccharidosis, 447
ochronosis, 439–441, 440*f*
Metabolic vasculopathies, 230
Metalloproteinases, Behçet's syndrome and, 414
Metamizole, exanthemic drug eruptions with, 311
Metamyelocytes, extramedullary hematopoiesis and, 956
Metaplastic carcinoma, 1099
Metaplastic ossification, 1089–1090
histopathology of, 127, 1089–1090, 1090*f*
Metastatic adenocarcinomas, 1155
of eyelids, xanthelasma v., 682
gastrointestinal, 1155
Metastatic breast carcinoma, 1158
Metastatic calcification, with metastatic calcinosis cutis, 435
Metastatic calcinosis cutis, 435–436, 436*f*
histopathology of, 436, 436*f*
Metastatic carcinoma
extraskeletal myxoid chondrosarcoma v., 1098
of skin, 1151–1159
of the breast, 1152–1154, 1153*f*–1154*f*
carcinoid and neuroendocrine carcinomas, 1157–1158
gastrointestinal, 1155–1156
incidence and dissemination, 1151–1152, 1152*f,* 1152*t*
of the lung, 1154–1155
miscellaneous carcinomas, 1158–1159, 1158*f*
oral cavity, 1156
ovary, 1157
renal cell, 1156–1157, 1157*f*
Metastatic chondrosarcoma, 1099
Metastatic malignant melanoma
histopathology of, 123
pigmentary presentations of, 692–693
vitiligo with, 694
Metastatic melanoma, 774–775
extraskeletal myxoid chondrosarcoma v., 1098
generalized melanosis in, 775
histopathology of, 774–775, 774*f*
malignant blue nevus v., 772
nodular melanoma v., 750
Metastatic neuroendocrine carcinoma, 1158
histopathology of, 122
Metatypical epitheliomas, 832
Methenamine silver stains
Mycobacterium leprae staining with, 559
for starch granuloma, 375
Methicillin-resistant *Staphylococcus aureus* skin infections, 542
Methotrexate
for dermatomyositis, 294
radiation recall dermatitis and, 352
ultraviolet recall and, 346
Methyldopa, drug-induced lupus erythematosus with, 318
Meyerson's eczematous nevus. *See* Halo dermatitis around a melanocytic nevus
Meyerson's nevus, histopathology of, 108
MF. *See* Mycosis fungoides
MFH. *See* Malignant fibrous histiocytoma

MGCT. *See* Malignant granular cell tumor
Michaelis-Gutmann bodies, 549, 549*f*
"Michelin man," 1060
  smooth muscle hamartoma and, 1075
Michel's transport medium, for direct immunofluorescence, 71
Microcystic adnexal carcinoma, 896–897
  additional studies of, 897
  desmoplastic trichoepithelioma v., 860
  histopathology of, 123, 897, 897*f*
  syringoma v., 885
Microfibrils, of elastic fibers, 49
Microfilariae
  of onchocerciasis, 630–631, 630*f*
  of subcutaneous dirofilariasis, 628
Microinvasive melanoma, classification of, 739
Micronodular basal cell carcinoma, 824–825, 825*f,* 828*f*
Micronodular variant, of juvenile xanthogranuloma, 672
Microorganisms, in normal skin, 60, 60*f*
Microphthalmia transcription factor (MITF)
  in melanocyte detection, 16*t,* 17
  in melanocyte development, 14
Microsatellite instability
  dysplastic nevus and, 738
  in sebaceous hyperplasia, 872
Microscopic polyarteritis (MPA), 211–212
  c-ANCA and p-ANCA for, 207, 207*t*
  Churg-Strauss syndrome v., 214
  clinical features of, 212
  differential diagnosis of, 212
  histopathology of, 212
  parvovirus B19 in, 662
  Wegener's granulomatosis v., 215
Microscopic polyarteritis nodosa, 212
Microscopic schwannomatosis, 1111
Microsporum audouinii, 592–593
Microsporum canis, 592–593
Microsporum infections, 592, 595
Microvenular hemangioma, 1020–1021
  differential diagnosis of, 1021
  histopathology of, 126, 1020–1021, 1021*f*
  Kaposi's sarcoma v., 1035
Midborderline leprosy, 559, 559*f,* 562
  histopathology of, 562
Middermal elastolysis, 399
  histogenesis of, 399
  histopathology of, 120, 399
Midline scars, bone formation in, 1093
Miescher-Melkersson-Rosenthal. *See also* Cheilitis granulomatosa
  histopathology of, 118
Miescher's granuloma of the face. *See* Annular elastolytic giant cell granuloma
Miescher's radial nodules, in erythema nodosum, 512, 513*f*
Mikulicz cell, 570–571, 571*f*
Milia, 802
  histopathology of, 127, 802
  pathogenesis of, 802
Miliaria
  histopathology of, 108, 244–245, 244*f*
  pathogenesis of, 245
Miliaria crystallina, 244
  histopathology of, 112, 244
  pathogenesis of, 245
Miliaria profunda, 244
  histopathology of, 245
Miliaria rubra, 244
  histopathology of, 113, 244, 244*f*
  pathogenesis of, 245
Miliary tuberculosis, 551
  histopathology of, 118, 551
  papulonecrotic tuberculids v., 554
Milkers' nodules. *See* Parapoxvirus infections
Miller stain, for elastic tissues, 69, 69*t*
Milroy's disease. *See* Lymphedema
Mineral oil, paraffinoma and, 374
Minimal deviation melanoma, 749, 757–758
  histopathology of, 123
Minocycline
  DRESS with, 311
  drug-induced pigmentary alterations of, 692
  eosinophilic pustular folliculitis and, 466
  histopathology of, 121
Minocycline pigmentation, 324–325, 324*f*
  histogenesis of, 325
  histopathology of, 324–325, 324*f*
Mites, 626–627, 626*f*
  in HIV, 659–660
  perioral dermatitis and, 463
MITF. *See* Microphthalmia transcription factor
Mitoses
  of deep penetrating nevus, 730
  of granular cell nerve sheath tumor, 1131
  intradermal nevus and, 714
  in malignant nodular hidradenoma, 892
  neurothekeoma and, 1128
  in nodular melanoma, 751–752
  in pigmented spindle cell nevus, 724
  Spitz nevus and, 721
  of superficial spreading melanoma, 744
  in vertical growth phase melanoma, 741
Mitotic rate, for melanoma staging, 767
Mitsuda test, 566
Mixed biphasic cellular blue nevus, 704
Mixed carcinoma, 832
Mixed cellularity Hodgkin's lymphoma (MCHL), 934, 934*t*
Mixed connective tissue disease (MCTD), 292–293
  histogenesis of, 293
  histopathology of, 293
Mixed cryoglobulinemia (MC)
  hepatitis B with, 661
  hepatitis C with, 661
Mixed form rhabdomyosarcoma, 1085
Mixed tumor of the skin. *See* Chondroid syringoma
MNS. *See* Mucosal neuroma syndrome
Mobile encapsulated lipoma, 1066
Modified-type smallpox, 647
Mold, 592*t*
  dermatophytes, 591–595, 593*t,* 594*f*–595*f*
  zygomycosis, 599–601, 602*f*
Moll's glands, 57, 58*f*
  extramammary Paget's disease of, 839
Molluscum bodies, 649, 649*f*
Molluscum contagiosum, 649, 649*f,* 1175*f*
  histopathology of, 106, 649
  in HIV, 649, 659
Mondor's disease
  histopathology of, 111, 209
  pathogenesis of, 209
  superficial thrombophlebitis and, 209
Mongolian spot, 699–700
  common blue nevus v., 701
  dermal melanocytic hamartoma and, 701
  histopathology of, 117, 700
  nevus of Ota and, 700
Monkey esophagus, for antiepithelial antibody evaluation, 73
Monoblastic sarcoma, myeloid sarcoma, 957
Monoclonal component, in scleromyxedema, 444
Monocytes
  LCA and, 78–79
  lymphocytes v., 40
  macrophage development from, 40
  in mycosis fungoides, 937
  xanthogranuloma cells from, 671
Mononeuritis multiplex, Behçet's syndrome and, 413
Mononuclear cells, of indeterminate cell histiocytosis, 678
Mononuclear phagocytic system, macrophages of, 40
Mononuclear variant, of juvenile xanthogranuloma, 672, 673*f*
Mononucleosis, erythema nodosum with, 514
Monophasic synovial sarcoma, Kaposi's sarcoma v., 1035
Monsel's solution
  for shave biopsy, 6
  tattoo reactions and, 378, 379*f*
Monsel's tattoo, 379*f*
Montgomery giant cells, chronic actinic dermatitis and, 339, 339*f*
Montgomery's areola tubercles, sebaceous glands and, 31
Montgomery's tubercles, 872–873
  histopathology of, 872–873, 873*f*
Morbilliform drug eruption, histopathology of, 107, 115
Morbilliform viral exanthem, histopathology of, 89, 89*f,* 107, 112
Morbilliform viral infections, histopathology of, 116
Morphea, 296–299, 297*f*–298*f,* 299*t*
  atrophoderma of Pasini and Pierini v., 303
  burns v., 346
  chronic radiation dermatitis v., 352
  differential diagnosis of, 299, 299*t*
  eosinophilic fasciitis v., 303
  histopathology of, 130, 297–299, 297*f*–298*f*
  lichen sclerosus et atrophicus and, 304–305, 307
  lipomembranous panniculitis with, 531
  with Lyme disease, 587–588
  lymphocytoma cutis v., 588
  nephrogenic systemic fibrosis and, 301
  panniculitis with, 534–535
  subacute cutaneous lupus erythematosus with, 283
  systemic scleroderma v., 299–300
Morphea profunda. *See also* eosinophilic fasciitis
  histopathology of, 130
Morphea-like basal cell carcinoma, 825, 825*f,* 829*f*
  desmoplastic trichoepithelioma v., 860
Morphine, drug-induced scleroderma with, 316
Morton's neuroma, 1143, 1143*f*
  histopathology of, 126
Mosaic warts, 650
Mosquitoes
  as myiasis vector, 632–633
  reactions to bites of, 634–635, 634*f*
Mother yaws, 583
Mouth, lichen planus and, 190
MPA. *See* Microscopic polyarteritis
MPNST. *See* Malignant peripheral nerve sheath tumor
MPO. *See* Myeloperoxidase
MPS. *See* Mucopolysaccharidosis
MRH. *See* Multicentric reticulohistiocytosis
MSH. *See* Melanocyte-stimulating hormone
α-MSH. *See* α-Melanocyte-stimulating hormone
Mucin deposition
  in adenoid cystic carcinoma, 899
  follicular mucinosis and, 467–469
  granuloma annulare and, 361–362
  in lichen myxedematosus, 443
  in lipedematous alopecia, 489
  in mucinoses, 441
  in mucinous eccrine carcinoma, 898
  in necrobiosis lipoidica, 366
  palisaded granulomatous panniculitis with, 525
  palisaded neutrophilic and granulomatosis with, 369
  polymorphic light eruption and, 335
  in reticular erythematous mucinoses, 445
  with self-healing juvenile cutaneous mucinoses, 445

Mucinoses, 441–447. *See also* Follicular mucinosis
  generalized myxedema, 441
  lichen myxedematosus, 442–444, 443*f*
  pretibial myxedema, 441–442, 441*f*–442*f*
  reticular erythematous, 444–445, 444*f*–445*f*
  scleredema, 445–447, 446*f*
  self-healing juvenile cutaneous, 445
Mucinous eccrine carcinoma, 898
  additional studies of, 898
  histopathology of, 123, 898, 898*f*
Mucinous mucosal cyst, histopathology of, 121
Mucinous syringometaplasia, 888
  histopathology of, 123, 888
Mucin-producing squamous cell carcinoma, 818, 821–822
  histopathology of, 122, 821–822
Muciphages, in mucous cyst of the oral mucosa, 998
Muckle-Wells syndrome, urticaria and, 169
Mucoblasts, pretibial myxedema and, 442
Mucocele, histopathology of, 121
Mucocele of oral mucosa, histopathology of, 125
Mucocutaneous end-organs, in dermis, 54–55
Mucocutaneous leishmaniasis, 621, 622*t,* 624
  histopathology of, 624
Mucocutaneous lymph node syndrome, 184–185, 208–209
  histopathology of, 107, 113, 184–185, 209
  pathogenesis of, 185
Mucoepidermoid carcinoma, 898–899
  histopathology of, 122
  mucin-producing squamous cell carcinoma and, 821
Mucoid stroma, epithelioid hemangioma and, 1024
Mucopolysaccharides. *See also* Acid mucopolysaccharides
  PAS and, 68, 69*t*
  soft tissue chondromas and, 1094
Mucopolysaccharidosis (MPS), 447
  histogenesis of, 447
  histopathology of, 447
Mucor infection, 599
Mucorales infection, 599
Mucormycosis, 599–601, 600*t,* 602*f*
  histopathology of, 119
  in HIV, 659
Mucosa-associated lymphoid tissue (MALT) lymphoma, PCMZL of, 920–921
Mucosal epithelium, 10*f,* 12
Mucosal lentigines, 705–706, 710*t*
  differential diagnosis of, 706
  histopathology of, 705–706
  pathobiology of, 706
Mucosal lentiginous melanoma, 749
  classification of, 738, 739*f*
Mucosal melanotic macules. *See* Mucosal lentigines
Mucosal neuroma syndrome (MNS), 1137–1138
  histogenesis of, 1138
  histopathology of, 125, 1137–1138, 1137*f*
Mucosal-lentiginous melanoma, histopathology of, 105, 123
Mucous cyst of the oral mucosa, 997–998
  histopathology of, 998, 998*f*
Muir-Torre syndrome, 875
  genetics of, 875
  histopathology of, 875
  sebaceous adenoma with, 873
  sebaceous carcinoma and, 875
  solitary keratoacanthoma in, 836
Mulberry cell, in hibernoma, 1070
Multibacillary patients, 560
Multicentric Castleman disease, human herpesvirus in, 646
Multicentric reticulohistiocytosis (MRH), 675–676, 676*f*
  doubly refractile lipids in, 70
  histopathology of, 124
Multifocal systemic sporotrichosis, 613
Multinucleate cell angiohistiocytoma
  factor XIIIa and, 78
  histopathology of, 126
Multinucleate giant cells, 675
Multinucleated cell angiohistiocytoma, 994
  histogenesis of, 994
  histopathology of, 994
Multinucleated keratinocytes, of Bowenoid papulosis of genitalia, 656
Multiple angiokeratoma, 1011
Multiple benign cystic epithelioma. *See* Trichoepithelioma
Multiple endocrine neoplasia (MEN), 1111
Multiple hamartoma syndrome. *See* Cowden's disease
Multiple keratoacanthoma. *See* Keratoacanthoma, multiple
Multiple leiomyoma, 1076
Multiple lentiginosis syndrome, 708–709, 710*t*
  histopathology of, 709
Multiple miliary osteoma cutis, 1087
Multiple myeloma
  diffuse normolipemic plane xanthoma with, 684
  primary systemic amyloidosis relationship with, 426
Multiple schwannoma, 1111
  plexiform schwannoma of, 1120
Multiple self-healing keratoacanthoma, 837
Multiple sulfatase deficiencies, 137
Multiple symmetric lipomatosis, 1061–1062
Multiple trichoepithelioma, 857–858
  histopathology of, 858–859, 858*f*
Multivariable prognostic models, for malignant melanoma, 762
Munro abscesses, generalized pustular psoriasis, 178
Munro microabscesses
  formation of, 180
  psoriasis vulgaris and, 176–177
Murine bladder, for antiepithelial antibody evaluation, 73
Musca domestica, as myiasis vector, 632
Muscle cells. *See* Dermal muscle cells
Musculoaponeurotic fibromatosis. *See* Desmoid-type fibromatosis
Myalgias
  drug-induced lupus erythematosus with, 318
  microscopic polyarteritis and, 212
  polyarteritis nodosa and, 209
Myasthenia gravis, alopecia areata and, 475
Mycelium, of fungi, 591, 592*t*
Mycobacterial infections, 549–550. *See also* Leprosy; Nontuberculosis mycobacteria; Tuberculosis
Mycobacterial panniculitis, 534, 534*f*
  histopathology of, 102, 102*f,* 131–132
Mycobacterium abscessus, 558
Mycobacterium avium-intracellulare (MAI), 555, 555*f*–556*f*
  histopathology of, 117, 119
  leprosy v., 567
Mycobacterium bovis, 555
Mycobacterium chelonei, 558
Mycobacterium fortuitum, 558, 558*f*
Mycobacterium haemophilum, 558
Mycobacterium kansasii, 555, 555*f*
Mycobacterium leprae, 558–567, 559*f*–565*f*
  electron microscopy of, 565
  pathogenesis of, 566
  staining of, 559–560
Mycobacterium marinum, 555–556, 556*f*
  differential diagnosis of, 556
  granuloma annulare v., 363
  histopathology of, 118–119, 556, 556*f*
  sporotrichosis v., 614
Mycobacterium tuberculosis
  Behçet's syndrome and, 414
  erythema induratum and, 521
  lupus miliaris disseminatus faciei and, 466
  sarcoidosis and, 372
  in tuberculosis, 550–555, 551*f*–554*f*
Mycobacterium ulcerans, 556–558, 557*f*
  histopathology of, 120
Mycophenolate, for chronic actinic dermatitis, 338
Mycophenolate mofetil, for dermatomyositis, 294
Mycoplasma pneumoniae
  erythema nodosum with, 514
  Stevens-Johnson syndrome and, 268
Mycoses, 591
Mycosis fungoides (MF), 936–944. *See also* Acanthosis nigricans-like mycosis fungoides; Adnexotropic mycosis fungoides; Bullous/vesicular mycosis fungoides; Folliculotropic mycosis fungoides; Granulomatous mycosis fungoides; Granulomatous slack skin; Hyperpigmented mycosis fungoides; Hypopigmented mycosis fungoides; Ichthyosiform mycosis fungoides; Mycosis fungoides palmaris et plantaris; Poikiloderma vasculare atrophicans; Psoriasiform mycosis fungoides; Pustular mycosis fungoides; Solitary pagetoid reticulosis; Syringotropic mycosis fungoides; Verrucous/hyperkeratotic mycosis fungoides
  adult T-cell leukemia/lymphoma v., 955
  angiocentric, histopathology of, 116
  chronic spongiotic dermatitis and, 244
  clinical features of, 936–937, 936*f*
  differential diagnosis of, 939*t,* 944
  drug-induced pseudolymphoma syndrome and, 320
  early, histopathology of, 90, 90*f,* 108–109
  follicular mucinosis and, 467–468
  granuloma annulare v., 363
  granulomatous, histopathology of, 118
  histogenesis of, 942–944, 943*f*
  histopathology of, 91, 91*f,* 96, 96*f,* 108, 110–111, 937–942, 937*f*–941*f*
  Kaposi's varicelliform eruption with, 641
  Leser-Trélat sign with, 799
  peripheral T-cell lymphoma v., 952
  pigmentary presentations of, 692–693
  poikiloderma atrophicans vasculare and, 295, 296*f*
  primary cutaneous aggressive CD8-positive T-cell lymphoma v., 950
  primary cutaneous CD4-positive small-/medium-sized pleomorphic T-cell lymphoma v., 950
  scurvy v., 407
  Sézary syndrome v., 944
  small-plaque parapsoriasis and, 183
  subtypes of, 939–942
  xanthomas with, 686
Mycosis fungoides palmaris et plantaris, 942
Myeloblastic leukemia, with follicular mucinosis, 468
Myeloblasts
  extramedullary hematopoiesis and, 956
  myeloid leukemias with, 958
Myelodysplastic syndrome
  eosinophilic pustular folliculitis and, 466
  necrolytic migratory erythema and, 409
  with reactive angioendotheliomatosis, 1008
  with relapsing polychondritis, 493
Myelogenous leukemia, neutrophilic eccrine hidradenitis and, 491
Myeloid cells, in skin, 911
Myeloid leukemias. *See also* Acute myeloid leukemia; Chronic myeloid leukemia
  myeloid sarcoma v., 957
  pyoderma gangrenosum with, 411
Myeloid sarcoma, 957
  clinical features of, 957
  differential diagnosis of, 957

histogenesis of, 957
histopathology of, 957
Myeloma
histopathology of, 94, 94*f,* 96, 96*f,* 117, 122
pyoderma gangrenosum with, 411
Myeloperoxidase (MPO)
of azurophilic granules, 43
in myeloid leukemias, 958, 959*f*
p-ANCAs for, 207, 207*t*
Myiasis, 632–633, 633*f*
histopathology of, 96, 96*f,* 121, 633, 633*f*
pathogenesis of, 633
Myoepithelial cells
in eccrine spiradenoma, 889
S100 protein in, 77
Myoepithelioma, epithelioid hemangioendothelioma v., 1040
Myofiber degeneration, eosinophilic fasciitis and, 303
Myofibroblastic tumors
benign, 979–992
acral fibrokeratoma, 989–990, 990*f*
angiofibroblastoma of the skin, 991
angiofibromas, 987–988, 988*f*
angiomyofibroblastoma of the vulva, 990–991
collagenous fibroma, 983, 983*f*
dermatomyofibroma, 980–981, 981*f*
elastofibroma dorsi, 987, 987*f*
fibroma of tendon sheath, 982, 983*f*
fibromatosis colli, 991
fibrous hamartoma of infancy, 986, 986*f*
hypertrophic scar and keloid, 979–980, 980*f*
infantile digital fibromatosis, 986–987, 987*f*
ischemic fasciitis, 984, 985*f*
juvenile hyaline fibromatosis, 986
myofibroma/myofibromatosis, 984–986, 985*f*
nodular fasciitis, 983–984, 984*f*
nuchal-type fibroma, 990
pleomorphic fibroma, 981, 982*f*
sclerotic fibroma, 981–982, 982*f*
soft fibroma, 981
superficial acral fibromyxoma, 990, 991*f*
tuberous sclerosis, 988–989, 989*f*
intermediate biological potential (locally aggressive), 992–993
desmoid-type fibromatosis, 992, 992*f*
knuckle pads, 992–993
palmar fibromatosis, 992, 993*f*
intermediate biological potential (rarely metastasizing), 993–994
inflammatory pseudotumor, 993–994
solitary fibrous tumor, 993, 993*f*
Myofibroblasts
of dermis, 38–39
myopericytoma and, 1050
in nodular fasciitis, 983
Myofibroma, 984–986
giant cell angioblastoma v., 1039
histogenesis of, 986
histopathology of, 985–986, 985*f*
Myofibromatosis, 984–986
histogenesis of, 986
histopathology of, 985–986, 985*f*
myopericytoma v., 1050
Myolipoma, histopathology of, 1062–1063, 1064*f*
Myopericytoma, 1049–1051
differential diagnosis of, 1051
histopathology of, 1049–1051, 1049*f*–1050*f*
Myositis, mixed connective tissue disease with, 292
Myositis ossificans, 1090, 1091*f*
extraskeletal osteosarcoma and, 1093
histopathology of, 1093
Myrmecia warts, 652
epidermolytic hyperkeratosis v., 793
Myxofibrosarcoma, extraskeletal myxoid chondrosarcoma v., 1098
Myxoid chondrosarcoma, epithelioid hemangioendothelioma v., 1040
Myxoid lipoma, lipedema v., 527
Myxoid liposarcoma, 1072
benign lipoblastoma v., 1071
extraskeletal myxoid chondrosarcoma v., 1098
histopathology of, 1072–1074, 1073*f*
Myxoid melanoma, 749, 757
Myxoid neurofibromas
angiofibroblastoma v., 991
cutaneous myxoma v., 997
Myxoid stroma, pyogenic granuloma and, 1017
Myxolipoma, histopathology of, 1062, 1063*f*
Myxoma syndrome, 709
MZL. *See* Marginal zone lymphoma

Naegeli-Franceschetti-Jadassohn syndrome, 689
Naegeli's reticular pigmented dermatosis. *See* Naegeli-Franceschetti-Jadassohn syndrome
Nail(s), 36–38, 36*f*–37*f*
acral-lentiginous melanoma of, 747
aging of, 56
bacterial infections of, 507–508, 508*f*
biopsy of, 503
Candida infections of, 593, 595
ectodermal dysplasia and, 142
fungal infections of, 506–507, 507*f,* 593, 599
histopathology of, 100, 100*f,* 129
inflammatory diseases of, 503–508
bullous diseases, 506
connective tissue disease, 506
eczematous dermatitis, 503–504
infection, 506–508, 507*f*–508*f*
lichen planus, 505–506, 505*f*
psoriasis, 504–505, 540*f*
inflammatory processes of, 85
Laugier-Hunziker syndrome of, 716
lichen planus and, 185
onychomycosis of, 507, 507*f,* 593–595, 599
Nail bed
acral fibrokeratoma in, 989
anatomy of, 36–38, 36*f*–37*f*
argyria of, 327
biopsy of, 503
Bowen's disease and, 813
bullous disease of, 506
fungal infection of, 507
lichen planus of, 505–506
pachyonychia congenita of, 138
psoriasis of, 504
Nail dystrophy
with mycosis fungoides palmaris et plantaris, 942
Sézary syndrome with, 944
Nail fold
anatomy of, 36–37, 36*f*–37*f*
biopsy of, 503
Bowen's disease and, 813
bullous disease of, 506
psoriasis of, 504
Nail folds, *sarcoptes scabiei* and, 508, 508*f*
Nail matrix
acral-lentiginous melanoma of, 747
anatomy of, 36–38, 36*f*–37*f*
bullous disease of, 506
lichen planus of, 505–506
onychomadesis and, 506
psoriasis of, 504, 504*f*
Nail plate
aging of, 56
anatomy of, 36–38, 36*f*–37*f*
bacterial infection of, 507
biopsy of, 595
eczematous dermatitis of, 503–504
onychomycosis of, 507, 507*f*
Nalidixic acid, pseudoporphyria cutanea tarda with, 435
NALP1 gene, 694
NAME syndrome, 709
Nanogen hairs, in alopecia areata, 474–475, 475*f*
NAO. *See* Nodulosis-arthropathy-osteolysis
Naphthol AS-D chloroacetate esterase activity
demonstration of, 67
urticaria pigmentosa and, 159
Naproxen
drug-induced pseudoporphyria with, 320
pseudoporphyria cutanea tarda with, 435
Nasal glioma, histopathology of, 125
Nasal mucosa, oral white sponge nevus in, 794
Natural killer cell neoplasms, 936–951
cutaneous γ/δ T-cell lymphoma, 950–951
extranodal NK-/T-cell lymphoma, 948–949
mycosis fungoides, 936–944, 936*f*–941*f,* 939*t,* 943*f*
primary cutaneous aggressive CD8-positive T-cell lymphoma, 949–950
primary cutaneous CD4-positive small-/medium-sized pleomorphic T-cell lymphoma, 950
primary cutaneous CD30-positive T-cell, 945–947, 945*f*–947*f*
primary cutaneous peripheral T-cell lymphoma, 949
Sézary syndrome, 944–945, 945*f*
subcutaneous panniculitis-like T-cell lymphoma, 948, 948*f*
Natural killer (NK) cells, 45
in skin, 911
Nausea, with solar urticaria, 340
NDDH. *See* Neutrophilic dermatosis of the dorsal hands
Necrobiosis, 683–684, 684*f*
in necrobiosis lipoidica, 366
Necrobiosis lipoidica, 365–367, 365*f*–367*f*
annular elastolytic giant cell granuloma v., 365
differential diagnosis of, 367
doubly refractile lipids in, 70
granuloma annulare v., 361, 363
histopathology of, 118, 120, 130, 366–367, 366*f*–367*f*
lipomembranous panniculitis with, 531
palisaded neutrophilic and granulomatosis v., 368
pathogenesis of, 367
Necrobiosis lipoidica diabeticorum, necrobiotic xanthogranuloma with paraproteinemia v., 684
Necrobiotic xanthogranuloma
diffuse normolipemic plane xanthoma v., 685
histopathology of, 119, 124, 130–131
necrobiosis lipoidica v., 367
palisaded granulomatous panniculitis with, 525
sarcoidosis v., 371
Necrobiotic xanthogranuloma with paraproteinemia, 683–684, 684*f*
differential diagnosis of, 684
histopathology of, 683, 684*f*
pathogenesis of, 683–684
Necrolytic acral erythema
hepatitis C with, 661
histopathology of, 103, 109
Necrolytic migratory erythema, 409, 409*f*
acrodermatitis enteropathica v., 410
celiac disease and, 417
differential diagnosis of, 409
histopathology of, 103, 109, 112, 409, 409*f*
pathogenesis of, 409
pellagra v., 408, 451

Necrosis
with acanthamoebiasis, 625
of Buruli ulcer, 557, 557*f*
of leprosy, 566
Necrotic arachnidism, 634
Necrotic bullae, histopathology of, 114
Necrotic granuloma, of tuberculosis, 550, 552, 553, 554, 554*f*
Necrotic keratinocytes
with erythema ab igne, 348
erythema multiforme with, 312
fixed drug eruptions and, 314
with lichen planus of the nail, 505
lichen planus-like keratosis and, 191
lichen striatus and, 193–194
pityriasis lichenoides chronica and, 196
pityriasis rosea and, 183
toxic acral erythema with, 315
Necrotizing balanitis, 639
Necrotizing fasciitis, 541–542, 541*f*–542*f*
histopathology of, 102, 102*f,* 115, 131, 541–542, 541*f*–542*f*
Necrotizing panniculitis, histopathology of, 130–131
Necrotizing purpura, systemic lupus erythematosus and, 288
Necrotizing sialometaplasia, 813
differential diagnosis of, 813
histopathology of, 813
pathogenesis of, 813
Necrotizing sialometaplasia of the hard palate, histopathology of, 120
Necrotizing vasculitis, Churg-Strauss syndrome and, 213
Needles, injection abscess from use of, 567–568, 568*f*
Neisseria gonorrhoeae, chronic gonococcemia from, 548–549
Neisseria meningitides
acute septicemia from, 546–547
chronic meningococcemia from, 548
leukocytoclastic vasculitis and, 217
Nematodes
hookworm-related cutaneous larva migrans, 627–628, 627*f*
onchocerciasis, 629–631, 631*f*
strongyloidiasis, 628, 629*f*
Neonatal candidiasis, 597
Neonatal cephalic pustulosis, *Malassezia furfur* in, 596
Neonatal infection, with herpes simplex, 639
Neonatal lupus erythematosus, 283–285, 285*f*
histopathology of, 285, 285*f*
Neoplasms. *See also* Malignant neoplasms; Natural killer cell neoplasms; Secondary myeloid neoplasms; Spindle cell neoplasm; Systemic neoplasms; T-cell neoplasms
malignant, biopsies for, 5
of Schwann cell, 1116–1122
Nephrogenic fibrosing dermopathy. *See also* Nephrogenic systemic fibrosis
scleromyxedema v., 444
Nephrogenic systemic fibrosis (NSF), 301, 302*f,* 316, 316*f*
histopathology of, 120–121, 125, 301, 302*f,* 316, 316*f*
pathogenesis of, 301
Nerve(s)
anatomic relationships with, 1107
histopathology of, 99, 99*f,* 129
Nerve fibers, anatomic relationships with, 1107
Nerve growth factor (NGF), prurigo nodularis and, 174
Nerve sheath myxoma (NSM), 1126–1127
histogenesis of, 1127
histopathology of, 125, 1126–1127, 1127*f*
neurofibromatosis v., 1115
Nerve sheath tumor
malignant, histopathology of, 125
neurofibromas and, 1115
schwannomas v., 1118
storiform perineural cell fibroma v., 1133
Nestin, antibodies against, 75, 76*t*
Netherton's syndrome, 136
histopathology of, 127
Neumann type, of pemphigus vegetans, 250
Neural crest, Merkel cells from, 18
Neural neoplasms, extraskeletal myxoid chondrosarcoma v., 1098
Neural network, of dermal microvascular unit, 53–55, 54*f*
Neural nevus, of giant congenital melanocytic nevi, 725
Neural tissue
anatomic relationships of, 1107, 1108*f*
ontogeny and reactions to injury in, 1107–1108, 1108*f*
phenotypes and histochemical reactions in, 1108–1109, 1109*f*
tumors of, 1107–1144
cutaneous meningiomas and meningothelial heterotopias, 1141–1143, 1142*f*
degenerative nature, 1143–1144, 1143*f*
heterotopias, 1141, 1141*f*
malignant peripheral nerve sheath tumor, 1122–1126, 1122*f*–1126*f*
nerve sheath-like features, 1126–1132
neurofibromas, 1109–1110, 1109*f*–1110*f*
neurofibromatosis, 1110–1116, 1110*f*–1115*f*
neuromas, 1135–1138
perineural cells, 1132–1135
primitive neuroectodermal tumors, 1140–1141
Schwann cell neoplasms, 1116–1122
small blue round cell tumors, 1138–1140
Neurilemomas, histopathology of, 125
Neuritis, with herpes zoster, 643
Neuroblastoma, 1157
Neurocutaneous syndrome, with nevus sebaceus, 871
Neurodermatitis, acquired perforating dermatosis with, 396
Neuroendocrine carcinomas, metastatic carcinoma of skin, 1157–1158
histopathology, 1157–1158
immunoperoxidase and electron microscopy studies, 1158
Neuroendocrine tumor, histopathology of, 125
Neurofibromas, 1109–1110, 1109*f*–1110*f,* 1183*f*. *See also* Extraneural sporadic cutaneous neurofibromas
extraneural sporadic cutaneous neurofibromas, 1109–1110, 1109*f*–1110*f*
histopathology of, 98, 98*f,* 106, 125
malignant peripheral nerve sheath tumor and, 1122–1123
pacinian perineural cell fibroma v., 1135
schwannomas in, 1121
storiform perineural cell fibroma v., 1133
Neurofibromatosis, 1110–1116, 1110*f*–1111*f*
differential diagnosis of, 1115–1116
extraneural sporadic cutaneous neurofibromas v., 1110
histogenesis of, 1115
histopathology of, 125, 1111–1115, 1112*f*–1115*f*
malignant peripheral nerve sheath tumor and, 1126
melanotic macules of Albright's syndrome v., 705
Neurofibromatosis type 1 (NF1), 1110–1111
Neurofibromatosis type 2 (NF2), 1111
Neurofilaments
antibodies against, 75, 76*t*
Merkel cells and, 19
Neurogenic sarcoma, desmoplastic melanoma v., 754
Neuromas, 1135–1138. *See also* Extraneural neuromas; Intraneural neuromas; Palisaded and encapsulated neuroma; Plexiform neuroma; Rudimentary neuromas
extraneural, 1135
intraneural, 1135–1136
intraneural plexiform, 1136–1137
mucosal neuroma syndrome, 1137–1138, 1137*f*
pacinian, 1138
Neuronevoid cellular blue nevus, 704
Neurons, anatomic relationships with, 1107
Neuron-specific enolase (NSE)
antibodies against, 76*t,* 77
cutaneous small cell undifferentiated carcinoma, 1139
ganglioneuroma, 1140
granular cell nerve sheath tumor and, 1131
peripheral neuroblastoma, 1140
Neurosarcoma, melanoma in congenital nevi, 728
Neurosyphilis, 583
Neurothekeoma (NTK), 1126–1130
cutaneous myxoma v., 997
differential diagnosis of, 1129–1130
histogenesis of, 1129
histopathology of, 1126–1129, 1128*f*–1129*f*
Neurotized nevus, extraneural sporadic cutaneous neurofibromas v., 1110
Neurotrophin receptor, neurotropic melanoma and, 755
Neurotropic melanoma, 749, 753–756, 754*f*–755*f*
differential diagnosis of, 756
histopathology of, 99, 99*f,* 123, 129, 755, 755*f*
immunohistochemistry of, 755
neurothekeoma v., 1129
reexcision specimens of, 755
Neurotropic tumors, histopathology of, 129
Neutral lipid storage disease, 137
Neutrophil(s)
acute febrile neutrophilic dermatosis and, 223
acute generalized exanthematous pustulosis with, 315, 315*f*
alopecia areata and, 475
in androgenetic alopecia, 481
cicatricial pemphigoid and, 259–260
in clear cell acanthoma, 800
dermatitis herpetiformis and, 264–265
epidermolysis bullosa acquisita and, 261
erythema nodosum and, 511–513
erythema toxicum neonatorum and, 267
generalized pustular psoriasis and, 178
granuloma gluteale infantum and, 381
in halogenodermas, 326
hydroa vacciniforme and, 337
linear IgA dermatosis and, 265
macular atrophy and, 400
in mucous cyst of the oral mucosa, 998
with nail psoriasis, 504
palisaded neutrophilic and granulomatosis with, 369
perforating folliculitis and, 393
polymorphic light eruption with, 333
PUPPP and, 170
with pustular mycosis fungoides, 942
with rheumatoid nodules, 367
rosacea and, 463
solar urticaria and, 340
subcorneal pustular dermatosis and, 268
transient neonatal pustular melanosis and, 267
ultraviolet recall and, 346–347
Neutrophilic dermatoses, 223. *See also* Acute febrile neutrophilic dermatosis
erythema elevatum diutinum v., 221
histopathology of, 116–117
Neutrophilic dermatosis of the dorsal hands (NDDH), 315
histopathology of, 315

Neutrophilic drug eruptions, 314
Neutrophilic eccrine hidradenitis (NEH), 491–492
  histopathology of, 99, 99*f,* 129, 322, 491–492, 491*f*
Neutrophilic granulocytes, 42–43, 42*f*–43*f*
Neutrophilic perivasculitis with hemorrhage, in arthropod assault reactions, 634
Neutrophil-rich urticaria, histopathology of, 115
Nevi of flexural sites, 718
Nevic rests, melanoma v., 770
Nevirapine, DRESS with, 311
Nevoblast, 715
Nevoid basal cell carcinoma syndrome, 825–826, 931
  trichoepithelioma v., 859
Nevoid hyperkeratosis, of nipple and areola, 792–793
Nevoid melanoma, 749, 758, 759*f*
Nevus, 853. *See also* Acral-lentiginous nevi; Balloon cell nevus; Blue nevus; Blue rubber bleb nevus; Combined nevus; Common blue nevus; Compound melanocytic nevus; Congenital nevi; Connective tissue nevus; Dermal duct nevus; Dermal melanocytic nevus; Dermal nevus; Eccrine nevus; Epidermal nevus; Fascicular cellular blue nevus; Inflammatory linear verrucous epidermal nevus; Intradermal nevus; Lentiginous nevi; Malignant blue nevus; Neuronevoid cellular blue nevus; Oral white sponge nevus; Pigmented spindle cell nevus; Recurrent nevus; Spitz nevus
Nevus araneus, 1012
  histopathology of, 1012
Nevus cells
  of compound nevus, 712–713
  deep penetrating nevus and, 729
  development of, 714–715
  in dysplastic nevus, 735
  of halo nevus, 732
  of intradermal nevus, 714
  of junctional nevus, 711–712
  Masson's theory of, 714
  melanocytes and, 715
  of nevus of genital skin, 717
  overview of, 699, 700*t*
  Schwann cells and, 715
  in special sites, 715–716
  of Spitz nevus, 720–721
Nevus comedonicus, 793
  epidermolytic hyperkeratosis in, 793
  histopathology of, 127, 793
Nevus depigmentosa centrifugum. *See* Halo nevus
Nevus flammeus, 1010–1011
  histogenesis of, 1011
  histopathology of, 1011
Nevus fuscocaeruleus ophthalmomaxillaris. *See* Nevus of Ota
Nevus giant cells, in intradermal nevus, 714
Nevus lipomatosus superficialis, 1058
  differential diagnosis of, 1058
  histopathology of, 98, 98*f,* 126, 1058, 1059*f*
  pathogenesis of, 1058
Nevus of acral skin, 715–716
  histopathology of, 122, 715–716, 715*f*
Nevus of genital skin, 715–718
  histopathology of, 122, 717–718, 718*f*
Nevus of Hori, 700–701
  histopathology of, 700
Nevus of Ito, 700–701
  histopathology of, 94, 94*f,* 117, 700
Nevus of Ota, 700–701
  common blue nevus v., 701
  histopathology of, 94, 94*f,* 117, 123, 700
Nevus psiloliparus, 1062
Nevus sebaceus, 870–872
  additional studies of, 872
  histopathology of, 123–124, 871–872, 871*f*
  sebaceoma in, 874
  sebaceous hyperplasia v., 872
  syringocystadenoma papilliferum with, 879
  tumor of the follicular infundibulum v., 869
Nevus spilus. *See also* Speckled lentiginous nevus
  histopathology of, 105, 709
Nevus unius lateris, 791, 792*f*
Nevus with architectural disorder, 738
New World leishmaniasis, 621
Newborn
  fat necrosis of, 529–530, 530*f*
    clinical features of, 529
    differential diagnosis of, 530
    histopathology of, 529–530, 530*f*
    pathogenesis of, 530
  varicella of, 642
NF1. *See* Neurofibromatosis type 1
NF2. *See* Neurofibromatosis type 2
NGF. *See* Nerve growth factor
Niacin deficiency
  histopathology of, 103
  pellagra, 408
Nicein. *See* Laminin
NICH. *See* Noninvoluting congenital hemangiomas
Nicotinic acid
  acanthosis nigricans and, 448
  pellagra and, 451
Nidogen, in lamina lucida, 23–24
Night blindness, vitamin A deficiency and, 407
Night sweats, with angioimmunoblastic T-cell lymphoma, 952
Nipple. *See also* Areola
  erosive adenomatosis of, 881, 881*f*
  hyperkeratosis of, 106
  nevoid hyperkeratosis of, 792–793
  Paget's disease of, 838–839
  sebaceous glands and, 31
Nitric oxide (NO), Behçet's syndrome and, 415
Nitroglycerine, SJS and TEN with, 313
NK cells. *See* Natural killer cells
NLPHL. *See* Nodular lymphocyte-predominant Hodgkin's lymphoma
NO. *See* Nitric oxide
Nocardia asteroides, 574, 574*f*
Nocardia brasiliensis, 574
Nocardia, neutrophilic eccrine hidradenitis and, 491
Nocardiosis, 574, 574*f*
  histopathology of, 119, 574, 574*f*
  in HIV, 574, 659
Nodal follicular lymphoma, 926–928
  clinical features of, 927
  differential diagnosis of, 919*t,* 928
  histogenesis of, 928
  histopathology of, 927–928, 927*f*
  primary cutaneous follicle center lymphoma v., 918–919
Nodular amyloidosis, 429
  differential diagnosis of, 429
  histopathology of, 429
Nodular basal cell carcinoma, 824, 824*f,* 827*f*
  histopathology of, 826, 827*f*
Nodular colloid degeneration, 429–430, 430*f*
  histopathology of, 429–430, 430*f*
  pathogenesis of, 430
Nodular fasciitis, 983–984
  differential diagnosis of, 984
  histogenesis of, 984
  histopathology of, 125, 983–984, 984*f*
  inflammatory pseudotumor v., 994
  plexiform fibrohistiocytic tumor v., 977
Nodular hidradenoma, 891–892
  additional studies of, 892
  differential diagnosis of, 892
  histopathology of, 97, 97*f,* 891–892, 891*f*
  with nevus sebaceus, 871
Nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL), 933–934, 934*t*
Nodular melanoma, 749–753
  classification of, 738, 739*t*
  deep penetrating nevus v., 730
  differential diagnosis of, 752
  histopathology of, 750–751
    architectural features, 750, 751*f*
    cytological features, 750–752, 751*f*
  immunohistochemistry of, 752–753
  prognosis of, 768
Nodular perifolliculitis, fungal, 595
Nodular prurigo, actinic prurigo v., 336
Nodular scabies, 626–627
Nodular sclerosis Hodgkin's lymphoma (NSHL), 934, 934*t*
Nodular stage, of Kaposi's sarcoma, 1032–1033, 1033*f*
Nodular subepidermal fibrosis, 972
Nodular tertiary syphilis, 583
Nodular vasculitis. *See also* Erythema induratum
  erythema nodosum v., 515
  histopathology of, 100, 100*f,* 129–131
  pancreatic disease v., 529
Nodular-cystic fat necrosis, 1066
Nodularis amyloidosis, 425
Nodules
  of acne vulgaris, 459, 460*f*
  of coccidioidomycosis, 608–609
  of congenital self-healing reticulohistiocytosis, 669
  of eumycetoma, 614
  of indeterminate cell histiocytosis, 678
  of juvenile xanthogranuloma, 672, 673*f*
  of LCD, 669
  of lobomycosis, 606
  of papular xanthoma, 673, 674*f*
  of post-kala-azar dermal leishmaniasis, 624
  of Rosai-Dorfman disease, 678
  of sporotrichosis, 613
  of subcutaneous phaeohyphomycosis, 602
  of xanthoma disseminatum, 675
Nodulosis-arthropathy-osteolysis (NAO), Winchester syndrome and, 155
Nonbullous impetigo. *See* Impetigo contagiosa
Nongiant congenital melanocytic nevi, 725, 726*f*
  histopathology of, 727–728
Nonhealing chronic cutaneous leishmaniasis, 623–624
Non-Hodgkin's lymphoma
  anaplastic large cell lymphoma, 952
  eosinophilic pustular folliculitis and, 466
  erythema nodosum with, 514
  paraneoplastic autoimmune multiorgan syndrome and, 254
  with relapsing polychondritis, 493
Nonhuman *Schistosoma* species, 631
Noninflammatory halo nevus, 730
Noninvoluting congenital hemangiomas (NICH), 1013–1014
  differential diagnosis, 1013–1014
  histopathology of, 1013, 1014*f*
Nonmelanoma skin cancer, human papillomavirus in, 650
Nonnucleoside reverse transcriptase inhibitors, cutaneous manifestations of, 324
Nonscarring alopecia, 473–481
  anagen effluvium, 478
  androgenetic alopecia, 479–481, 480*f*
  telogen effluvium, 478–479, 479*f*
  traction alopecia, 477–478, 478*f*
  trichotillomania, 476–477, 476*f*–477*f*
Nonsteroidal anti-inflammatory drugs (NSAIDs)
  dermatomyositis and, 294
  drug-induced pigmentary alterations of, 692

Nonsteroidal anti-inflammatory drugs (*continued*)
drug-induced pseudoporphyria with, 320
lichenoid drug eruption and, 313
photoallergic drug eruption and, 318
SJS and TEN with, 313
toxic epidermal necrolysis and, 269
Nontuberculosis mycobacteria (NTM) infections, 555–558, 555*f*–558*f*
Buruli ulcer, 556–558, 557*f*
histopathology of, 118–119
Mycobacterium avium-intracellulare, 555, 555*f*–556*f*
Mycobacterium kansasii, 555, 555*f*
Mycobacterium marinum, 555–556, 556*f*
other, 558, 558*f*
Nontumorigenic melanoma, 743–749
acral-lentiginous, 747–748, 748*f*
classification of, 738–739, 739*t*
definition of, 741, 741*f*
dysplastic nevus v., 738, 739*t*
lentigo maligna melanoma, 745–747, 746*f*
morphology of, 740–742, 740*f*–742*f*
mucosal lentiginous, 749
superficial atypical melanocytic proliferation of uncertain significance, 749
superficial spreading melanoma, 743–745, 745*f*
Nonvenereal treponematoses, 583–589, 584*f,* 586*f*–587*f*
Lyme disease, 585–589, 586*f*–587*f*
acrodermatitis chronica atrophicans, 586–587, 587*f*
borrelial lymphocytoma cutis, 588–589
erythema chronicum migrans, 586, 586*f*
other atrophying and sclerosing disorders of, 587–588, 587*f*
pinta, 584–585
endemic syphilis, 585
yaws, 583–584, 584*f*
primary, 583
secondary, 583
tertiary, 584
Normolipemic xanthomas, 683–686, 684*f*–685*f*
diffuse normolipemic plane xanthoma, 684–685, 685*f*
necrobiotic xanthogranuloma with paraproteinemia, 683–684, 684*f*
verruciform xanthomas, 685–686, 685*f*
North American blastomycosis, 600*t,* 603–605, 605*f*
differential diagnosis of, 604–605
histopathology of, 118–120, 131–132, 604, 605*f*
paracoccidioidomycosis v., 606
pathogenesis of, 604
Norwegian scabies, 626–627
Nose
cicatricial pemphigoid and, 259
mucosal lentiginous melanoma of, 749
sebaceous trichofolliculoma in, 855
vellus hairs and sebaceous glands of, 56, 57*f*
NRAS, compound nevus and, 713
NSAIDs. *See* Nonsteroidal anti-inflammatory drugs
NSE. *See* Neuron-specific enolase
NSF. *See* Nephrogenic systemic fibrosis
NSHL. *See* Nodular sclerosis Hodgkin's lymphoma
NSM. *See* Nerve sheath myxoma
NTK. *See* Neurothekeoma
NTM infections. *See* Nontuberculosis mycobacteria infections
Nuchal-type fibroma, 990
differential diagnosis of, 990
histogenesis of, 990
histopathology of, 990
Nuclear anaplasia, in malignant nodular hidradenoma, 892
Nuclear lamins, antibodies against, 75, 76*t*
Nucleoside reverse transcriptase inhibitors
cutaneous manifestations of, 324
SJS and TEN with, 313
Nummular dermatitis, 241–242
histopathology of, 239*f,* 241–242
pathogenesis of, 242
psoriasis vulgaris v., 181
Nummular eczema, histopathology of, 89, 89*f,* 92, 92*f,* 108–109, 113
Nutritional deficiencies
chronic spongiotic dermatitis and, 244
telogen effluvium and, 478
Nylon, foreign-body reactions and, 373, 373*f*

Oat cell carcinoma, 1154
Obesity, striae distensae and, 398
Obsessive compulsive disorder, trichotillomania and, 476
OCA. *See* Oculocutaneous albinism
Occupational acro-osteolysis, 401
Ochronosis, 439–441, 440*f*
histopathology of, 439–440, 440*f*
pathogenesis of, 440–441
sarcoidosis and, 370
Ocular albinism, 693
Oculocutaneous albinism (OCA), 693
Oculocutaneous tyrosinosis, 451–452
histogenesis of, 452
histopathology of, 103, 452
Odland bodies, function of, 12
Ofuji's disease. *See* Eosinophilic pustular folliculitis
"Oil drop sign," of nail psoriasis, 504, 504*f*
Oil red O stain, for paraffinoma, 374
Old World leishmaniasis, 621
Onchocerca volvulus, 629–631, 631*f*
Onchocercal dermatitis, 630–631
Onchocerciasis, 629–631, 631*f*
histopathology of, 121, 630–631, 630*f*
pathogenesis of, 631
Onchocercomas, 630–631, 630*f*
Oncocytic macrophages, 675
Oncogene-induced senescence, melanoma and, 743
Ontogeny, of benign appendageal tumors, 853
Onychokeratinization, of nails, 37–38
Onychomadesis, nail matrix and, 506
Onychomycosis, 593–595
Candida, 599
histopathology of, 100, 100*f,* 129
of the nail unit, 507, 507*f*
Operation Desert Storm, viscerotropic leishmaniasis in veterans of, 625
Opiate dependency, necrolytic migratory erythema and, 409
Optic atrophy, with onchocerciasis, 630
Oral cavity
epithelioid hemangioma of, 1023
metastatic carcinoma of skin, 1156
histopathology of, 1156
mucosal lentigines of, 705
verruciform xanthomas in, 685–686, 685*f*
verrucous carcinoma in, 822
Oral contraceptives
drug-induced pseudoporphyria with, 320
erythema nodosum with, 515
melasma with, 690
superficial thrombophlebitis and, 209
Oral epithelial nevus, oral focal epithelial hyperplasia v., 657
Oral florid papillomatosis, 822. *See also* Verrucous carcinoma
Oral focal epithelial hyperplasia, 657, 657*f*
differential diagnosis of, 657
histogenesis of, 657
histopathology of, 657, 657*f*
oral white sponge nevus v., 794
Oral hairy leukoplakia, 644–645
in HIV, 644–645, 659–660
Oral lesions
of histoplasmosis, 611–612
of paracoccidioidomycosis, 605
Oral leukoplakia, 811–812
differential diagnosis of, 812
erythroplakia of oral mucosa v., 812
histopathology of, 103, 812, 812*f*
Oral lichen planus, 187, 188*f*
oral leukoplakia v., 812
Oral mucosa
acute febrile neutrophilic dermatosis and, 223
argyria of, 327
cicatricial pemphigoid and, 259
Darier's disease and, 149, 151
discoid lupus erythematosus and, 280
dyskeratosis congenita, 139, 139*f*
eruptive keratoacanthoma in, 837
erythroplakia of, 104, 812
keratosis lichenoides chronica and, 191
Langerhans cells in, 21
leukoedema of, 794–795
leukoplakia on, 812
lichen planus and, 185, 185*f*
Merkel cells in, 18
microanatomy of, 10*f,* 12
mucosal lentiginous melanoma of, 749
mucous cyst of, 997–998
oral lichen planus and, 187, 188*f*
oral white sponge nevus in, 794
pachyonychia congenita of, 138
pemphigus vulgaris and, 247, 248*f*
permeability barrier of, 12
with sarcoidosis, 372
warty dyskeratoma of, 806–807
Oral white sponge nevus, 794
differential diagnosis of, 794
histopathology of, 104, 794
leukoedema of the oral mucosa v., 794–795
pathogenesis of, 794
Orbit, melanoma of, 700
Orceinophilic granules, cutis laxa and, 157
Orf. *See also* Parapoxvirus infections
histopathology of, 105, 114
Ornithodorus species, Lyme disease from, 585
Ornithosis, erythema nodosum with, 514
Orofacial herpes. *See* HSV-1
Oropharyngeal pemphigus, 317
Oropharyngeal squamous cell carcinoma, human papillomavirus in, 650
Orthohyperkeratosis, generalized myxedema and, 441
Orthokeratosis
lichen planopilaris and, 188
lichen planus and, 186
pityriasis rubra pilaris with, 195
Orthokeratotic hyperkeratosis, oculocutaneous tyrosinosis and, 452
Osler-Weber-Rendu disease. *See* Hereditary hemorrhagic telangiectasia
Osseous and chondroid lesions, 1099–1100, 1100*f*
Osseus tissue, tumors of, 98, 98*f,* 127
Ossifying fibromyxoid tumor, extraskeletal osteosarcoma v., 1094
Ossifying lipomas, 1063, 1063*f*
Osteoblastic cells, fibroblasts and, 1089
Osteoclasts, 1087
Osteodystrophy, metastatic calcinosis cutis with, 435
Osteogenesis imperfecta, elastosis perforans serpiginosa and, 394
Osteogenic desmoplastic melanoma, desmoplastic melanoma v., 754

Osteoma cutis, 1087–1089
  histopathology of, 98, 98*f,* 127, 1087–1088, 1088*f*–1089*f*
  pathogenesis of, 1089
Osteomyelitis
  metastatic calcinosis cutis and, 435
  pseudocarcinomatous hyperplasia and, 822
Osteopoikilosis, connective tissue nevus with, 154
Osteosarcoma, radiation-induced, 351
Ova, of schistosomiasis, 631–632
Ovary, metastatic carcinoma of skin, 1157
  histopathology of, 1157
  immunoperoxidase studies, 1157
Overlap syndrome, 286
  immunofluorescence for, 190
  of lichen planus, 186, 189
Oxalosis
  calciphylaxis and, 230
  histopathology of, 131
Oxicam, SJS and TEN with, 313
Oxytalan fibers
  in aging skin, 49
  of lamina densa, 24
  solar elastosis and, 389

P2 protein, granular cell nerve sheath tumor and, 1131
p16, compound nevus and, 713
p16INK4, in benign nevi, 715
p53
  epidermal tumors and, 835
  lentigo maligna melanoma and, 747
  melanin and, 18
p63, expression of, 13–14, 13*f*
p200, 263
Pachydermoperiostosis, 158
Pachyonychia congenita, 138–139, 138*f*
  histopathology of, 138
  oral white sponge nevus v., 794
  pathogenesis of, 139
Pacinian neurofibroma, 1133–1134
  histopathology of, 125
Pacinian neuroma, 1138
  histopathology of, 1138
Pacinian perineural cell fibroma, 1134–1135, 1134*f*
Paclitaxel, drug-induced scleroderma with, 316
Pagetoid cells, of sebaceous carcinoma, 876
Pagetoid extension, junctional nevus, 711–712
Pagetoid melanocytosis
  with nevi of acral skin, 716
  with pigmented spindle cell nevus, 724
Pagetoid melanoma. *See also* Superficial spreading melanoma
  extramammary Paget's disease v., 840
  Paget's disease v., 839
Pagetoid pattern
  of mycosis fungoides, 937
  of nontumorigenic melanoma, 743
Pagetoid reticulosis, histopathology of, 88, 88*f,* 105
Pagetoid Spitz nevus, 720
Pagetoid squamous cell carcinoma
  Bowen's disease v., 815
  histopathology of, 88, 88*f,* 105
Paget's disease, 832, 838–839
  Bowen's disease v., 815
  CEA in, 76
  differential diagnosis of, 839
  erosive adenomatosis of the nipple v., 881
  extramammary Paget's disease v., 839
  histopathology of, 88, 88*f,* 105, 838, 838*f*
  pathogenesis of, 838–839
  solitary pagetoid reticulosis and, 941
  superficial spreading melanoma v., 744–745
Pain, burns and, 343
Palisaded and encapsulated neuroma (PEN), 1135–1136
  histopathology of, 125, 1136, 1136*f*–1137*f*
  intraneural plexiform neuroma v., 1136
Palisaded angiolipoleiomyoma, 1079
Palisaded granulomas, histopathology of, 130
Palisaded granulomatous panniculitis, 524–525
  clinical features of, 524
  differential diagnosis of, 525
  histopathology of, 524–525, 524*f*
  pathogenesis of, 525
Palisaded neutrophilic and granulomatosis (PNGD), 368–370, 368*f*–369*f*
  differential diagnosis of, 369–370
  histopathology of, 119, 369, 369*f*
  interstitial granulomatous drug reaction v., 381
  pathogenesis of, 369
Palisading necrotizing granulomatous inflammation
  histopathology of, 119
  of schistosomiasis, 631
Palmar erythema
  Crohn's disease with, 415
  systemic lupus erythematosus with, 285
Palmar fibromatosis, 992
  histogenesis of, 992
  histopathology of, 992, 993*f*
Palmar xanthomas, with cholestasis, 680
Palmar-plantar erythrodysesthesia syndrome. *See* Toxic acral erythema
Palmar-plantar keratodermas
  eccrine syringofibroadenoma with, 888
  pityriasis rubra pilaris, 195
Palmoplantar hidradenitis, 491
  histopathology of, 129
Palms
  acral skin of, 56
  eccrine glands on, 32
  epidermal cysts of, 802
  Reiter's disease and, 181
  Vater-Pacini corpuscles at, 55
Palpable migratory arciform erythema, Jessner's lymphocytic infiltration of the skin v., 291
Palpable purpura, microscopic polyarteritis and, 212
PAMS. *See* Paraneoplastic autoimmune multiorgan syndrome
PAN. *See* Polyarteritis nodosa
Panarteritis, Takayasu's arteritis and, 208
p-ANCAs. *See* Perinuclear antineutrophil cytoplasmic antibodies
Pancreas, hereditary hemochromatosis and, 449
Pancreatic carcinoma, 1156, 1158
Pancreatic disease, subcutaneous nodular fat necrosis in, 528–529, 528*f*
  clinical features of, 528, 528*f*
  differential diagnosis of, 529
  histopathology of, 528, 528*f*
  pathogenesis of, 528
  systemic lesions of, 528
Pancreatic fat necrosis, histopathology of, 130
Pancreatic panniculitis
  calciphylaxis and, 230
  histopathology of, 101, 101*f,* 131
Pancytopenia
  dyskeratosis congenita, 139, 139*f*
  with histiocytic cytophagic panniculitis, 533
Panniculitis. *See also* Calcifying panniculitis; Cold panniculitis; Connective tissue panniculitis; Eosinophilic panniculitis; Histiocytic cytophagic panniculitis; Lipomembranous panniculitis; Lobular panniculitis; Lupus erythematosus panniculitis; Lupus panniculitis; Mycobacterial panniculitis; Necrotizing panniculitis; Pancreatic panniculitis; Traumatic panniculitis
  with alpha-1 antitrypsin deficiency, 516–517, 516*f*–517*f*
    clinical features of, 516, 516*f*
    differential diagnosis of, 516–517
    histopathology of, 516, 516*f*–517*f*
  biopsy for, 5–6
  with bromides and iodides, 534
  classification of, 509–511, 510*t*
  dermatomyositis with, 294
  due to physical or chemical agents, 525–526, 526*f*
    clinical features of, 525–526
    histopathology of, 526, 526*f*
    pathogenesis of, 526
  histopathology of, 102, 102*f*
  subcutaneous panniculitis-like T-cell lymphoma v., 948
Panniculitis Rothmann-Makai, 524
Papillary dermal elastolysis, 399
  histogenesis of, 399
  histopathology of, 399
Papillary dermal fibrosis, with syringolymphoid hyperplasia, 491
Papillary dermal pattern, of benign cephalic histiocytosis, 677–678
Papillary dermis
  acropustulosis of infancy and, 267
  actinic keratosis in, 808
  adult colloid milium and, 429, 430*f*
  bullous pemphigoid and, 256, 257*f*
  chilblains and, 353, 353*f*–354*f*
  chronic actinic dermatitis and, 339
  collagen fibers and, 47
  compound nevus and, 713
  dermatitis herpetiformis and, 263–264
  in dysplastic nevus, 735
  erythema dyschromicum perstans and, 172
  Gianotti-Crosti syndrome and, 184
  lichen simplex chronicus and, 243
  lichen striatus and, 193
  linear focal elastosis in, 398
  lymphangioma circumscriptum, 1044, 1045*f*
  mucocutaneous end-organs in, 54–55
  nerve fibers of, 53–54
  parapsoriasis and, 182
  pigmented purpuric dermatosis, 226, 227*f*
  PLEVA and, 196
  prurigo nodularis and, 174
  ultraviolet recall and, 346
Papillary eccrine adenoma, 890–891
  additional studies of, 891
  aggressive digital papillary adenocarcinoma v., 899
  histopathology of, 123, 890, 890*f*
  tubular apocrine adenoma v., 880
Papillary intralymphatic angioendothelioma (PILA), 1036–1037
  differential diagnosis of, 1037
  histopathology of, 1036, 1037*f*
  pathogenesis of, 1037
Papilloma, of verruciform xanthomas, 685*f*
Papillomatosis
  acanthotic seborrheic keratosis and, 798
  of condyloma acuminatum, 654, 655*f*
  confluent and reticulated papillomatosis, 449
  halogenodermas and, 326
  in hyperkeratotic seborrheic keratosis, 798
  of hypertrophic actinic keratosis, 808
  lichen simplex chronicus and, 242
  with linear epidermal nevus, 791
  of nipple and areola, 792–793
  prurigo nodularis and, 174
  seborrheic keratosis and, 795
  smooth muscle hamartoma and, 1075
  soft fibroma and, 981
  syringocystadenoma papilliferum with, 879
  of verruca vulgaris, 650, 651*f*

Papillomatous, histopathology of, 105
Papillomatous hyperkeratotic surfaces, 650
Papillomaviridae, 649–656, 651*f*–655*f*
  condyloma acuminatum, 654–656, 655*f*
  deep palmoplantar warts, 652–653, 652*f*
  epidermodysplasia verruciformis, 653–654, 654*f*
  giant condyloma acuminata of Buschke and Loewenstein, 655*f,* 656
  verruca plana, 653, 653*f*
  verruca vulgaris, 650–652, 651*f*
Papillon-Lefevre syndrome, 137
Papovaviridae, 637
Papular acrodermatitis
  of childhood, 184. *See also* Gianotti-Crosti syndrome
  with hepatitis B virus, 418
  histopathology of, 107–108, 115
Papular eruptions, of AIDS, 660
Papular mucinosis. *See also* Lichen myxedematosus
  histopathology of, 121
Papular urticaria, 634
  histopathology of, 93, 93*f,* 115
Papular xanthoma (PG), 673–674, 674*f,* 677
  benign cephalic histiocytosis v., 678
  differential diagnosis of, 674
  histopathology of, 124, 673, 674*f*
  pathogenesis of, 673–674
Papular-purpuric gloves and socks syndrome, 645, 662
Papules
  of aspergillosis, 599
  of eruptive xanthomas, 680, 681*f*
  of erythema chronicum migrans, 586
  of generalized eruptive histiocytosis, 678
  of indeterminate cell histiocytosis, 678
  of juvenile xanthogranuloma, 672
  of LCD, 669, 670*f*
  of lupus miliaris disseminatus faciei, 465–466
  of molluscum contagiosum, 649, 649*f*
  of oral focal epithelial hyperplasia, 657
  of papular xanthoma, 673
  of perioral dermatitis, 462
  polyarteritis nodosa and, 210
  of post-kala-azar dermal leishmaniasis, 624
  of reticulohistiocytosis, 675
  of rosacea, 463
  of Rosai-Dorfman disease, 678
  of verruca plana, 653, 653*f*
  of verruca vulgaris, 650
  of xanthoma disseminatum, 675
Papulonecrotic tuberculids, 550, 553–554, 554*f*
  differential diagnosis of, 554
  histopathology of, 116, 120, 554, 554*f*
Papulovesicular acrolocated syndrome, 184
Papulovesicular type, of scabies, 626–627
Paracoccidioides brasiliensis, 600*t,* 605–606, 606*f*
Paracoccidioidomycosis, 600*t,* 605–606, 606*f*
  differential diagnosis of, 606
  histopathology of, 118–119, 132, 606, 606*f*
Paraffin
  foreign-body reactions and, 374
  scleroderma and, 296
  for specimen processing, 68
Paraffinoma, 374
  histopathology of, 117, 374
  silicone granuloma v., 375
Paraimmunoblasts, in chronic lymphocytic lymphoma/small lymphocytic lymphoma, 926
Parakeratosis
  acanthoma fissuratum and, 357
  atopic dermatitis and, 242
  calcaneal petechiae and, 356
  clear cell acanthoma and, 800
  of condyloma acuminatum, 654
  discoid lupus erythematosus and, 280
  ILVEN and, 194, 194*f*
  lichen planus and, 190
  with nail psoriasis, 504
  parapsoriasis and, 182
  of perioral dermatitis, 462
  pityriasis lichenoides chronica and, 196
  pityriasis rubra pilaris with, 195
  psoriasis vulgaris and, 176, 181
  seborrheic dermatitis and, 243
Parakeratosis variegata. *See* Poikiloderma parapsoriasis
Parakeratotic cells, in verrucae vulgares, 650
Parakeratotic scale, of syphilis, 581, 581*f*–582*f*
Paramyxoviridae, 637
Paraneoplastic autoimmune multiorgan syndrome (PAMS), 254, 255*f*. *See also* Paraneoplastic pemphigus
  histopathology of, 254, 255*f*
  immunofluorescence testing for, 254, 255*f*
  pathogenesis of, 246*t,* 254
Paraneoplastic pemphigus (PNP), histopathology of, 110, 112, 114
Paraneoplastic phenomena, 381
Paraneoplastic vasculitis, 221
  Behçet's syndrome v., 414
Paraneoplastic vulgaris, indirect immunofluorescence and, 73–74
Paraneurofibroma, 1114, 1114*f*
Parapoxvirus infections, 647–648, 648*f*
  histogenesis and viral identification of, 648
  histopathology of, 648
Paraprotein, in scleromyxedema, 444
Paraproteinemias
  diffuse normolipemic plane xanthoma with, 684
  histopathology of, 119, 130–131
  with reactive angioendotheliomatosis, 1008
Paraproteins, with vasculitides, 219–220, 220*f*
Parapsoriasis, 182–183, 182*f*
  histopathology of, 90, 90*f,* 107–110, 182, 182*f*
  lymphoma relationship of, 183
  pathogenesis of, 182–183
Parapsoriasis variegata, 182
  poikiloderma atrophicans vasculare and, 295
Parasites
  eosinophils and, 44
  histopathology of, 130
Parasitic infection, 626–635
  arthropod assault reactions, 634–635, 634*f*
  eosinophilic panniculitis and, 515
  hookworm-related cutaneous larva migrans, 627–628, 627*f*
  myiasis, 632–633, 633*f*
  onchocerciasis, 629–631, 631*f*
  scabies, 626–627, 626*f*
  schistosomiasis, 631–632, 632*f*
  strongyloidiasis, 628, 629*f*
  subcutaneous cysticercosis, 632, 632*f*
  subcutaneous dirofilariasis, 628–629, 629*f*
  tungiasis, 633–634, 633*f*
Parathyroidectomy, for metastatic calcinosis cutis, 436
Paravaccinia viruses, 647–648, 648*f*
Parenchymatous syphilis, 583
Paronychia, with acrodermatitis enteropathica, 410
Partial albinism, 693
Parvoviridae, 637
Parvovirus B19, 661–662, 662*f*
  leukocytoclastic vasculitis and, 218
  in Rosai-Dorfman disease, 679
PAS. *See* Periodic acid Schiff stain
Pathology, cutaneous
  disease listings by site, pattern, and cytology, 103–132
    acantholytic, vesicular, and pustular disorders, 112–115
    epidermis and stratum corneum, 103–104
    localized superficial epidermal or melanocytic proliferations, 104–106
    perivascular, diffuse, and granulomatous infiltrates of reticular dermis, 115–121
    skin appendage inflammatory disorders, 127–129
    subcutis disorders, 129–132
    superficial cutaneous reactive unit disorders, 106–112
  introduction to, 83–84
  site categories of, 85
  site, pattern, and cytologic categories of, 86–102
    acantholytic, vesicular, and pustular disorders, 92–93, 92*f*–93*f*
    epidermis and stratum corneum, 86–87, 86*f*–87*f*
    localized superficial epidermal or melanocytic proliferations, 87–89, 87*f*–89*f*
    perivascular, diffuse, and granulomatous infiltrates of reticular dermis, 93–96, 93*f*–96*f*
    skin appendage inflammatory disorders, 99–100, 99*f*–100*f*
    subcutis disorders, 100–102, 100*f*–102*f*
    superficial cutaneous reactive unit disorders, 89–91, 89*f*–91*f*
    tumors and cysts of dermis and subcutis, 96–98, 96*f*–98*f,* 121–127
Pattern recognition method, 83
Patterned leukoderma. *See* Piebaldism
Paucibacillary patients, 560
Pautrier microabscesses
  with adnexotropic mycosis fungoides, 939
  T-cell lymphomatoid hyperplasias v., 935, 935*f*
PC-ALCL. *See* Primary cutaneous anaplastic large cell lymphoma
PCFCL. *See* Primary cutaneous follicle center lymphoma
PCLBCL. *See* Primary cutaneous diffuse large B-cell lymphoma
PCMZL. *See* Primary cutaneous marginal zone lymphoma
PCNA, for Spitz nevus, 722
PCR. *See* Polymerase chain reaction
PCT. *See* Porphyria cutanea tarda
Pearly penile papules, 988
  histopathology of, 988
Pedunculated melanoma. *See* Polypoid melanoma
Peeling technique, for direct immunofluorescence, 71
Pellagra
  acrodermatitis enteropathica v., 410
  chronic spongiotic dermatitis and, 244
  differential diagnosis of, 408
  Hartnup's disease v., 409, 451
  histopathology of, 86, 86*f,* 90, 90*f,* 103, 109–110, 112, 408, 451
  kwashiorkor v., 410
  necrolytic migratory erythema v., 409
  pathogenesis of, 408
Pellagrins, pellagra and, 408
Pemphigoid. *See also* Anti-p200 pemphigoid
  assays for, 74
Pemphigoid antibodies, bullous pemphigoid and, 258–259
Pemphigus, 245–253. *See also* IgA pemphigus
  histopathology of, 129
  pathophysiology of, 245–247, 246*t,* 247*f*
Pemphigus erythematosus
  differential diagnosis of, 252
  histopathology of, 112–113, 252, 252*f*
  immunofluorescence testing of, 252
  subcorneal pustular dermatosis v., 268
  ultrastructural study of, 252
Pemphigus foliaceus, 11, 250–252, 251*f*
  differential diagnosis of, 252
  direct immunofluorescence and, 72, 251, 251*f*

eczema herpeticum with, 638
eosinophils and, 44
histopathology of, 112–113, 250–251, 251*f*
IgA pemphigus v., 253–254
impetigo contagiosa v., 539
indirect immunofluorescence and, 73, 251–252
Kaposi's varicelliform eruption with, 641
pathogenesis of, 252
pemphigus erythematosus v., 252
pemphigus herpetiformis v., 252
subcorneal pustular dermatosis v., 268
transient acantholytic dermatosis with, 273
ultrastructural study of, 252
Pemphigus herpetiformis, 252–253
histopathology of, 252
immunofluorescence testing of, 252–253
Pemphigus vegetans, 250
differential diagnosis of, 250
eosinophils and, 44
histopathology of, 92, 92*f,* 110, 114, 250, 250*f*
indirect immunofluorescence and, 250
pathogenesis of, 250
Pemphigus vegetans of Hallopeau, 546
Pemphigus vulgaris, 11, 247–249, 248*f,* 1168*f*
acantholytic actinic keratosis v., 810
differential diagnosis of, 249
direct immunofluorescence and, 72, 248–249, 248*f*
eosinophils and, 44
familial benign pemphigus v., 149
histopathology of, 93, 93*f,* 114, 247–248, 248*f*
indirect immunofluorescence of, 73, 249
nail involvement in, 506
pathogenesis of, 249
transient acantholytic dermatosis v., 273
ultrastructural study of, 249
PEN. *See* Palisaded and encapsulated neuroma
Penicillamine
dermatomyositis and, 294
dermatoses induced by, 325–326, 325*f*–326*f*
drug-induced bullous disease and, 317, 317*t*
drug-induced pemphigus and, 253
drug-induced scleroderma with, 316
elastosis perforans serpiginosa, 325–326, 325*f*–326*f*
elastosis perforans serpiginosa and, 394
lichenoid drug eruption and, 313
skin atrophy and, 325
Penicillamine-induced atrophy, histopathology of, 120
Penicillamine-induced elastosis perforans, histopathology of, 120
Penicillin
drug-associated bullous pemphigoid and, 259
drug-induced pemphigus and, 253
leukocytoclastic vasculitis and, 221
for syphilis, 579
Penicillium marneffei, molluscum contagiosum v., 649
Penis. *See also* Pearly penile papules
mucosal lentigines of, 705
sebaceous hyperplasia in, 872
Pentazocine (Talwin)
drug-induced scleroderma with, 316
panniculitis with, 525
scleroderma and, 296
Perforating calcific elastosis, 396–397
histogenesis of, 396–397
histopathology of, 121, 396, 397*f*
pseudoxanthoma elasticum and, 153
Perforating disorder of renal failure and diabetes, histopathology of, 120
Perforating disorders, 391–396
acquired perforating dermatosis, 395–396
elastosis perforans serpiginosa, 393–395
Kyrle's disease, 392, 392*f*
perforating folliculitis, 392–393, 394*f*
reactive perforating collagenosis, 395
Perforating folliculitis, 392–393, 394*f*
acquired perforating dermatosis v., 396
differential diagnosis of, 393, 393*t*
elastosis perforans serpiginosa v., 395
histogenesis of, 393
histopathology of, 120, 393, 394*f*
Perforating folliculitis of hemodialysis. *See* Acquired perforating dermatosis
Perforating granuloma annulare, 361–364
histopathology of, 121, 361–362, 362*f*–363*f*
papulonecrotic tuberculids v., 554
Perforating pseudoxanthoma elasticum. *See* Perforating calcific elastosis
Perforin, anaplastic large cell lymphoma, 953
Perianal region
extramammary Paget's disease of, 839
hidradenoma papilliferum on, 878
mucocutaneous end-organs in, 54
Pericapillary hyalin deposits, with lipoid proteinosis, 431
Perichondrial tissue, chondrodermatitis nodularis helicis and, 494
Perichondrium, relapsing polychondritis in, 494
Pericytes
acquired elastotic hemangioma and, 1026
in glomeruloid hemangioma, 1010
Periderm, of epidermis, 7–8, 8*f*
Perifollicular elastolysis, 401
histogenesis of, 401
histopathology of, 401
Perifollicular fibroplasia, tufted hair folliculitis with, 488
Perifolliculitis capitis abscedens et suffodiens
in follicular occlusion triad, 544
histopathology of, 120, 128
Perifolliculitis, fungal, 594–595
Perilesional biopsy, for direct immunofluorescence, 71
Perineal region, hidradenoma papilliferum on, 878
Perineural cells, tumors of, 1132–1135
Perineural lipoma, 1060
Perineural variants, of neurofibromatosis, 1111
Perineuriomas, 1132–1135. *See also* Intraneural perineurioma
acral perineuriomas, 1133–1134
histopathology of, 125
pacinian perineural cell fibroma, 1134–1135, 1134*f*
storiform perineural cell fibroma, 1132–1133, 1133*f*
Perineurium, anatomic relationships with, 1107
Perinuclear antineutrophil cytoplasmic antibodies (p-ANCAs)
Churg-Strauss syndrome and, 213
for MPO, 207, 207*t*
Periodic acid Schiff stain (PAS), 68, 69*t*
for aluminum granuloma, 377
for basement membrane zone, 22
for cactus granuloma, 375
for colloid bodies, 430
for eccrine and apocrine glands, 36
for infundibulum, 30
for nail fungal infections, 507
for nail psoriasis, 504
pilomatricoma and, 865
for starch granuloma, 375
Perioral dermatitis, 462–463
histopathology of, 115–116, 128, 462, 462*f*
pathogenesis of, 463
Peripheral nerve sheath tumors, extraskeletal osteosarcoma v., 1094
Peripheral nerves, leprosy involvement of, 564
Peripheral neuroblastoma, 1139–1140
histopathology of, 1139–1140, 1140*f*
Peripheral neuroectodermal tumor, mesenchymal chondrosarcoma v., 1099
Peripheral neuroepithelioma (PNE)
differential diagnosis of, 1141
histogenesis of, 1141
histopathology of, 1140–1141
Peripheral T-cell lymphoma, 951–952
clinical features of, 951
differential diagnosis of, 952
histogenesis of, 951
histopathology of, 951, 951*f*
Peritoneum, argyria of, 327
Peritumoral lacunae, basal cell carcinoma and, 826*f,* 830
Periumbilical perforating pseudoxanthoma elasticum. *See* Perforating calcific elastosis
Periungual fibroma. *See* Acral fibrokeratoma
Periungual telangiectases
with dermatomyositis, 293
systemic lupus erythematosus with, 285
Perivascular cells, tumors of, 1047–1051
Perivascular fibrosis, lupus erythematosus profundus/panniculitis and, 283
Perivascular inflammation, with chemical burns, 346
Pernicious anemia, alopecia areata and, 475
Pernio. *See* Chilblains
Perniosis, histopathology of, 115–116, 129
Peroxidase, of eosinophils, 43
Peroxisomal proliferator activator receptors (PPARs), acne vulgaris and, 459–461
Persistent arthropod bite reaction, 634
histopathology of, 119
Persistent light eruptions, xanthomas with, 686
Persistent light reaction. *See* Chronic actinic dermatitis
Persistent nevus, recurrent nevus v., 732
Persistent nodular scabies, histopathology of, 117
Persistent scabietic nodules, 626–627
Persistent xanthoma disseminatum, 675
Petechiae
of LCD, 669
of strongyloidiasis, 628
Petriellidium boydii, 614, 615*f*
Peutz-Jeghers syndrome (PJS), 709, 710*t*
PFH. *See* Plexiform fibrous histiocytoma
PG. *See* Papular xanthoma; Pyoderma gangrenosum
PGP 9.5
granular cell nerve sheath tumor and, 1131
neurothekeoma, 1129
Phaeohyphomycosis
histopathology of, 119, 132
in HIV, 659
Phaeohyphomycotic cyst, 602, 602*f*
histopathology of, 119
Phage group II staphylococci, impetigo from, 539–541
Phagocytic macrophages, 40–41, 40*f*
of dermis, 38
Phagocytosis, neutrophilic granulocytes and, 43
Phagolysosomes, 41
with clofazimine-induced pigmentation, 325
of keratinocytes, 13
neutrophils and, 43
Phagosomes, of keratinocytes, 13
Phenacetin
drug-associated bullous pemphigoid and, 259
erythema nodosum with, 515
Phenobarbital, SJS and TEN with, 313
Phenol, ochronosis and, 440
Phenolphthalein, fixed drug eruptions with, 314
Phenols, chemical depigmentation with, 691
Phenothiazines
drug-induced pigmentary alterations of, 692
photoallergic drug eruption and, 318
T-cell lymphomatoid hyperplasias and, 936
Phenylbutazone, fixed drug eruptions with, 314
Phenylketonuria, scleroderma and, 295–296

Phenytoin
drug-induced pseudolymphoma syndrome with, 320
eosinophilic fasciitis and, 303
SJS and TEN with, 313
Pheomelanin melanosomes
in dysplastic nevus, 738
in hair, 31
Phialophora gougerotii, 603
Phialophora infection, 601
Phialophora verrucosa, 607
Phimosis, lichen sclerosus et atrophicus and, 303
Phlebitis, relapsing polychondritis with, 494
Phlebotomus, as leishmaniasis vector, 621
Phlebotomy, for hemochromatosis, 450
Phospholipase, in pancreatic disease, 528
Phosphorylase
in clear cell acanthoma, 800
in nodular hidradenoma, 892
in syringoma, 885
Photo recall. *See* Ultraviolet recall
Photoallergic dermatitis, 241
histopathology of, 241
Photoallergic drug eruption, 318, 319*f*
histopathology of, 108, 113, 318, 319*f*
Photoallergic reaction, histopathology of, 116
Photodermatitis reactivation. *See* Ultraviolet recall
Photodermatoses, hydroa vacciniforme v., 337–338
Photodistributed hyperpigmentation, 319–320, 319*f*–320*f*
histogenesis of, 320
histopathology of, 319–320, 319*f*–320*f*
Photophobia, with acrodermatitis enteropathica, 410
Photosensitive eczema. *See* Chronic actinic dermatitis
Photosensitivity
with chilblains, 353
with dermatomyositis, 293
drug-induced, 318–319, 319*f*
in pellagra, 408
systemic lupus erythematosus with, 285
Photosensitivity dermatitis. *See* Chronic actinic dermatitis
Photosensitivity disorders, 333–341
actinic prurigo, 335–336, 336*f*
chronic actinic dermatitis, 338–340, 338*f*–340*f*
hydroa vacciniforme, 337–338, 337*f*
polymorphic light eruption, 333–335, 334*f*
solar urticaria, 340, 341*f*
Phototoxic drug eruption, 318–319, 319*f*
histopathology of, 319, 319*f*
PHP. *See* Pseudohypoparathyroidism
Phrynoderma. *See also* Vitamin A deficiency
histopathology of, 127
Phycomycosis, 599–601, 600*t,* 602*f*
Physical agents, panniculitis due to, 525–526, 526*f*
Physical trauma, 355–357
acanthoma fissuratum, 357, 357*f*
friction-induced blister, 355–356, 356*f*
surgery-associated, 357, 358*f*–359*f*
talon noir, 356, 356*f*
Phytonadione-induced pseudoscleroderma, histopathology of, 120
Phytonadione-induced scleroderma, 316
Phytophotodermatitis, histopathology of, 691
Phytosterolemia, histopathology of, 124
Pianic onychia, 583
PIBIDS syndrome, 136
Picornaviridae, 637, 658–659, 658*f*
hand-foot-and-mouth disease, 658, 658*f*
hepatitis A virus, 659
Picric acid, ochronosis and, 440
Piebaldism, 693–694
histogenesis of, 693–694
histopathology of, 104, 693
melanocytes and, 14
Piezogenic papules, 1060
differential diagnosis of, 1060
histopathology of, 1060
Pigment casts, with trichotillomania, 476–477, 476*f*
Pigment synthesizing melanoma. *See* Animal-type melanoma
Pigmentary disorders, 689–695
Addison's disease, 690
albinism, 693
berloque dermatitis, 691
Chediak-Higashi syndrome, 694–695
chemical depigmentation, 691
congenital diffuse melanosis, 689
of cutaneous and systemic diseases, 692–693
drug-induced pigmentary alterations, 692
idiopathic guttate hypomelanosis, 691
linear and whorled nevoid hypermelanosis, 690
melasma, 690
phytophotodermatitis, 691
piebaldism, 693–694
pityriasis (tinea) versicolor, 596, 596*f,* 598*t*
postinflammatory pigmentary alteration, 690–691, 691*f*
progressive macular hypopigmentation, 691
psoralen and ultraviolet A-induced pigment alterations, 691–692
reticulate pigmentary anomalies, 689–690
vitiligo, 694, 695*f*
Pigmented actinic keratosis, 810
histopathology of, 104
Pigmented basal cell carcinoma, 767, 825, 829*f,* 1180*f*
Pigmented Bowen's disease, 692–693
Pigmented epidermotropic metastatic breast carcinoma, 693
Pigmented epithelioid melanocytoma, 757, 758*f*
cellular blue nevus v., 704
histopathology of, 123
Pigmented follicular cyst, 804
histopathology of, 127, 804
Pigmented lesions, benign, 699–738
blue nevi, 701–704
dermal melanocytoses and hamartomas, 699–701
freckles and hyperpigmentations, 704–706
lentigines, 706–709, 710*t*
melanocytic nevi, 710–738
Pigmented Paget's disease, 692–693
Pigmented purpuric dermatosis (PPD), 225–228, 227*f*–228*f*
differential diagnosis of, 227–228
histopathology of, 89, 89*f,* 107, 110–111, 226–227, 227*f*–228*f*
pathogenesis of, 228
Pigmented spindle cell nevus, 724
differential diagnosis of, 724
histopathology of, 724, 725*f*
minimal deviation melanoma v., 758
Pigmented spindle cell nevus of Reed, histopathology of, 122
Pigment-synthesizing dermal neoplasms, histopathology of, 122
PILA. *See* Papillary intralymphatic angioendothelioma
Pilar cysts, 802–803, 802*f*–803*f*
differential diagnosis of, 803
histopathology of, 803, 803*f*
pathogenesis of, 803
Pilar sheath acanthomas, 855
histopathology of, 123, 127, 855, 855*f*–856*f*
Pilar smooth muscle hamartoma, Becker's melanosis, 706
Pilar tumors, 97, 97*f,* 123–124
Pili multigemini, 56–57, 57*f*
Pilomatric carcinoma, 865
Pilomatricoma, 864–865
additional studies of, 865
differential diagnosis of, 865
foreign-body reactions and, 373
histopathology of, 123, 864–865, 864*f*–865*f*
macular atrophy and, 400
Pilomatrix carcinoma, 865–866
additional studies of, 866
histopathology of, 124, 865–866, 866*f*
Pilonidal sinus, 375, 545
histopathology of, 120, 128, 375
Pilosebaceous mesenchyme tumors, histopathology of, 123
Pilosebaceous units
collagen fibers and, 47
perifollicular elastolysis and, 401
Pinch purpura, primary systemic amyloidosis with, 425, 426*f*
Pinta, 584–585
endemic syphilis, 585
histogenesis of, 585
histopathology of, 585
primary, histopathology of, 108, 110–111
secondary, histopathology of, 108, 110–111
tertiary, histopathology of, 108, 112
Pintids, 585
Piroxicam, photoallergic drug eruption and, 318
Pituitary tumors, pigmentary presentations of, 692
Pityriasis folliculorum, 464
Pityriasis lichenoides
differential diagnosis of, 197
histopathology of, 196–197, 196*f*
pathogenesis of, 197
secondary syphilis v., 583
subacute spongiotic dermatitis and, 243
Pityriasis lichenoides acuta, papulonecrotic tuberculids v., 554
Pityriasis lichenoides chronica, 196
histopathology of, 107, 110, 116, 196
Pityriasis lichenoides et varioliformis acuta (PLEVA), 196
differential diagnosis of, 197
histopathology of, 107, 110, 112, 115–116, 196–197, 196*f*
neutrophils and, 43
pathogenesis of, 197
Pityriasis rosea, 183–184, 183*f*
acantholytic dyskeratosis and, 794
acute spongiotic dermatitis and, 243
differential diagnosis of, 184
histopathology of, 107–109, 113, 183–184, 183*f*
human herpesvirus in, 646
pathogenesis of, 184
Pityriasis rubra pilaris, 195–196, 195*f*
differential diagnosis of, 195–196
eczema herpeticum with, 638
histopathology of, 109, 195*f*
necrolytic migratory erythema v., 409
pathogenesis of, 196
psoriasis vulgaris v., 181
scurvy v., 407
Sézary syndrome v., 944
Pityriasis (tinea) versicolor, 596, 596*f,* 598*t*
Pityrosporum folliculitis, histopathology of, 128
Pityrosporum orbiculare, 596
confluent and reticulated papillomatosis, 449
Pityrosporum ovale, 596
PJS. *See* Peutz-Jeghers syndrome
Plakoglobin, 11
pemphigus and, 245
Plakophilin, pemphigus and, 245
Plane xanthomas, 680–682, 682*f*
Plant material, foreign-body reactions and, 374, 374*f*
Plantar verrucous carcinoma, 822
Plantar wart, 652–653
Plaque morphea. *See* Morphea

Plaque stage, of Kaposi's sarcoma, 1032, 1032*f*
Plaquelike mucinosis. *See* Reticular erythematous mucinoses
Plaques
  of acute mucocutaneous candidiasis, 597
  of coccidioidomycosis, 609
  of erythema nodosum, 511*f*
  on eyelids, 681–682, 683*f*
  of juvenile xanthogranuloma, 672
  of LCD, 669
  of necrobiotic xanthogranuloma with paraproteinemia, 683
  of oral focal epithelial hyperplasia, 657
Plasma cells, 42*f,* 46
  in actinic keratosis, 810
  alopecia areata and, 475
  in balanitis circumscripta plasmacellularis, 816
  cheilitis glandularis and, 381
  chronic actinic dermatitis and, 339
  exogenous plasmacytoma and, 922
  granuloma gluteale infantum and, 381
  in inflammatory pseudotumor, 994
  Jessner's lymphocytic infiltration of the skin and, 291
  in lymphomatoid granulomatosis, 933
  macular atrophy and, 400
  in mycosis fungoides, 937
  primary systemic amyloidosis with, 426
  in solar cheilitis, 810
  with subcutaneous panniculitis-like T-cell lymphoma, 948
  in titanium granuloma, 377
  tumors of, 96, 96*f,* 122
Plasmacytoid dendritic cells/monocytes, xanthogranuloma cells from, 671
Plasmacytoid differentiation, small lymphocytic lymphoma and, 925
Plasmacytoma
  histopathology of, 94, 94*f,* 117
  macular atrophy and, 400
Plasmapheresis, for solar urticaria, 340
Plectin, of hemidesmosomes, 23
Pleomorphic fibroblasts, in nodular fasciitis, 984
Pleomorphic fibroma, 981
  differential diagnosis of, 981
  histogenesis of, 981
  histopathology of, 981, 982*f*
Pleomorphic hyalizing angiectatic tumor, symplastic hemangioma v., 1028
Pleomorphic large cell lymphoma, histopathology of, 124–125
Pleomorphic lipoma, 1066–1067
  differential diagnosis of, 1067
  histopathology of, 127, 1066–1067, 1067*f*
Pleomorphic liposarcoma, histopathology of, 1074–1075, 1074*f*
Pleomorphic mitochondria, hibernoma and, 1070
Pleomorphic peripheral T-cell lymphoma, histopathology of, 124
Pleomorphic rhabdomyosarcoma, 1085
Pleomorphism, fibroma of tendon sheath, 982
PLEVA. *See* Pityriasis lichenoides et varioliformis acuta
Plexiform fibrohistiocytic tumor, 977
  differential diagnosis of, 977
  histogenesis of, 977
  histopathology of, 125, 977, 977*f*
Plexiform fibrous histiocytoma (PFH)
  giant cell angioblastoma v., 1039
  neurofibromatosis v., 1115
  neurothekeoma v., 1130
Plexiform granular cell nerve sheath tumor, histopathology of, 125
Plexiform neuroma, neurofibromatosis v., 1115
Plexiform schwannoma, 1120–1121
  histopathology of, 125, 1120–1121, 1120*f*
  intraneural plexiform neuroma v., 1136
  neurofibromatosis v., 1115
Plexiform spindle cell nevus. *See* Deep penetrating nevus
Pluripotential cells, of hair matrix, 28
Plywood fibroma. *See* Sclerotic fibroma
PMLE. *See* Polymorphic light eruption
PMS. *See* Psammomatous melanotic schwannoma
PNE. *See* Peripheral neuroepithelioma
PNET. *See* Primitive neuroepithelial tumors
Pneumocystis carinii, in HIV, 660
Pneumonitis, with minocycline pigmentation, 324
PNGD. *See* Palisaded neutrophilic and granulomatosis
PNL2 immunostain, for melanocyte labeling, 16–17, 16*t*
PNP. *See* Paraneoplastic pemphigus
PO protein, granular cell nerve sheath tumor and, 1131
Podophyllum resin, changes induced by, 657
POEMS syndrome, 684
  glomeruloid hemangioma with, 1010
Poikiloderma atrophicans vasculare, 295, 296*f*
  histopathology of, 108, 110, 295, 296*f*
Poikiloderma congenitale, 143–144
  histopathology of, 143–144, 144*f*
  poikiloderma atrophicans vasculare and, 295
Poikiloderma parapsoriasis, poikiloderma atrophicans vasculare and, 295
Poikiloderma vasculare atrophicans, 941
  Hartnup's disease v., 408–409
  histopathology of, 112
Poikiloderma, with dermatomyositis, 293
Polariscopic examination, 69–70, 70*f*
Polarized epidermis, histopathology of, 114
Polyarteritis nodosa (PAN), 209–211, 211*f*
  Behçet's syndrome v., 414
  Churg-Strauss syndrome v., 214
  clinical features of, 209–210
  Crohn's disease v., 416
  differential diagnosis of, 210–211
  giant cell arteritis v., 208
  with hepatitis B, 660–661
  histopathology of, 111, 116, 210
  microscopic polyarteritis v., 212
  pathogenesis of, 211
  subcutaneous, 517–518
    clinical presentation of, 517–518
    differential diagnosis of, 518
    histopathology of, 518, 518*f*
  superficial thrombophlebitis v., 209
  Takayasu's arteritis v., 208
  thrombophlebitis v., 518
Polyarthralgia, fibroblastic rheumatism and, 307
Polyarthritis
  bowel-associated dermatosis-arthritis syndrome and, 412
  fibroblastic rheumatism and, 307
  of reticulohistiocytosis, 675
Polychondritis, with pseudocyst of the auricle, 494
Polycythemia rubra vera
  eosinophilic fasciitis and, 303
  eosinophilic pustular folliculitis and, 466
Polydimethylsiloxane, reactions to, 378–379
Polyketide mycolactone, 558
Polymerase chain reaction (PCR)
  of mycobacterial DNA, 553
  of nail fungi, 595
Polymethylmethacrylate, reactions to, 378–379
Polymorphic light eruption (PMLE), 333–335, 334*f*
  actinic prurigo v., 335–336
  chilblains v., 355
  differential diagnosis of, 335
  discoid lupus erythematosus v., 282–283
  histopathology of, 108, 114–115, 333–334, 334*f*
  Jessner's lymphocytic infiltration of the skin v., 291
  pathogenesis of, 334–335
Polymorphous drug eruption, histopathology of, 107
Polymyalgia rheumatica
  alopecia areata and, 475
  with reactive angioendotheliomatosis, 1008
Polymyositis, dermatomyositis v., 293
Polypoid dermal nevi, histopathology of, 106
Polypoid melanoma, 749, 756
  histopathology of, 106
Polysaccharides, PAS for, 68
Polyvinyl chloride, scleroderma and, 296
POMC. *See* Pro-opiomelanocortin
Pork tapeworm, subcutaneous cysticercosis, 632, 632*f*
Porocarcinoma. *See also* Malignant eccrine poroma
  histopathology of, 123
Porokeratosis, 139–141, 140*f*
  differential diagnosis of, 140–141
  forms of, 139
  histopathology of, 105, 108, 139–140, 140*f*
  pathogenesis of, 140
Porokeratosis plantaris, palmaris, et disseminata, 139
Porokeratotic eccrine duct nevus, histopathology of, 103
Porokeratotic eccrine ostial, 793
  histopathology of, 793
Porphyria(s), 431–435, 432*t,* 433*f*–434*f*
  erythropoietic, 431, 432*t*
  erythropoietic protoporphyria, 432, 432*t*
  hereditary coproporphyria, 433
  histopathology of, 433–434, 434*f*
  hydroa vacciniforme v., 337
  lipoid proteinosis v., 431
  macular atrophy and, 400
  pathogenesis of, 434–435
  polymorphic light eruption v., 335
  pseudoporphyria cutanea tarda, 435
  variegata, 432, 432*t*
Porphyria cutanea tarda (PCT), 432–433, 432*t*
  drug-induced pseudoporphyria v., 320–321
  familial form, 433
  hepatitis and, 419
  hepatitis C with, 661
  hepatoerythropoietic form, 433
  histopathology of, 93, 93*f,* 112, 114, 116, 121, 433–434, 434*f*
  in HIV, 660
  milia and, 802
  nephrogenic systemic fibrosis and, 301
  pathogenesis of, 434–435
  scleroderma and, 296
  sporadic form, 432–433
Porphyria variegata, 432, 432*t*
  histopathology of, 433–434, 434*f*
  pathogenesis of, 434–435
Port-wine stain. *See* Nevus flammeus
Post perioral dermabrasion, eczema herpeticum with, 638
Postchemotherapy hyperpigmentation, histopathology of, 107, 322
Postinflammatory elastolysis and cutis laxa, 399
Postinflammatory hyperpigmentation, histopathology of, 87, 87*f,* 91, 91*f,* 104, 107, 111
Postinflammatory pigmentary alteration, 690–691, 691*f*
  histopathology of, 691, 691*f*
Postinflammatory pigmentation, histopathology of, 89, 89*f*
Postinjury ossification, 1090–1093, 1091*f*–1092*f*
  histopathology of, 1092*f,* 1093
Postirradiation angiosarcoma, 1041
Post-kala-azar dermal leishmaniasis, 621, 622*t,* 624
  histopathology of, 624

Postmenopausal frontal fibrosing alopecia, 488–489
histopathology of, 128, 488, 488*f*
pathogenesis of, 488–489
Postoperative/posttraumatic spindle cell nodule, 984
Poststeroid panniculitis, histopathology of, 130
Postvaccinial encephalitis, 647
Potassium, eccrine glands and, 35
Poxviridae, 637, 646–649, 648*f*–649*f*
human cowpox infection, 647
molluscum contagiosum, 649, 649*f*
parapoxvirus infections, 647–648, 648*f*
vaccinia virus, 647
variola, 647
PPARs. *See* Peroxisomal proliferator activator receptors
PPB. *See* Pseudopelade of Brocq
PPD. *See* Pigmented purpuric dermatosis
PR. *See* Progesterone receptor
Precursor B-cell acute lymphoblastic lymphoma (B-ALL), precursor B-cell lymphoblastic lymphoma as, 923
Precursor B-cell lymphoblastic lymphoma (B-LBL), 922–925
clinical features of, 923–924
differential diagnosis of, 919*t*–920*t*, 924*f*, 925
histogenesis of, 924–925, 924*f*
histopathology of, 924, 924*f*
Precursor plasmacytoid dendritic cell lineage, 959–960
clinical features of, 960
differential diagnosis of, 960
histogenesis of, 960
histopathology of, 960
Pregnancy, striae distensae and, 398
Premalignant tumors, description of, 791
Prepubertal melanoma, 761–762
Prepuce
eccrine glands of, 35
lichen sclerosus et atrophicus and, 303
mucocutaneous end-organs in, 54
Pretibial mucinosis, pretibial myxedema v., 442
Pretibial myxedema, 441–442, 441*f*–442*f*
differential diagnosis of, 442
histopathology of, 121, 441–442, 442*f*
pathogenesis of, 442
Pretibial pigmented patches in diabetes, histopathology of, 104
Primary adrenal carcinomas, xanthelasma v., 682
Primary biliary cirrhosis, 417–418, 418*f*
histopathology of, 417, 418*f*
pathogenesis of, 417–418
pyoderma gangrenosum with, 411
Primary carcinoids, 1151, 1157
Primary cutaneous aggressive CD8-positive T-cell lymphoma, 949–950
clinical features of, 950
differential diagnosis of, 950
histogenesis of, 950
histopathology of, 950
Primary cutaneous anaplastic large cell lymphoma (PC-ALCL), 945–947
anaplastic large cell lymphoma v., 952
primary cutaneous aggressive CD8-positive T-cell lymphoma v., 950
Primary cutaneous B-cell lymphoproliferative disease
B-cell lymphomatoid hyperplasia, 195*f*, 196*t*, 197*f*, 915–916
exogenous plasmacytoma, 922
primary cutaneous diffuse large B-cell lymphoma
leg type, 921–922
other, 922
primary cutaneous follicle center lymphoma, 917–920, 918*f*–919*f*, 919*t*–920*t*
primary cutaneous marginal zone lymphoma, 920–921, 921*f*
Primary cutaneous CD4-positive small-/medium-sized pleomorphic T-cell lymphoma, 950
Primary cutaneous CD30-positive T-cell lymphoproliferative disorders, 945–947
clinical features of, 945
differential diagnosis of, 946–974
histogenesis of, 946, 947*f*
histopathology of, 946, 946*f*
Primary cutaneous cryptococcosis, 609
Primary cutaneous diffuse large B-cell lymphoma (PCLBCL)
leg type, 921–922
clinical features of, 921
differential diagnosis of, 920*t*, 922
histogenesis of, 921–922
histopathology of, 921
other, 922
Primary cutaneous follicle center lymphoma (PCFCL), 917–920
B-cell lymphomatoid hyperplasia v., 916, 919
clinical features of, 917–918, 918*f*
differential diagnosis of, 919–920, 919*t*–920*t*
histogenesis of, 918–919, 919*f*
histopathology of, 918, 918*f*
mantle cell lymphoma v., 928
nodal follicular lymphoma v., 927–928
primary cutaneous diffuse large B-cell lymphoma, leg type v., 922
Primary cutaneous inoculation blastomycosis, 603
Primary cutaneous inoculation coccidioidomycosis, 608–609
Primary cutaneous inoculation histoplasmosis, 611
Primary cutaneous marginal zone lymphoma (PCMZL), 920–921
B-cell lymphomatoid hyperplasia v., 919
clinical features of, 920–921
differential diagnosis of, 919*t*, 921
histogenesis of, 921
histopathology of, 921, 921*f*
Primary cutaneous myeloid hyperplasia/neoplasia
extramedullary hematopoiesis, 956–957
myeloid sarcoma, 957
Primary cutaneous peripheral T-cell lymphoma (PTCL), 949
clinical features of, 949
differential diagnosis of, 949
histogenesis of, 949
histopathology of, 949
primary cutaneous CD4-positive small-/medium-sized pleomorphic T-cell lymphoma v., 950
Primary cutaneous signet ring cell carcinoma, 1153–1154
Primary cutaneous T-cell lymphoproliferative disease, 935–936
T-cell lymphomatoid hyperplasias, 935–936, 935*f*
Primary cutaneous zygomycosis, 599–601
Primary effusion lymphoma, human herpesvirus in, 646
Primary HSV-2 infection, transmission of, 639
Primary lesion
of endemic syphilis, 585
of pinta, 584–585
of yaws, 583–584, 584*f*
Primary mucinous carcinoma of the skin, 1153–1154
Primary pulmonary histoplasmosis, 611
Primary syphilis, 579–581, 580*f*–581*f*
differential diagnosis of, 581
histogenesis of, 581
Primary systemic amyloidosis, 425–427, 426*f*
histopathology of, 425–426, 426*f*
multiple myeloma relationship with, 426
pathogenesis of, 426–427
scleroderma and, 296
Primary tuberculosis, 550–551, 551*f*
histopathology of, 551, 551*f*
Primary varicella pneumonia, 642
Primary yaws, 583
Primitive neuroectodermal tumors, 1140–1141
Ewing's sarcoma and peripheral neuroepithelioma, 1140–1141
melanotic neuroectodermal tumor of infancy, 1141
Primitive neuroepithelial tumors (PNET), histopathology of, 122
Pristinamycin, acute generalized exanthematous pustulosis with, 314
Procainamide, drug-induced lupus erythematosus with, 318
Processing, of specimen, 68
Profundus, histopathology of, 131
Progeria of the adult. *See also* Werner's syndrome
scleroderma and, 295–296
Progesterone receptor (PR), PUPPP and, 170
Progressive cribriform and zosteriform hyperpigmentation, 689
Progressive lymphangioma, 1045
differential diagnosis of, 1045
histopathology of, 126, 1045, 1046*f*
Progressive macular hypopigmentation, 691
histogenesis of, 691
histopathology of, 691
Progressive nodular histiocytoma, histopathology of, 124–125
Progressive nodular histiocytosis, 676*f*, 677
benign cephalic histiocytosis v., 678
differential diagnosis of, 677
histopathology of, 677
Progressive pigmented purpura, histopathology of, 107
Progressive symmetric erythrokeratodermia. *See* Erythrokeratodermia variabilis
Progressive systemic sclerosis, malignant atrophic papulosis and, 232
Progressive vaccinia, 647
Proliferating pilar tumor. *See* Proliferating trichilemmal cyst
Proliferating trichilemmal cyst, 866–867
additional studies of, 867
differential diagnosis of, 867
histopathology of, 866–867, 867*f*
with nevus sebaceus, 871–872
Proliferating trichilemmal, histopathology of, 123
Proliferations, histiocytoses v., 668
Proliferative fasciitis, 984
Proliferative nodules, in congenital nevi, 729
Proliferative reactions, in LCD, 669
Prolymphocytes, in chronic lymphocytic lymphoma/small lymphocytic lymphoma, 926
Promastigote stage, of *Leishmania,* 621
Pro-opiomelanocortin (POMC), melanin and, 18
Propionibacterium acnes
acne vulgaris and, 459–461
hypopigmentation with, 691
Propylthiouracil, drug-induced lupus erythematosus with, 318
Prosector's wart, 551*f*
Prostate-specific antigen, 1158
Protease inhibitors, cutaneous manifestations of, 324
Protease, neutral, of azurophilic granules, 43
Protease secretion, by hookworm-related cutaneous larva migrans, 628
Proteinase 3, c-ANCAs for, 207, 207*t*
Proteinases, pemphigus vulgaris and, 249
Proteoglycans, systemic scleroderma and, 300–301
Proteus syndrome, 1062
Protoporphyrin, erythropoietic protoporphyria and, 432
Prototheca infections, 615–616, 616*f*
Protothecosis, 591, 615–616, 616*f*
histopathology of, 118–119, 132

Protozoan infection, 621–625
  acanthamoebiasis, 625, 625*f*
  erythema nodosum with, 514
  leishmaniasis, 621–625, 622*t,* 623*f*–624*f*
    chronic cutaneous leishmaniasis, 621, 623–624
    diffuse (acute) cutaneous leishmaniasis, 621–623, 622*t,* 624*f*
    localized (acute) cutaneous leishmaniasis, 621–622, 622*t,* 623*f*
    mucocutaneous leishmaniasis, 621, 622*t,* 624
    Post-kala-azar dermal leishmaniasis, 621, 622*t,* 624
    visceral leishmaniasis, 621, 622*t,* 624–625
    viscerotropic leishmaniasis, 621, 622*t,* 625
Proximal subungual onychomycosis (PSO), 593
Prurigo nodularis
  acquired perforating dermatosis v., 396
  actinic prurigo v., 336
  differential diagnosis of, 174
  hepatitis C with, 661
  histopathology of, 90, 90*f,* 106, 109–110, 173–174, 173*f*
  pathogenesis of, 174
  with strongyloidiasis, 628
Prurigo simplex
  differential diagnosis of, 173
  histopathology of, 115, 173
Pruritic and urticarial papules and plaques of pregnancy (PUPPP), 170
  histopathology of, 115, 170
  pathogenesis of, 170
Pruritic papular eruption, in HIV, 659
Pruritus
  acquired perforating dermatosis and, 396
  burns and, 343
  nephrogenic systemic fibrosis and, 301
Pruritus secondary to liver disease, acquired perforating dermatosis with, 396
Psammoma bodies, 1157
Psammomatous malignant schwannoma, histopathology of, 125
Psammomatous melanocytic schwannoma, pigmented epithelioid melanocytoma and, 757
Psammomatous melanotic schwannoma (PMS), 1121
Pseudallescheria boydii, 614
Pseudocarcinomatous hyperplasia, 822–823. *See also* Pseudoepitheliomatous hyperplasia
  of blastomycosis-like pyoderma, 546
  differential diagnosis of, 823
  histopathology of, 822–823, 823*f*
  in sarcoidosis, 373
  squamous cell carcinoma v., 821
Pseudocyst of the auricle, 494, 494*f,* 1100, 1100*f*
  histopathology of, 125, 494, 494*f*
  pathogenesis of, 494
Pseudoepitheliomatous hyperplasia
  of blastomycosis, 604, 605*f*
  with botryomycosis, 573, 573*f*
  of chromomycosis, 607, 607*f*
  histopathology of, 95, 95*f,* 106, 110, 118
  of nodular melanoma, 750
  of paracoccidioidomycosis, 606, 606*f*
Pseudofollicles, in chronic lymphocytic lymphoma/small lymphocytic lymphoma, 926
Pseudofolliculitis of the beard, 544
  histopathology of, 128, 544
Pseudogout, calciphylaxis and, 230
Pseudohyphae, 591, 592*t*
Pseudohypoparathyroidism (PHP), 1086
Pseudolymphoma syndrome, drug-induced, 320, 320*f*
Pseudolymphomatous infiltrate, of scabies, 627
Pseudolymphomatous tattoo reaction, histopathology of, 122
Pseudomaturation, in nodular melanoma, 751
Pseudomelanoma. *See* Recurrent nevus
Pseudomonas aeruginosa
  folliculitis with, 543
  neutrophilic eccrine hidradenitis, 491
  in *Pseudomonas* septicemia, 547–548
Pseudomonas cepacia, in *Pseudomonas* septicemia, 547–548
Pseudomonas folliculitis, 542–543
  histopathology of, 128, 543
  neutrophilic eccrine hidradenitis, 491
  pathogenesis of, 543
Pseudomonas hot-foot syndrome, 491–492
Pseudomonas septicemia, 547–548, 547*f*
  histopathology of, 547–548, 547*f*
Pseudomonas sp., nail infections of, 507
Pseudo-ochronosis, 439–440
Pseudopelade of Brocq (PPB), 483–485, 483*f*
  histopathology of, 128, 484–485, 484*f*
  pathogenesis of, 485
Pseudoporphyria
  direct immunofluorescence for, 71
  drug-induced, 320–321
  histogenesis of, 321
  histopathology of, 320
Pseudoporphyria cutanea tarda, 435
  histopathology of, 435
  pathogenesis of, 435
Pseudopseudohypoparathyroidism, 1086
Pseudopyogenic granuloma, 1023
Pseudorheumatoid nodules, 367
  histopathology of, 131
Pseudorosettes, of cutaneous small cell undifferentiated carcinoma, 1138–1139
Pseudosclerodermatous plaques, of Lyme disease, 586–587
Pseudovasculitis, 206, 228–233, 229*t*
  calciphylaxis, 230, 230*f*
  coagulopathies and vascular thrombosis, 228–230, 229*f*
  connective tissue deficiencies, 231
  cutaneous cholesterol embolism, 230–231
  metabolic vasculopathies, 230
Pseudoxanthoma elasticum (PXE), 152–154, 153*f,* 1166*f*
  connective tissue nevus v., 154
  differential diagnosis for, 154
  elastosis perforans serpiginosa and, 394
  histogenesis of, 154
  histopathology of, 96, 96*f,* 120, 153–154, 153*f*
  late-onset focal dermal elastosis v., 397
  linear focal elastosis and, 398
  papillary dermal elastolysis v., 399
  perforating calcific elastosis v., 396
  solar elastosis v., 390
Psittacosis, erythema nodosum with, 514
PSO. *See* Proximal subungual onychomycosis
Psoralen and ultraviolet A-induced (PUVA) pigment alterations, 691–692
  histogenesis of, 692
  histopathology of, 692
Psoralen photochemotherapy (PUVA)
  for actinic prurigo, 335
  for hydroa vacciniforme, 337
  for PMLE, 333
  for solar lentigines, 707
  for solar urticaria, 340
Psoralens, phototoxic drug eruption and, 319
Psoriasiform dermatitis, histopathology of, 109
  histopathology of, 90, 90*f*
Psoriasiform drug eruptions
  histopathology of, 109
  secondary syphilis v., 583
Psoriasiform epidermal hyperplasia
  chancre v., 581
  of syphilis, 581, 581*f*–582*f*
  with syringolymphoid hyperplasia, 491
Psoriasiform inflammation, verruciform xanthomas with, 685
Psoriasiform mycosis fungoides, 941–942, 941*f*
Psoriasiform plaques
  with mycosis fungoides palmaris et plantaris, 942
  of pinta, 585
Psoriasis, 174–181. *See also* Localized pustular psoriasis
  AIDS and, 175
    histopathology of, 179
    pathogenesis of, 180–181
  celiac disease and, 417
  chronic spongiotic dermatitis and, 244
  generalized pustular, 174–175
    clinical features of, 174–175
    histopathology of, 178, 178*f*
  histopathology of, 105, 109, 129
  in HIV, 660
  localized pustular, 175, 175*f*
    clinical features of, 175, 175*f*
    histopathology of, 178–179
    pathogenesis of, 180
  of the nail, 504–505, 504*f*
  neutrophils and, 43
  pellagra v., 451
  pityriasis rubra pilaris v., 195–196
  seborrheic dermatitis and, 243
  secondary syphilis v., 583
  Sézary syndrome v., 944
  T cells in, 913
  transient acantholytic dermatosis with, 273
  vulgaris, 174, 174*f*
    clinical features of, 174, 174*f*
    differential diagnosis of, 181
    histopathology of, 90, 90*f,* 109, 175–178, 176*f*–178*f*
    pathogenesis of, 179–180
Psoriasis vulgaris
  clinical features of, 174, 174*f*
  differential diagnosis of, 181
  histopathology of, 90, 90*f,* 109, 175–178, 176*f*–178*f*
  pathogenesis of, 179–180
    electron microscopy, 179
    epidermal cell cycle kinetics, 179–180
    immunohistopathology, 180
    keratinocyte differentiation, 180
Psoriatic arthritis, psoriasis vulgaris with, 174, 174*f*
Psychodopygus, as leishmaniasis vector, 621
Psychotropics, drug-induced pigmentary alterations of, 692
Pt OCA, 693
PTCL. *See* Primary cutaneous peripheral T-cell lymphoma
Pulmonary blastomycosis, 604
Pulmonary coccidioidomycosis, 608–609
Pulmonary dirofilariasis, 628
Pulmonary disease
  mixed connective tissue disease with, 292
  tattoo reactions and, 378
Pulmonary emboli, systemic lupus erythematosus and, 288
Pulmonary fibrosis, eosinophilic fasciitis and, 303
Pulmonary LCD, 671
Pulmonary sporotrichosis, 613
Pulmonary symptoms, of strongyloidiasis, 628
Pulmonary vasculitis, ulcerative colitis with, 416
Punch biopsy
  for alopecia, 470–472, 471*f*
  for direct immunofluorescence, 71
  for inflammatory dermatoses, 5

Punch biopsy (*continued*)
of melanoma, 762
of nail unit, 503
for senescent alopecia, 489
Punctate porokeratosis, 139
PUPPP. *See* Pruritic and urticarial papules and plaques of pregnancy
Purple manganese, tattoo reactions and, 377
Purpura, 275
acute generalized exanthematous pustulosis with, 314–315
of hepatitis C, 661
of strongyloidiasis, 628
Purpura pigmentosa chronica, histopathology of, 116
Pustular dermatophytosis, psoriasis vulgaris v., 181
Pustular disorders, 85
intraspinous keratinocyte separation
acantholytic, 92, 92*f*
spongiotic, 92, 92*f*
subcorneal or intracorneal separation, 92, 92*f*
subepidermal vesicular dermatitis, 93, 93*f*
suprabasal keratinocyte separation, 93, 93*f*
Pustular drug eruption
histopathology of, 109
psoriasis vulgaris v., 181
Pustular eruptions, of blastomycosis, 605*f*
Pustular lesions, of secondary syphilis, 582
Pustular mycosis fungoides, 942
Pustular psoriasis
acute generalized exanthematous pustulosis v., 315
histopathology of, 92, 92*f,* 109, 113
lingua geographica v., 795
subcorneal pustular dermatosis v., 268
Pustular secondary syphilis, histopathology of, 109
Pustular vasculitides, bowel-associated dermatosis-arthritis syndrome v., 412
Pustules
of acne vulgaris, 459, 460*f*
of acute mucocutaneous candidiasis, 597–598
folliculitis decalvans and, 487
of Kaposi's varicelliform eruption, 642
with mycosis fungoides palmaris et plantaris, 942
of rosacea, 463
of steroid acne, 461, 461*f*
Pustulosis palmaris et plantaris, 175, 175*f,* 178
PUVA. *See* Psoralen photochemotherapy
PUVA lentigines, 692, 707
PUVA pigment alterations. *See* Psoralen and ultraviolet A-induced pigment alterations
PXE. *See* Pseudoxanthoma elasticum
Pycnodystosis, acro-osteolysis and, 401
Pyoderma gangrenosum (PG), 411–412, 411*f,* 535
Behçet's syndrome and, 413–414
bowel-associated dermatosis-arthritis syndrome v., 413
Crohn's disease with, 415–416
differential diagnosis of, 411–412
hepatitis and, 419
hepatitis C with, 661
histopathology of, 95, 95*f,* 115, 117, 120, 128, 131, 224, 225*f,* 411, 411*f*
neutrophils and, 43
pathogenesis of, 412
pseudocarcinomatous hyperplasia and, 822
sclerosing cholangitis with, 417
Takayasu's arteritis v., 208
ulcerative colitis with, 416–417, 416*f*
Pyoderma vegetans. *See also* Blastomycosis-like pyoderma
histopathology of, 118
pemphigus vegetans v., 250
Pyodermite végétante of Hallopeau. *See* Blastomycosis-like pyoderma
Pyogenic granuloma, 1016–1019, 1016*f*
differential diagnosis of, 1018–1019, 1018*f*
epithelioid dermatofibroma v., 973–974
graft-*versus*-host disease and, 271
histopathology of, 98, 98*f,* 126, 1017, 1017*f*
Kaposi's sarcoma v., 1035
pathogenesis of, 1017–1018
Pyostomatitis vegetans, Crohn's disease with, 415
Pyrazinamide, pellagra and, 408
Pyridoxine, drug-induced pseudoporphyria with, 320

Quinacrine, lichenoid drug eruption and, 313
Quinidine
dermatomyositis and, 294
drug-induced lupus erythematosus with, 318
lichenoid drug eruption and, 313
Quinine, photoallergic drug eruption and, 318
Quinolones
acute generalized exanthematous pustulosis with, 314
phototoxic drug eruption and, 319

Radial growth phase melanoma. *See also* Nontumorigenic melanoma
definition of, 741, 741*f*–742*f*
Radiation dermatitis
acute, histopathology of, 114
burns v., 346
differential diagnosis of, 352
grades of, 348–349
histopathology of, 90, 90*f,* 108, 112, 349–352, 349*f*–351*f*
Radiation fibrosis, histopathology of, 120
Radiation recall dermatitis, 352
histopathology of, 352
Radiation therapy, for verrucous carcinoma, 822
Radiation-induced malignancies, 351–352
Radiation-induced skin alterations, 348–352
acute, subacute, and chronic radiation dermatitis, 348–352, 349*f*–351*f*
radiation recall dermatitis, 352
Rapidly involuting congenital hemangiomas (RICH), 1013
differential diagnosis of, 1013
histopathology of, 1013, 1013*f*
Rashes
of Epstein-Barr virus, 644–645
of erythema chronicum migrans, 586
with hepatitis B, 661
herpes simplex, 638
of herpes zoster, 643, 643*f*
in HIV, 659
of measles, 662
with minocycline pigmentation, 324
of parvovirus B19, 662
polyarteritis nodosa and, 210
of rickettsial infections, 568
of rubella, 662
of syphilis, 580
of varicella, 642, 642*f*
of variola, 647
Raynaud's phenomenon, 220
with acro-osteolysis, 401
with chilblains, 353
eosinophilic fasciitis and, 303
fibroblastic rheumatism and, 307
mixed connective tissue disease with, 292
of nail unit, 506
systemic scleroderma and, 299
Reactive angioendotheliomatosis, 1008–1010
differential diagnosis of, 1009–1010
histogenesis of, 1009
histopathology of, 1008–1009, 1009*f*
Reactive hemophagocytic lymphohistiocytosis. *See* Macrophage activation syndrome
Reactive lymphoid hyperplasia, Hodgkin's lymphoma v., 935
Reactive perforating collagenosis (RPC), 395
acquired perforating dermatosis v., 396
differential diagnosis of, 393*t,* 395
histogenesis of, 395
histopathology of, 120, 395, 395*f*
Rectal mucosa, oral white sponge nevus in, 794
Recurrent cutaneous leishmaniasis. *See* Leishmaniasis recidivans
Recurrent infantile digital fibromatosis, histopathology of, 125
Recurrent infection, of HSV, 639
Recurrent melanocytic nevi, histopathology of, 105
Recurrent melanoma, recurrent nevus v., 732
Recurrent nevus, 732–733
histogenesis of, 733
histopathology of, 732–733, 733*f*
superficial spreading melanoma v., 744
Reed-Sternberg cells
in Hodgkin's lymphoma, 933–934
in inflammatory pseudotumor, 994
Refsum's syndrome, 137
Regressed pigmented lesion, histopathology of, 107
Regressed primary melanoma, 767
Regressive fibrosis, recurrent nevus v., 732
Reiter's disease, 181–182, 181*f*
differential diagnosis of, 182
histopathology of, 109, 113, 182
in HIV, 660
pathogenesis of, 182
Relapsing chronic cutaneous leishmaniasis. *See* Leishmaniasis recidivans
Relapsing febrile nodular nonsuppurative panniculitis. *See* Weber-Christian disease
Relapsing polychondritis (RP), 493–494
Behçet's syndrome v., 414
histopathology of, 120, 494
lymphocytoma cutis v., 588
pathogenesis of, 494
REM. *See* Reticulated erythematous mucinosis
Remicade. *See* Infliximab
Renal cell carcinoma, balloon cell melanoma v., 756
Renal cell, metastatic carcinoma of skin, 1156–1157
histopathology of, 1156, 1157*f*
immunoperoxidase studies, 1156–1157
Renal disease
calcifying panniculitis with, 531
with reactive angioendotheliomatosis, 1008
Renal vascular thrombosis, systemic lupus erythematosus and, 288
Reoviridae, 637
Resection, for melanoma, 769–770
Resorcinol, ochronosis and, 440
Rete ridges
acanthoma fissuratum and, 357
acrokeratosis verruciformis of Hopf and, 152
with Becker's melanosis, 706
in Bowen's disease, 814
dermatitis herpetiformis and, 263
dermatofibroma and, 969
discoid lupus erythematosus and, 280
in dysplastic nevus, 735
epidermolytic hyperkeratosis in, 793
graft-*versus*-host disease and, 272
ILVEN and, 194
intraepidermal eccrine duct from, 32, 33*f*
in junctional nevus, 712
lichen nitidus and, 192
linear epidermal nevus and, 791
Merkel cells at, 18, 19*f*

with nevi of acral skin, 715
poikiloderma atrophicans vasculare and, 295
psoriasis vulgaris and, 176–177, 176*f,* 181
with solar lentigines, 707
Reticular degeneration, 235
of hand-foot-and-mouth disease, 658, 658*f*
in herpes simplex infection, 640, 640*f*
of human cowpox infection, 647
of Kaposi's varicelliform eruption, 642
of variola, 647
Reticular dermis
apocrine nevus in, 876
collagen fibers and, 47
compound nevus and, 713
inflammation of, 85
linear focal elastosis in, 398
morphea and, 297
neoplastic nodules and cysts of, 85
deposition of material in, 96, 96*f,* 121
dermal matrix fiber disorders, 96, 96*f,* 120–121
diffuse infiltrates of, 94, 94*f,* 117–118
diffuse or nodular infiltrates with epidermal proliferation, 95, 95*f,* 118–120
nodular inflammatory infiltrates of, 95, 95*f*
superficial and deep perivascular infiltrates, 93, 93*f,* 115–116
vasculitis and vasculopathies, 94, 94*f,* 116
nephrogenic systemic fibrosis and, 316
PLEVA and, 196
recurrent nevus in, 732
solar elastosis and, 389
of trunk, 56, 57*f*
Reticular erythematous mucinoses, 444–445, 444*f*–445*f*
differential diagnosis of, 445
histopathology of, 444–445, 445*f*
Reticulate acropigmentation of Kitamura, 689–690
Reticulate erythema, middermal elastolysis and, 399
Reticulate pigmentary anomalies, 689–690
histogenesis of, 690
histopathology of, 689–690
Reticulated erythematous mucinosis (REM), histopathology of, 115, 121
Reticulated hyperpigmentations, histopathology of, 104, 109
Reticulated lentigo, 706
Reticulated papillomatosis, 449, 449*f*
histogenesis of, 449
histopathology of, 106, 449
Malassezia furfur in, 596
Reticulated seborrheic keratosis, 797–798
Reticulated vesicles, of parapoxvirus infections, 648*f*
Reticulin, dermatitis herpetiformis and, 265
Reticuloendothelial system, mononuclear phagocytic system and, 40
Reticulohistiocyte, 671
Reticulohistiocytic granuloma, histopathology of, 117
Reticulohistiocytosis, 675–676, 676*f*
differential diagnosis of, 676
histopathology of, 675, 676*f*
pathogenesis of, 676
Reticulum fibers
collagen fibers and, 47
cross-striations of, 49
Reticulum stain, for sarcoidosis, 372
Retiform hemangioendothelioma, 1022, 1035–1036
composite hemangioendothelioma and, 1037, 1037*f*
differential diagnosis of, 1036
histopathology of, 126, 1036, 1036*f*
hobnail hemangioma v., 1022
Retiform perineurioma, 1134
Retina, tuberous sclerosis in, 989
Retinoids, hyperlipidemia from, 680
Retroperitoneal melanoma, 726
Retroviridae, 637, 659–660
acquired immunodeficiency syndrome, 659–660
Reversal reactions, 564, 564*f,* 566
Reye's syndrome, 642
RGP regression, 766
Rhabdomyoblasts, melanoma in congenital nevi and, 728
Rhabdomyoma, 1083–1084, 1083*f*
differential diagnosis of, 1084
hibernoma v., 1070
histopathology of, 1083*f,* 1084
Rhabdomyomatous mesenchymal hamartoma, 1083
differential diagnosis of, 1083
histopathology of, 1083
Rhabdomyosarcoma, 1084–1085
differential diagnosis of, 1085
histogenesis of, 1085
histopathology of, 122, 126, 1084–1085, 1084*f*–1085*f*
malignant peripheral nerve sheath tumor v., 1125
Rheumatic fever, rheumatoid nodules and, 368
Rheumatic nodule, histopathology of, 119
Rheumatoid arthritis
alopecia areata and, 475
Behçet's syndrome v., 414
chilblains v., 353
Crohn's disease v., 416
erythema elevatum diutinum v., 222
histopathology of, 111–112
leukocytoclastic vasculitis and, 220
middermal elastolysis and, 399
palisaded granulomatous panniculitis with, 524–525
palisaded neutrophilic and granulomatosis with, 368–369
pyoderma gangrenosum with, 411
with reactive angioendotheliomatosis, 1008
with relapsing polychondritis, 493
reticulohistiocytosis v., 676
rheumatoid nodules with, 367–368, 368*f*
Rheumatoid factor, rheumatoid nodules with, 367
Rheumatoid neutrophilic dermatosis, histopathology of, 115, 117
Rheumatoid nodules, 367–368, 368*f*
differential diagnosis of, 368
granuloma annulare v., 361, 364
histopathology of, 118, 130, 131, 367–368, 368*f*
necrobiotic xanthogranuloma with paraproteinemia v., 684
palisaded granulomatous panniculitis with, 524–525
pathogenesis of, 368
Rheumatoid nodulosis, 367
Rheumatoid papules. *See* Palisaded neutrophilic and granulomatosis
Rhinocerebral zygomycosis, 599
Rhinocladiella aquaspersa, 607
Rhinophyma
histopathology of, 124
rosacea and, 463–464
sebaceous hyperplasia v., 872
Rhinoscleroma, 570–571, 571*f*
differential diagnosis, 571
granuloma inguinale v., 570
histopathology of, 117, 119, 570–571, 571*f*
histoplasmosis v., 312
plasma cells and, 46
Rhinosporidiosis, 600*t,* 615, 616*f*
differential diagnosis of, 615
histopathology of, 117–118, 615, 616*f*
Rhinosporidium seeberi, 615
Rhizopus infection, 599
Rhodococcus equi, malakoplakia with, 549
Ribonucleoprotein particles, keratohyaline granules and, 12
RICH. *See* Rapidly involuting congenital hemangiomas
Richner-Hanhart syndrome. *See* Oculocutaneous tyrosinosis
Richter syndrome, small lymphocytic lymphoma and, 925
Rickettsia conorii, 568, 568*f*–569*f*
Rickettsia rickettsii, 568
histopathology of, 116
Rickettsial infections, 568–569, 568*f*–569*f*
histopathology of, 568–569, 568*f*–569
leukocytoclastic vasculitis and, 217
sarcoidosis and, 372
Ritter's disease. *See* Staphylococcal scalded skin syndrome
RMSF. *See* Rocky Mountain spotted fever
Rochalimaea henselae. See Bartonella henselae
Rocky Mountain spotted fever (RMSF), 568
histopathology of, 116
leukocytoclastic vasculitis and, 217
Rodents, as human cowpox infection host, 647
Roentgen rays, basal cell carcinoma and, 824
Root sheath
inner
anatomy of, 26*f*–27*f,* 29
central centrifugal cicatricial alopecia and, 485–486, 485*f*–486*f*
of hair follicles, 25
keratinization of, 28
in steatocystoma multiplex, 803–804
in trichofolliculoma, 854
outer
anatomy of, 27*f,* 30
basal cell carcinoma and, 833
basal cell carcinomas and, 830
central centrifugal cicatricial alopecia and, 486, 486*f*
of hair follicles, 25–26, 26*f*
proliferating trichilemmal cyst, 867
recurrent nevus in, 733
in steatocystoma multiplex, 803–804
in trichofolliculoma, 854
tufted hair folliculitis with, 488
Rosacea, 463–464
Crohn's disease with, 415–416
Demodex folliculorum in, 60
histopathology of, 128, 463–464, 463*f*
lupus miliaris disseminatus faciei v., 465
pathogenesis of, 464
perioral dermatitis v., 462
polymorphic light eruption v., 335
subtypes of, 463
Rosacea-like demodicidosis, 464
Rosai-Dorfman disease, 678–679, 679*f*
histopathology of, 117, 130–131, 678–679, 679*f*
pathogenesis of, 679
Rosettes, 1157
Rothmund-Thomson syndrome. *See also* Poikiloderma congenitale
elastosis perforans serpiginosa and, 394
scleroderma and, 295–296
Round cell liposarcoma, 1072
histopathology of, 1074, 1074*f*
Rowell's syndrome, 286
RP. *See* Relapsing polychondritis
RPC. *See* Reactive perforating collagenosis
Rubella, 662
Rudimentary neuromas, histopathology of, 1135
Rud's syndrome, 136
Rufous OCA, 693
Rupial secondary syphilis, histopathology of, 90, 90*f,* 110, 113
Rupial syphilis, 582

Ruptured cyst, histopathology of, 119, 130–131
Ruptured follicles, histopathology of, 130–131
Russell bodies, plasma cells and, 46

S100 antigen technique
  for dermal microvasculature neural network, 53, 53*f*
  eccrine and apocrine glands and, 32, 34*f,* 36
  for eccrine glands, 34*f*
  Langerhans cells and, 20–21
  for melanocyte labeling, 16, 16*t*
S100 protein
  antibodies against, 76*t,* 77
  chondroid syringoma and, 894
  common blue nevus and, 701
  granular cell epulis of infancy, 1131
  granular cell nerve sheath tumor and, 1131
  halo nevus and, 732
  lipofibromatosis, 1070
  neurothekeoma, 1129
  in nodular hidradenoma, 892
  nodular melanoma and, 752
  peripheral neuroblastoma, 1140
  schwannoma and, 1119
  Spitz nevi and, 722
  storiform perineural cell fibroma, 1132
S100A6 protein, in intradermal nevus, 714
SAA. *See* Serum amyloid A
Saber shin deformities, 584
Salicylates, erythema nodosum with, 515
Salivary gland, cheilitis glandularis and, 381
Salmon patch. *See* Nevus flammeus
Salmonella, Reiter's disease and, 182
Salt-split skin studies
  for anti-p200 pemphigoid, 263
  for bullous pemphigoid, 257–258, 258*f*
  for bullous systemic lupus erythematosus, 263
  for epidermolysis bullosa acquisita, 261
  for linear IgA dermatosis, 265
SAMPUS. *See* Superficial atypical melanocytic proliferation of uncertain significance
Sand flea, as tungiasis vector, 633
Sand flies, as leishmaniasis vector, 621
Sandwich sign, of fungal infections, 595
Sanfilippo's syndrome, mucopolysaccharidosis and, 447
Sarcoidal granulomata
  primary biliary cirrhosis with, 417
  with secondary syphilis, 582
Sarcoidosis, 370–373, 370*f*–372*f*
  Behçet's syndrome v., 414
  berylliosis v., 377
  cheilitis granulomatosa v., 380
  Crohn's disease v., 416
  differential diagnosis of, 372–373
  erythema nodosum with, 514
  with follicular mucinosis, 468
  granuloma annulare and, 361
  histopathology of, 95, 95*f,* 118, 130, 370–372, 371*f*–372*f*
  leprosy v., 566
  lichen scrofulosorum v., 554
  macular atrophy and, 400
  necrobiosis lipoidica v., 366–367
  palisaded granulomatous panniculitis with, 525
  pathogenesis of, 372
  pigmentary presentations of, 692–693
  with reactive angioendotheliomatosis, 1008
  reticulohistiocytosis v., 676
  secondary syphilis v., 583
  silica granuloma v., 376
  systemic lesions of, 372
  tuberculosis v., 553
Sarcomas. *See also* Chordoid sarcoma; Epithelioid sarcoma; Histiocytic sarcoma; Myeloid sarcoma; Spindle cell sarcoma
  acanthosis nigricans and, 448
  nodular fasciitis v., 984
Sarcomatoid carcinoma, 1100
Sarcomatoid malignant melanoma, extraskeletal osteosarcoma v., 1094
Sarcoptes sarcoptes scabiei, 626
Sarcoptes scabiei, nail unit and, 508, 508*f*
Sarcoptes scabiei var. *hominis,* 626
Satellite cell necrosis, graft-*versus*-host disease and, 271
Satellite lesions, of acute mucocutaneous candidiasis, 597
Satellites
  melanoma prognosis and, 768
  metastatic melanoma and, 774–775
Saucerization technique, 5–6
Scabetic nodule, histopathology of, 119
Scabies, 626–627, 626*f*
  acropustulosis of infancy v., 267
  actinic prurigo v., 336
  histopathology of, 100, 100*f,* 108, 129, 626–627, 626*f*
  in HIV, 659–660
  nail unit and, 508, 508*f*
  pathogenesis of, 627
Scalloped cell xanthogranuloma, 674, 674*f*
Scalloped macrophages, 674–675, 674*f*
Scalp
  angiosarcoma of, 1040, 1041*f*
  dermatitis herpetiformis and, 263
  discoid lupus erythematosus and, 280
  hair follicles of, 56, 57*f*
Scalp biopsies, for alopecia, 5, 470–472, 471*f*
Scalpel biopsy, for comparison, 5
SCAP. *See* Syringocystadenoma papilliferum
Scapula, dermatitis herpetiformis and, 263
Scar formation, dermal dendrocytes and, 39
Scar, keloid, histopathology of, 120
Scarlatiniform lesions, polyarteritis nodosa and, 210
Scarring alopecia, 481–489, 482*f*–483*f*
  central centrifugal cicatricial alopecia, 485–487, 485*f*–486*f*
  classification of, 481–483
  end stage of, 482–483, 482*f*
  eosinophilic pustular folliculitis with, 466
  folliculitis decalvans, 486*f*–487*f,* 487
  histopathology of, 128
  postmenopausal frontal fibrosing alopecia, 488–489, 488*f*
  pseudopelade of Brocq, 483–485, 483*f*–484*f*
  scalp biopsies for, 5
  tufted hair folliculitis, 487–488, 487*f*–488*f*
Scarring, of follicular occlusion triad (hidradenitis suppurativa, acne conglobata, perifolliculitis capitis abscedens et suffodiens), 544–545
Schamberg's disease, 225–226
  histopathology of, 107
Schaumann bodies, in sarcoidosis, 371–372
Scheie's syndrome, mucopolysaccharidosis and, 447
Schistosoma haematobium, 631
Schistosoma infection, 631–632, 632*f*
Schistosoma japonicum, 631–632
Schistosoma mansoni, 631–632
Schistosomiasis, 631–632, 632*f*
  eosinophils and, 44
  histopathology of, 121, 631–632, 632*f*
  ova of, 631–632
  pathogenesis of, 632
Schistosomides, 631
Schnitzler's syndrome, urticaria and, 169
Schopf's syndrome, eccrine syringofibroadenoma with, 888
Schwann cells
  anatomic relationships with, 1107
  compound nevus and, 713
  of dermal microvasculature, 53, 53*f*
  ganglioneuroma, 1140
  in intradermal nevus, 714
  malignant blue nevus and, 772
  in Meissner corpuscles, 55
  mucopolysaccharidosis and, 447
  neoplasms of, 1116–1122
  in neurofibromas, 1115
  Nevus cells and, 715
  photodistributed hyperpigmentation and, 320
  S100 protein in, 77
  in Vater-Pacini corpuscles, 55
Schwannomas, 1116–1122. *See also* Atypical schwannoma; Cellular schwannoma; Epithelioid schwannoma; Glandular schwannoma; Infiltrating and fascicular epithelioid malignant schwannoma; Infiltrating fascicular schwannoma; Plexiform schwannoma
  differential diagnosis of, 1116*f,* 1118, 1119
  extraneural sporadic cutaneous neurofibromas v., 1110
  histogenesis of, 1118
  histopathology of, 124–125, 1116–1117, 1116*f*–1118*f*
  malignant peripheral nerve sheath tumor and, 1122
  in neurofibroma, 1121
  storiform perineural cell fibroma v., 1133
  variant types of, 1118–1122
    cellular, 1118–1119, 1118*f*–1119*f*
    epithelioid, 1119–1120, 1120*f*–1121*f*
    infiltrating fascicular, 1121
    plexiform, 1120–1121, 1120*f*
    psammomatous melanotic, 1121
    transformed, 1121–1122
Schweninger-Buzzi anetoderma, 399–400
Scirrhous carcinoma, 1153
Scl-70 antibodies, systemic scleroderma and, 301
SCLE. *See* Subacute cutaneous lupus erythematosus
Scleredema, 445–447, 446*f*
  differential diagnosis of, 446–447
  histopathology of, 121, 446, 446*f*
  lipedema v., 527
  pathogenesis of, 446
  systemic lesions of, 446
Scleredema adultorum. *See* Scleredema
Scleredema of Buschke, staining methods for, 67
Sclerema neonatorum, 529
  clinical features of, 529
  differential diagnosis of, 529
  histopathology of, 101, 101*f,* 131, 529
  pathogenesis of, 529
  subcutaneous fat necrosis v., 530
  systemic lesions of, 529
Sclerodactyly, fibroblastic rheumatism and, 307
Scleroderma, 295–301
  acro-osteolysis v., 401
  Behçet's syndrome v., 414
  burns v., 346
  chronic radiation dermatitis v., 352
  drug-induced, 315–316
  graft-*versus*-host disease v., 273
  histopathology of, 101, 101*f,* 116, 121
  lymphocytoma cutis v., 588
  morphea, 296–299, 297*f*–298*f,* 299*t*
  panniculitis with, 534–535
  pseudopelade of Brocq v., 483
  systemic, 299–301, 300*t*
Scleroderma/morphea, histopathology of, 93, 93*f,* 96, 96*f,* 100, 100*f,* 116, 120, 128–130

Scleromyxedema, 444
  histopathology of, 121
  lichen myxedematosus and, 442–443
  lipedema v., 527
  nephrogenic systemic fibrosis v., 301
  pathogenesis of, 444
Sclerosing cholangitis, 417–418, 418*f*
  histopathology of, 417, 418*f*
  pathogenesis of, 417–418
  pyoderma gangrenosum with, 411
Sclerosing disorders, of Lyme disease, 587–588, 587*f*
  histopathology of, 588
Sclerosing epithelial hamartoma. *See* Desmoplastic trichoepithelioma
Sclerosing hemangioma. *See* Dermatofibroma
Sclerosing lesions, of Lyme disease, 586–587, 587*f*
Sclerosing lipogranuloma. *See also* Paraffinoma
  histopathology of, 131
Sclerosing myofibroblastoma, neurothekeoma v., 1130
Sclerosis, porphyria cutanea tarda with, 433
Sclerotic fibroma, 981–982
  angiofibroblastoma v., 991
  histogenesis of, 982
  histopathology of, 981–982, 982*f*
Sclerotic lipoma, histopathology of, 1062, 1063*f*
Sclerotic variant of atypical fibroxanthoma, 979
Scolex, of *Taenia solium* larva, 632
Scoliosis, Ehlers-Danlos syndrome and, 156
Scopulariopsis sp., 593
  nail unit and, 506–507
Scrofuloderma, 550, 552
  histopathology of, 119, 552
  pseudocarcinomatous hyperplasia and, 822
Scrotal leiomyosarcoma, 1080
Scrotum, idiopathic calcinosis cutis of, 437
Scurvy, 407
  connective tissue deficiencies and, 231
  differential diagnosis of, 407
  histopathology of, 86, 86*f,* 103, 127, 407
  pathogenesis of, 407
Scutula, 593
Scyballa, 627
Scytalidium (Hendersonula) infections, 593
Sea urchin granuloma, 374–376
  histopathology of, 375
  pathogenesis of, 376
Sea-urchin spines, foreign-body reactions and, 374
Sebaceoma, 873–874
  differential diagnosis of, 874
  histopathology of, 874, 874*f*
  rippled-pattern sebaceoma, 874
Sebaceous adenoma, 873
  differential diagnosis of, 873
  histopathology of, 97, 97*f,* 124, 873, 873*f*
  with Muir-Torre syndrome, 875
  sebaceoma v., 874
Sebaceous carcinoma, 875–876
  additional studies of, 876
  differential diagnosis of, 876
  histopathology of, 124, 874*f*–876*f,* 875–876
  with nevus sebaceus, 871–872
Sebaceous cells
  in sebaceoma, 874
  in sebaceous adenoma, 873, 873*f*
Sebaceous cysts. *See* Pilar cysts
Sebaceous duct, hair follicle and, 30
Sebaceous epithelioma. *See also* Sebaceoma
  histopathology of, 97, 97*f,* 124
  sebaceous adenoma v., 873
Sebaceous glands
  acne vulgaris and, 459–461
  in dermoid cyst, 804
  formation of, 25, 30
  function of, 30
  inflammatory processes of, 85
  necrosis in coma, 317
  nevus comedonicus in, 793
  of nose, 56, 57*f*
  regional variation of, 31
  rosacea and, 464
  sensory nerves to, 53
  in steatocystoma multiplex, 804
  in trichofolliculoma, 854
  tumors of, 97, 97*f,* 124
  vitamin A deficiency and, 407–408
Sebaceous hyperplasia, 872
  additional studies of, 872
  differential diagnosis of, 872
  histopathology of, 124, 872, 872*f*
  sebaceous adenoma v., 873
Sebaceous trichofolliculoma, 855
  differential diagnosis of, 855
  histopathology of, 124, 855
Sebaceus epithelioma, with nevus sebaceus, 871
Sebaceus glands, tumors with differentiation toward, 870–876
  Fordyce's spots and Montgomery's tubercles, 872–873, 873*f*
  Muir-Torre syndrome, 875
  nevus sebaceus, 870–872, 871*f*
  sebaceoma, 873–874, 874*f*
  sebaceous adenoma, 873, 873*f*
  sebaceous carcinoma, 875–876, 875*f*–876*f*
  sebaceous hyperplasia, 872, 872*f*
Sebocytes, in sebaceous hyperplasia, 872
Seborrheic dermatitis, 243
  androgenetic alopecia and, 481
  clear cell acanthoma v., 799
  disseminated epidermolytic acanthoma v., 793
  eczema herpeticum with, 638
  histopathology of, 89, 89*f,* 108–109, 113, 243, 243*f*
  in HIV, 243, 659–660
  Kaposi's varicelliform eruption with, 641
  keratosis lichenoides chronica with, 191
  Malassezia furfur in, 596
  microorganisms and, 60
  neutrophils and, 43
  pathogenesis of, 243, 243*f*
  perioral dermatitis v., 462
  psoriasis vulgaris v., 181
  Sézary syndrome v., 944
Seborrheic keratosis, 795–798, 795*f*
  acanthosis nigricans-like mycosis fungoides v., 942
  acanthotic type, 798
  adenoid or reticulated type, 797–798
  clonal type, 798
  cutaneous horn and, 811, 811*f*
  eccrine poroma v., 887
  histopathology of, 87–88, 87*f*–88*f,* 104, 106, 795–797, 795*f*–797*f*
  hyperkeratotic type, 798
  irritated type, 795, 796*f*–797*f*
  Leser-Trélat sign with, 799
  linear epidermal nevus v., 791–792, 792*f*
  melanoacanthoma, 798
  solar lentigines v., 707
  superficial spreading melanoma v., 743
  tumor of the follicular infundibulum v., 870
  verrucous trichoadenoma v., 863
  vulvar, 656
Sebum, acne vulgaris and, 459–461
Secondary B-cell lymphoproliferative disease, 922–935
  chronic lymphocytic leukemia/small lymphocytic lymphoma, 925–926, 926*f*
  diffuse large B-cell lymphoma, 930–932, 931*f*
  Hodgkin's lymphoma, 933–935, 934*f,* 934*t*
  intravascular large B-cell lymphoma, 932–933, 932*f*
  lymphomatoid granulomatosis, 933, 933*f*
  mantle cell lymphoma, 928–930, 929*f*
  nodal follicular lymphoma, 926–928, 927*f*
  precursor B-cell lymphoblastic lymphoma, 922–925, 924*f*
Secondary cutaneous oxalosis, Crohn's disease with, 415
Secondary lesion
  of endemic syphilis, 585
  of pinta, 585
  of yaws, 584
Secondary myeloid neoplasms, 957–960
  acute and chronic myeloid leukemia, 957–958, 958*f*–959*f,* 958*t*
  precursor plasmacytoid dendritic cell lineage, 959–960
Secondary ossification, 1089–1090
  histopathology of, 1089–1090, 1090*f*
Secondary syphilis, 579, 581–583, 581*f*–582*f*
  differential diagnosis of, 583
  histogenesis of, 583
  in HIV, 659
Secondary systemic amyloidosis, 427
  histopathology of, 427
  pathogenesis of, 427
Secondary T-/NK-cell lymphoproliferative disease, 951–956
  adult T-cell leukemia/lymphoma, 953–955, 954*f*
  anaplastic large cell lymphoma, 952–953, 953*f*
  angioimmunoblastic T-cell lymphoma, 952
  peripheral T-cell lymphoma, 951–952, 951*f*
  precursor T-lymphoblastic leukemia/lymphoblastic lymphoma, 955
  T-cell prolymphocytic leukemia, 955–956
Secondary yaws, 583
Second-degree burns, 274–275, 343, 345, 345*f*
Secretagogue, mast cells and, 41
Secretory portion, 33*f*
  of apocrine glands, 34–35, 35*f*
  of eccrine glands, 32–33, 33*f*
Segmental hyalinizing vasculitis, histopathology of, 111
Segmental lentigines, 708
Segmental morphea. *See* Morphea
Selective lymphadenectomy, for melanomas, 770–771
Selective serotonin reuptake inhibitors, erythema multiforme with, 312
Self-healing juvenile cutaneous mucinoses, 445
  histopathology of, 445
Senear-Usher syndrome. *See* Pemphigus erythematosus
Senescence, compound nevus and, 713
Senescent alopecia, 489
  histopathology of, 489
  pathogenesis of, 489
Senile lentigines. *See* Solar lentigo
Senile purpura, connective tissue deficiencies and, 231
Sensitivity, of diagnosis, 1
Sentinel lymph node dissection, 770–771
  melanocytic tumors of uncertain malignant potential and, 773
Septae, of subcutaneous fat, 55–56
Septal panniculitis
  mixed with lobular, 102, 102*f*
  relapsing polychondritis with, 494
  without vasculitis, 100, 100*f*
Septicemia. *See also* Acute septicemia; Chronic septicemia
  histopathology of, 111, 116
Serologic approach, to virus detection, 637–638
Serositis
  drug-induced lupus erythematosus with, 318
  systemic lupus erythematosus with, 288
Serotonin, Merkel cells and, 19
Serpiginous urticarial lesions, of strongyloidiasis, 628

Serratia marcescens, neutrophilic eccrine hidradenitis and, 491
Serum amyloid A (SAA), secondary systemic amyloidosis and, 427
Serum sickness, 220
Serum sickness-like syndrome, 661
Sestamibi, erythema multiforme with, 312
Severe dysplasia, dysplastic nevus and, 736
Sex hormones, acne vulgaris and, 459
Sexually transmitted diseases
  chancroid, 120, 569–570, 569*f*
  condyloma acuminatum, 654–656, 655*f*
  granuloma inguinale, 46, 110, 117–118, 120, 570, 570*f*
  HSV-2, 638
  lymphogranuloma venereum, 120, 514, 571
  molluscum contagiosum, 649, 649*f*
Sézary syndrome, 944–945
  adult T-cell leukemia/lymphoma v., 955
  clinical features of, 944
  differential diagnosis of, 944–945
  with follicular mucinosis, 468
  histogenesis of, 944
  histopathology of, 108, 110, 944, 945*f*
  Kaposi's varicelliform eruption with, 641
  T-cell prolymphocytic leukemia v., 955
Shadow cells, pilomatricoma and, 865–866, 865*f*
Shagreen patches, in tuberous sclerosis, 988–989
Shave biopsy
  application of, 5–6
  for direct immunofluorescence, 71
  for keratoacanthoma, 836
  of melanoma, 762
  for recurrent nevus, 732
  technique for, 6
Shigella, Reiter's disease and, 182
Shingles. *See* Herpes zoster infection
Shock, with acute meningococcemia, 546–547
Shoulder parakeratosis, seborrheic dermatitis and, 243
Sialidase, for mucin-producing squamous cell carcinoma, 821
Sialomucin
  from dark cells, 32
  in mucinous eccrine carcinoma, 898
  in mucous cyst of the oral mucosa, 998
  PAS and, 68, 69*t*
Siderophages, in aneurysmal fibrous histiocytoma, 970
Siderosis, hemochromatosis and, 450
Sign of Leser-Trélat, acanthosis nigricans and, 448
Signet cell melanoma, 749, 757
Signet ring cell
  of breast carcinoma, 1153
  carcinoma of, 1153–1154
Sildenafil, lichenoid drug eruption and, 313
Silica granuloma, 70, 374, 376, 376*f*
  Crohn's disease v., 416
  histopathology of, 376, 376*f*
  pathogenesis of, 376
Silicone
  panniculitis with, 525
  reactions to, 379
  scleroderma and, 296
Silicone granuloma, 374–375, 375*f*
  histopathology of, 117, 121
Silicone mammoplasty, middermal elastolysis and, 399
Silk, foreign-body reactions and, 373, 373*f*
Silver staining, of syphilis, 580, 581*f,* 582
Simple ephelis, histopathology of, 104
Simulium, as onchocerciasis vector, 629
Simvastatin
  eosinophilic fasciitis and, 303
  radiation recall dermatitis and, 352
Sinus histiocytosis
  histopathology of, 124
  with massive lymphadenopathy. *See* Rosai-Dorfman disease
Sinusoidal hemangioma, 1019–1020
  histopathology of, 126, 1019–1020, 1019*f*–1020*f*
Sjögren-Larsson syndrome, 136, 221
  Behçet's syndrome v., 414
  drug toxicities of, 311
  macular atrophy and, 400
  subacute cutaneous lupus erythematosus with, 283
Sjögren's syndrome
  lymphocytoma cutis v., 588
  with relapsing polychondritis, 493
SJS. *See* Stevens-Johnson syndrome
Skeletal deformities
  mucopolysaccharidosis and, 447
  with nevus sebaceus, 871
Skeletal muscle, eosinophilic fasciitis and, 303
Skin
  absence of, 143
  adenocarcinoma of, 1151
  age- and environmental-related variations, 56, 56*f*
  aged, histopathology of, 108
  angiofibroblastoma of, 991
  basement membrane zone of, 21–24, 22*f*–23*f*
  cold injury to, 352–355
  dermal fibroblasts of, 38–46, 39*f*–43*f,* 45*f*
    dermal muscle cells, 46
    emigrant inflammatory cells, 42–46, 42*f*–43*f,* 45*f*
    mast cells, 41–42, 41*f*
    perivascular and interstitial dendritic cells, 39–40, 39*f*
    phagocytic macrophages, 40–41, 40*f*
  dermal microvascular unit, 50–55
    dermal lymphatics, 51*f,* 53
    endothelial cells, 50–52, 51*f*
    glomus cells, 52–53, 53*f*
    neural network, 53–55, 54*f*
  dermis of, 38–55
    dermal fibroblasts, 38–46, 39*f*–43*f,* 45*f*
    dermal microvascular unit, 50–55
    extracellular matrix, 46–50, 47*f*–48*f*
  eccrine and apocrine glands of, 31–36
    embryology of, 32
    normal microanatomy of, 32–35, 33*f*–35*f*
    regional variation, 35, 35*f*
    special stains, 34*f*–35*f,* 36
    specialized structure and function, 35–36
  epidermis of, 7–38
    basement membrane zone, 21–24, 22*f*–23*f*
    eccrine and apocrine glands, 31–36
    hair follicles, 24–31, 24*f*–29*f*
    keratinocytes, 7–14, 8*f*–11*f,* 13*f*
    Langerhans cells, 19–21, 20*f*
    melanocytes, 14–18, 14*f*–15*f,* 16*t*
    Merkel cells, 18–19, 19*f*
    nails, 36–38, 36*f*–37*f*
  extracellular matrix of, 46–50, 47*f*–48*f*
    collagen fibers, 46–49, 47*f*–48*f*
    elastic fibers, 49
    ground substance, 49–50
  extramedullary hematopoiesis in, 956–957
  hair follicles of, 24–31, 24*f*–29*f*
    embryology, 24–25, 24*f*–25*f*
    normal microanatomy, 25–30, 25*f*–29*f*
    regional variation, 30–31
    sebaceous glands, 28*f,* 30
    specialized structure and function, 31
  histology of, 7, 8*f*–9*f*
  incidental findings in, 58–60
    focal acantholytic dyskeratosis, 59–60, 59*f*
    focal epidermolytic hyperkeratosis, 58–59, 59*f*
  keratinocytes of, 7–14
    embryology, 7–8, 8*f*
    normal microanatomy of, 8–12, 9*f*–11*f*
    specialized structure and function, 11*f,* 12–14, 13*f*
  Langerhans cells of, 19–21, 20*f*
    embryology, 19–20, 20*f*
    normal microanatomy, 20–21, 20*f*
    regional variation, 21
    specialized structure and function, 21
  major functions of, 911
  melanocytes of, 14–18
    embryology, 14
    normal microanatomy, 14–16, 14*f*–15*f*
    regional and racial variation, 17
    specialized structure and function, 17–18
    in sun-exposed areas, 15*f,* 17
    ultrastructure, 15*f,* 17
  Merkel cells of, 18–19, 19*f*
    embryology of, 18
    normal microanatomy of, 18–19, 19*f*
    regional variation of, 19
    specialized structure and function of, 19
  metabolic diseases of, 425–452
    acanthosis nigricans, 447–448, 448*f*–449*f*
    amyloidosis, 425–429
    calcinosis cutis, 435–438
    colloid milium and nodular colloid degeneration, 429–430, 430*f*
    gout, 438–439, 438*f*–439*f*
    lipoid proteinosis, 430–431, 431*f*
    mucinoses, 441–447
    mucopolysaccharidosis, 447
    ochronosis, 439–441, 440*f*
  metastatic carcinoma of, 1151–1159
    of the breast, 1152–1154, 1153*f*–1154*f*
    carcinoid and neuroendocrine carcinomas, 1157–1158
    gastrointestinal, 1155–1156
    incidence and dissemination, 1151–1152, 1152*f,* 1152*t*
    of the lung, 1154–1155
    miscellaneous carcinomas, 1158–1159, 1158*f*
    oral cavity, 1156
    ovary, 1157
    renal cell, 1156–1157, 1157*f*
  microorganisms in normal, 60, 60*f*
  nails of, 36–38, 36*f*–37*f*
  nodal follicular lymphoma of, 927
  penicillamine-induced atrophy of, 325
  primary mucinous carcinoma of, 1153–1154
  radiation-induced alterations in, 348–352
    acute, subacute, and chronic radiation dermatitis, 348–352, 349*f*–351*f*
    radiation recall dermatitis, 352
  regional variation of, 56–57, 57*f*
  squamous cell carcinoma metastatic to, 1154
  subcutaneous fat of, 55–56, 55*f*
SLE. *See* Systemic lupus erythematosus
SLL. *See* small lymphocytic lymphoma
SMA. *See* Smooth muscle antigen
Small blue round cell tumors, 1138–1140
  cutaneous small cell undifferentiated carcinoma, 1138–1140, 1138*f*–1139*f*
  ganglioneuroma, 1140
  peripheral neuroblastoma, 1139–1140, 1140*f*
Small cell carcinomas, 1158
  histopathology of, 122
Small cell melanoma, histopathology of, 122
Small lymphocytic lymphoma (SLL), 925–926
  clinical features of, 925
  differential diagnosis of, 919*t,* 926
  histogenesis of, 925–926
  histopathology of, 121, 925, 926*f*
Small round cell tumors, 96, 96*f,* 121–122

Small-plaque parapsoriasis, 182
Smallpox. *See* Variola
Small-vessel leukocytoclastic vasculitis, histopathology of, 116
Smokers, palmar fibromatosis and, 992
Smooth muscle
  of dermis, 46, 57
  tumors of, 1075–1083
    leiomyoma, 1076–1080, 1077*f*–1079*f*
    leiomyosarcoma, 1080–1083, 1081*f*–1082*f*
    smooth muscle hamartoma, 1075–1076, 1076*f*
Smooth muscle antigen (SMA), schwannoma and, 1119
Smooth muscle hamartoma, 1075–1076
  differential diagnosis of, 1076
  histopathology of, 126, 1075–1076, 1076*f*
  pathogenesis of, 1076
Sneddon's syndrome, 518
Sneddon-Wilkinson. *See also* Subcorneal pustular dermatosis
  IgA pemphigus v., 254
Sodium, eccrine glands and, 35
Sodium valproate, drug-induced pseudolymphoma syndrome with, 320
Soft fibroma, 981
  histopathology of, 89, 89*f,* 106, 981
  tuberous sclerosis, 988–989
Soft tissue chondromas, 1094–1096
  differential diagnosis of, 1096, 1096*f*
  histopathology of, 98, 98*f,* 127, 1094, 1095*f*
  pathogenesis of, 1096
Soft tissue myoepitheliomas, extraskeletal myxoid chondrosarcoma v., 1098
Solar cheilitis, 807, 810
Solar degeneration, 1174*f*
Solar elastosis, 56, 56*f,* 389–391, 390*f*
  acquired elastotic hemangioma and, 1026
  adult colloid milium and, 430
  with chondrodermatitis nodularis helicis, 493–494
  differential diagnosis of, 390
  erythema ab igne v., 348
  histogenesis of, 389–390
  histopathology of, 120, 389, 390*f*
  localized expressions of, 390–391
    actinic comedonal plaques, 391
    of the ears, 390–391
    Favre-Racouchot syndrome, 127, 390–391
    of the forearm, 391
    of hands, 391
  pseudoxanthoma elasticum v., 154
Solar elastotic bands of the forearm, 391
  histopathology of, 391
Solar keratoses
  epidermolytic hyperkeratosis in, 793
  lentigo maligna melanoma v., 745
  xeroderma pigmentosum with, 141
Solar lentigines, lichen planus and, 190
Solar lentigo, 706–708, 710*t*
  differential diagnosis of, 708
  freckles v., 704–705
  histogenesis of, 708
  histopathology of, 87, 87*f,* 104, 707–708, 707*f*
  lichen planus and, 190
  lichen planus-like keratosis and, 191
  reticulated seborrheic keratosis and, 798
Solar urticaria (SU), 340, 341*f*
  differential diagnosis of, 340
  histopathology of, 115, 340, 341*f*
  pathogenesis of, 340
Soles
  acral skin of, 56
  acral-lentiginous melanoma of, 747
  eccrine glands on, 32
  eccrine poroma on, 885
  epidermal cysts of, 802
  Reiter's disease and, 181
  Vater-Pacini corpuscles at, 55
Solid cystic hidradenoma, 891
Solid glomus tumors, histopathology of, 1047
Solitary angiokeratoma, 1011
Solitary angioleiomyoma, 1076
Solitary epithelioid histiocytoma, 675
Solitary fibrous tumor, 993
  histopathology of, 993, 993*f*
  myopericytoma and, 1049
Solitary giant xanthogranuloma, 672
Solitary keratoacanthoma. *See* Keratoacanthoma, solitary
Solitary myofibroma, histopathology of, 126
Solitary pagetoid reticulosis, 940–941
Solitary piloleiomyoma, 1076
Solitary reticulohistiocytic granuloma, doubly refractile lipids in, 70
Solitary trichoepithelioma, 857–858
  histopathology of, 859
Somatostatin analog, radiation recall dermatitis and, 352
Sore throat, microscopic polyarteritis and, 212
South American blastomycosis, 600*t,* 605–606, 606*f*
  histopathology of, 119
SPCF. *See* Storiform perineural cell fibroma
SPD. *See* Subcorneal pustular dermatosis
Special site nevi, 715–716
  superficial spreading melanoma v., 744
Specificity, of diagnosis, 1–2
  improvement of, 4
Specimen, preparation of, 67–68
  enzyme activity demonstration, 67
  fixation, 67
  grossing, 67, 68*f*
  processing, 68
  staining, 68
Speckled erythroplakia, 812
Speckled lentiginous nevus, 708, 710*t*
  histopathology of, 709
Sphingomyelinase D, 635
Spider nevus, histopathology of, 126
Spindle cell hemangioendothelioma, histopathology of, 126
Spindle cell hemangioma, 1027–1028
  composite hemangioendothelioma and, 1037
  differential diagnosis of, 1028
  histopathology of, 1027, 1027*f*–1028*f*
  Kaposi's sarcoma v., 1035
  pathogenesis of, 1028
Spindle cell lipoma, 1066
  differential diagnosis of, 1066
  histopathology of, 127, 1066, 1066*f*
Spindle cell liposarcoma, histopathology of, 1072
Spindle cell macrophages, 673, 676*f*
Spindle cell melanoma
  deep penetrating nevus v., 730
  desmoplastic melanoma v., 756
Spindle cell neoplasm, dermatofibrosarcoma protuberans, 974
Spindle cell nevus. *See also* Spitz nevus
  deep penetrating nevus v., 730
  neurothekeoma v., 1129
Spindle cell sarcoma, paraneoplastic autoimmune multiorgan syndrome and, 254
Spindle cell squamous cell carcinoma, 820
Spindle cell variant of atypical fibroxanthoma, 978
Spindle cell xanthogranuloma, 676, 676*f,* 677
Spindle cells
  in atypical fibroxanthoma, 978
  deep penetrating nevus and, 729
  dermatofibroma and, 969
  dermatofibrosarcoma protuberans, 974–976
  in dermatomyofibroma, 980
  desmoid-type fibromatosis and, 992
  in fibrous hamartoma of infancy, 986
  in inflammatory pseudotumor, 994
  in myofibroma/myofibromatosis, 985
  in nodular fasciitis, 984
  nodular melanoma and, 750
  pigmented spindle cell nevus, 724–725, 725*f*
  in solitary fibrous tumor, 993, 993*f*
  Spitz nevus and, 721
  tumors of, 98, 98*f,* 125–127
  of xanthoma disseminatum, 675*f*
Spine, of schistosomiasis ova, 631–632
Spirochetal infection. *See* Treponemal diseases
Spirometra species, subcutaneous dirofilariasis v., 629
Spiruriids, 627
Spitz nevus, 718–724, 719*f*–720*f*
  angiomatoid, 722
  deep penetrating nevus v., 729
  desmoplastic, histopathology of, 126
  diagnostic and prognostic markers of, 722
  differential diagnosis of, 722–724
  epithelioid dermatofibroma v., 973–974
  histogenesis of, 722
  histopathology of, 104–106, 718–722, 719*f*–720*f*
  hyalinizing, 722
  junctional nevus v., 712
  juvenile xanthogranuloma v., 673
  melanoma v., 719*f*–720*f,* 720–721, 723–724, 723*t,* 735
  minimal deviation melanoma v., 758
  neurothekeoma v., 1129
  nodular melanoma v., 750
  papular xanthoma v., 674
  pigmented spindle cell nevus v., 724
  superficial spreading melanoma v., 744
Spitzoid melanomas
  of childhood, 762
  Spitz nevi v., 723
Spleen, argyria of, 327
Splendore-Hoeppli phenomenon, 613
Splenomegaly, drug-induced lupus erythematosus with, 318
Splinter hemorrhages, microscopic polyarteritis and, 212
Spongiform pustule of Kogoj
  generalized pustular psoriasis and, 178
  psoriasis vulgaris and, 176–177, 177*f,* 181
  ultrastructural studies of, 179
Spongiosis, 85, 235. *See also* Eosinophilic spongiosis
  acanthoma fissuratum and, 357
  in arthropod assault reactions, 634
  chilblains and, 355
  chronic actinic dermatitis with, 338–339
  clear cell acanthoma and, 800
  with eosinophilic pustular folliculitis, 467
  erythema annulare centrifugum and, 171
  Fox-Fordyce disease and, 492
  ILVEN and, 194
  incontinentia pigmenti and, 161
  of measles, 662
  parapsoriasis and, 182
  of perioral dermatitis, 462
  photoallergic drug eruption and, 318
  with pinta, 585
  pityriasis rosea and, 183
  polymorphic light eruption with, 333
  psoriasis vulgaris and, 181
  superficial perivascular dermatitis with, 89, 89*f*
  with syringolymphoid hyperplasia, 491
Spongiotic dermatitis, 89, 89*f,* 108. *See also* Acute spongiotic dermatitis; Chronic spongiotic dermatitis; Early spongiotic dermatitis; Subacute spongiotic dermatitis

Spongiotic dermatitis (*continued*)
with chemical burns, 346
definition and evaluation of, 237, 239*f*–240*f*
differential diagnosis of, 243–244
with follicular mucinosis, 468
histopathology of, 113, 129
immunologic deficiency diseases with, 245
other disorders with
erythroderma and generalized exfoliative dermatitis, 244
miliaria, 244–245, 244*f*
T-cell lymphomatoid hyperplasias and, 935
transient acantholytic dermatosis v., 273
types of
allergic contact dermatitis, 237–239, 239*f*
atopic dermatitis, 242
dyshidrotic dermatitis, 240–241, 241*f*
id reaction, 241
irritant contact dermatitis, 240, 240*f*
lichen simplex chronicus, 242–243
nummular dermatitis, 239*f,* 241–242
photoallergic dermatitis, 241
seborrheic dermatitis, 243
stasis dermatitis, 243
Spongiotic drug eruption
acute spongiotic dermatitis and, 243
subacute spongiotic dermatitis and, 243
Sporadic cutaneous neurofibroma, histopathology of, 125
Sporangia, 592*t*
of protothecosis, 616
Sporangioblasts, 592*t*
Sporothrix schenckii, 600*t,* 604, 612–614, 614*f*
Sporotrichosis, 600*t,* 612–614, 614*f*
differential diagnosis, 614
histopathology of, 95, 95*f,* 118–119, 132, 613, 614*f*
pathogenesis of, 613–614
Spotted grouped pigmented nevi, 725, 728
SPTCL. *See* Subcutaneous panniculitis-like T-cell lymphoma
Squamous cell carcinoma, 817–821, 818*f,* 1178*f*. *See also* Acantholytic squamous cell carcinoma; Adenoid squamous cell carcinoma; Verrucous carcinoma
acanthosis nigricans and, 448
from actinic keratosis, 807
actinic keratosis v., 810
in albinism, 693
from arsenical keratosis, 817
atypical fibroxanthoma v., 979
basal cell carcinoma v., 834
Bowenoid papulosis of genitalia in, 656
Bowen's disease and, 813–814
burn scars and, 346
cheilitis glandularis and, 381
condyloma acuminatum in, 654
cutaneous horn and, 811, 811*f*
desmoplastic trichilemmoma v., 868
differential diagnosis of, 820–821, 821*f*
EMA antibodies and, 76
epidermal cysts with, 802
in epidermodysplasia verruciformis, 653–654
with erythema ab igne, 347
erythroplasia of Queyrat and, 815
with follicular mucinosis, 468
histopathology of, 97, 97*f,* 104, 110, 118, 122, 818–820, 818*f*–819*f*
irritated seborrheic keratosis v., 795
keratoacanthoma v., 836–837
lichen planus v., 190
malignant proliferating trichilemmal tumor v., 867
metastatic, histopathology of, 122
metastatic to the skin, 1154
North American blastomycosis v., 604–605
pathogenesis of, 820
porokeratosis and, 139
primary, histopathology of, 97, 97*f,* 122
proliferating trichilemmal cyst v., 866–867
pseudocarcinomatous hyperplasia v., 822–823
radiation-induced, 351
sebaceous carcinoma and, 876
superficial, histopathology of, 88, 88*f,* 106
superficial spreading melanoma v., 744
verrucous carcinoma v., 813
verrucous melanoma and, 756
xeroderma pigmentosum with, 141
Squamous cell carcinoma *in situ*, Bowenoid papulosis of genitalia v., 656–657
Squamous eddies
of irritated seborrheic keratosis, 795, 796*f*–797*f*
in proliferating trichilemmal cyst, 866
Squamous hyperplasia, vulvar intraepithelial neoplasia v., 816
Squamous layer, of keratinocytes, 8, 8*f*–11*f,* 10–11
Squamous papilloma, nonspecific, histopathology of, 106
SSM. *See* Superficial spreading melanoma
SSSS. *See* Staphylococcal scalded skin syndrome
Staging, of melanoma, 762–770
biological markers, 769
Breslow's thickness of tumor, 765, 765*f*
Clark's levels of invasion, 764–765
local excision, 769–770
mitotic rate, 767
other clinicopathologic prognostic factors, 768–769
partial and complete regression, 766–767, 766*f*
pathology of microstaging attributes, 764
satellites, 768
TNM staging system, 762–764, 763*t*–764*t*
tumor-infiltrating lymphocytes, 766*f,* 767
ulceration, 767–768, 767*f*
vascular or lymphatic invasion, 768, 768*f*
vertical growth phase, 764
Staining
histochemical, 68–69, 69*t,* 70*f*
of *Mycobacterium leprae,* 559–560
for pseudoxanthoma elasticum, 153–154
of specimen, 68
for urticaria pigmentosa, 160
Stains
for basement membrane zone, 22, 22*f*
for melanocytes, 16–17, 16*t*
Staphylococcal enterotoxins, 546
Staphylococcal scalded skin syndrome (SSSS), 539–541
differential diagnosis of, 541
histopathology of, 92, 92*f,* 112, 540
pathogenesis of, 540
pemphigus foliaceus and, 252
Staphylococcal sepsis, leukocytoclastic vasculitis and, 217
Staphylococcal syndrome, 546
Staphylococci, folliculitis from, 542–543
Staphylococcus aureus
atopic dermatitis and, 242
botryomycosis from, 573
folliculitis decalvans and, 487
in HIV, 659
impetigo from, 539–541
malakoplakia with, 549
miliaria rubra and, 245
nail infections of, 507
necrotizing fasciitis from, 541–542
neutrophilic eccrine hidradenitis and, 491
tufted hair folliculitis with, 487–488
Staphylococcus epidermis
perifollicular elastolysis and, 401
in skin, 60, 60*f*
Starch granuloma
foreign-body reactions and, 374–375
histopathology of, 117, 121, 375
Stasis dermatitis, 243
histopathology of, 107–108, 113, 115, 243
pigmented purpuric dermatosis v., 227
pseudocarcinomatous hyperplasia and, 822
Stasis ulcers, systemic lupus erythematosus and, 288
Steatocystoma multiplex, 803–804, 803*f*–804*f*
eruptive vellus hair cysts v., 806
histopathology of, 127, 804, 804*f*
pathogenesis of, 804
Steatocystoma simplex. *See* Steatocystoma multiplex
Stelae, 473, 473*f*
Steroid acne, 461–462
histopathology of, 461, 461*f*
pathogenesis of, 461–462
Steroid therapy
for chronic actinic dermatitis, 338
Mycobacterium avium-intracellulare infection with, 555
tuberculosis with, 550
Sterol, xanthomas from, 683
Stevens-Johnson syndrome (SJS), 268–270, 269*f*–270*f,* 312–313, 313*f*
differential diagnosis of, 270
EM and TEN v., 268–269, 269*f*
histopathology of, 112, 114, 269, 270*f,* 313, 313*f*
immunofluorescence testing for, 270
paraneoplastic autoimmune multiorgan syndrome v., 254
pathogenesis of, 270
ultrastructural study of, 270
Stings, reactions to, 634–635, 634*f*
Stomatitis areata migrans, psoriasis vulgaris, 174, 174*f*
Stomatitis, with acrodermatitis enteropathica, 410
Storiform collagenoma. *See* Sclerotic fibroma
Storiform nerve sheath tumor, histopathology of, 125
Storiform perineural cell fibroma (SPCF), 1132–1133
differential diagnosis of, 1133
histogenesis of, 1132–1133
histopathology of, 1132, 1133*f*
STP. *See* Superficial thrombophlebitis
Stratum basalis, of keratinocytes, 7–10, 8*f*–11*f*
Stratum corneum
calcaneal petechiae and, 356
with cryotherapy-induced injury, 355, 355*f*
discoid lupus erythematosus and, 280
disorders of, 85–87, 86*f*–87*f*
hyperkeratosis with hypogranulosis, 86, 86*f,* 103
hyperkeratosis with normal or hypergranulosis, 86, 86*f,* 103
hyperkeratosis with parakeratosis, 86, 86*f,* 103
localized or diffuse hypopigmentation/depigmentation, 87, 87*f,* 104
friction blisters and, 274
granuloma gluteale infantum and, 381
of keratinocytes, 8, 8*f*–11*f,* 10–12
miliaria crystallina and, 245
pemphigus foliaceus and, 250–251
Stratum germinativum, development of, 7, 8*f*
Stratum granulosum
friction blisters and, 274, 356
of keratinocytes, 8, 8*f*–11*f,* 11
Stratum intermedium, development of, 7, 8*f*
Stratum lucidum, of keratinocytes, 8–9, 8*f*–11*f*
Stratum malpighii
familial benign pemphigus and, 148–149
hyperkeratosis lenticularis perstans in, 397–398
lichen sclerosus et atrophicus and, 305
poikiloderma atrophicans vasculare and, 295
Stratum spinosum
of keratinocytes, 8, 8*f*–11*f,* 10–11
necrolytic migratory erythema and, 409

Strawberry nevus. *See also* Infantile hemangioma
  histopathology of, 126
  tufted angioma v., 1016
Strawberry tongue, mucocutaneous lymph node syndrome and, 184
Streptavidin peroxidase technique, 75
Streptococcal infections
  erythema nodosum with, 514
  mucocutaneous lymph node syndrome v., 184
  neutrophilic eccrine hidradenitis and, 491
Streptococcus pneumoniae, necrotizing fasciitis from, 541
Stress, telogen effluvium and, 478
Striae distensae, 398
  histogenesis of, 398
  histopathology of, 120, 398
  linear focal elastosis v., 399
Striated muscle, 46
  morphea and, 297*f*–298*f,* 298
"String of pearls," with linear IgA dermatosis, 266
Stroma. *See also* Cellular stroma; Desmoplastic stroma; Fibrous stroma
  basal cell carcinoma and, 830, 833
  in chondroid syringoma, 893–894
  discoid lupus erythematosus and, 280
  in eccrine spiradenoma, 889
  in eccrine syringofibroadenoma, 888, 888*f*
  lichen amyloidosis and macular amyloidosis and, 429
  in malignant eccrine poroma, 888
  in myofibroma/myofibromatosis, 986
  neurothekeoma and, 1128
  in nodular fasciitis, 983
  in trichofolliculoma, 854
Strongyloides sp., 627
Strongyloides stercoralis, 628, 629*f*
Strongyloidiasis, 628, 629*f*
  histopathology of, 121, 628, 629*f*
Strophulus infantum. *See* Papular urticaria
Stucco keratosis, 795, 797*f,* 799
  histopathology of, 104, 799
  large cell acanthoma v., 799
Sturge-Weber syndrome, port-wine stain of, 1010
SU. *See* Solar urticaria
Subacute annular pustular psoriasis, 175
  systemic lupus erythematosus v., 285
Subacute cutaneous lupus erythematosus (SCLE), 283, 285*f*
  with dermatomyositis, 293
  histopathology of, 283, 285*f*
  necrolytic migratory erythema v., 409
  neonatal lupus erythematosus v., 283
Subacute progressive juvenile paracoccidioidomycosis, 606
Subacute radiation dermatitis, 348–352, 349*f*–351*f*
  differential diagnosis of, 352
  histopathology of, 351, 351*f*
Subacute spongiotic dermatitis
  definition and evaluation of, 237, 239*f*
  differential diagnosis of, 243
Subcorneal blister, pemphigus foliaceus and, 251
Subcorneal pustular dermatosis (SPD), 267–268, 268*f*
  acropustulosis of infancy v., 267
  acute generalized exanthematous pustulosis v., 315
  differential diagnosis for, 268
  histopathology of, 112–113, 267–268, 268*f*
  IgA pemphigus v., 253
  immunofluorescence testing for, 268
  impetigo contagiosa v., 539
  pathogenesis of, 268
  pemphigus foliaceus v., 252
  ultrastructural study of, 268
Subcutaneous cysticercosis, 632, 632*f*
  histopathology of, 121, 632, 632*f*
Subcutaneous dirofilariasis, 628–629, 629*f*
  differential diagnosis of, 629
  histopathology of, 121, 628–629, 629*f*
Subcutaneous fat
  inflammatory diseases of, 509–536
    alpha-1 antitrypsin deficiency panniculitis, 516–517, 516*f*–517*f*
    calcifying panniculitis, 530–531, 531*f*
    eosinophilic panniculitis and fasciitis, 515–516, 515*f*
    erythema induratum, 519–521, 519*f*–520*f*
    erythema nodosum, 511–515, 511*f*–514*f*
    histiocytic cytophagic panniculitis, 532–534, 532*f*–533*f*
    lipedema, 527
    lipomembranous panniculitis, 531–532, 532*f*
    localized lipoatrophy and lipodystrophy, 526–527
    lupus erythematosus panniculitis, 521–523, 522*f*
    miscellaneous panniculitis, 534–535, 534*f*
    palisaded granulomatous panniculitis, 524–525, 524*f*
    panniculitis classification, 509–511, 510*t*
    panniculitis due to physical or chemical agents, 525–526, 526*f*
    panniculitis Rothmann-Makai, 524
    sclerema neonatorum, 529
    subcutaneous fat necrosis of the newborn, 529–530, 530*f*
    subcutaneous nodular fat necrosis in pancreatic disease, 528–529, 528*f*
    subcutaneous polyarteritis nodosa, 517–518, 518*f*
    superficial migratory thrombophlebitis, 517, 517*f*
    Weber-Christian disease, 523–524, 523*f*
  lipedematous alopecia and, 489
  morphea and, 297
  necrosis of, of newborn, 529–530, 530*f*
  pseudopelade of Brocq and, 484
  of skin, 55–56, 55*f*
  systemic interactions with, 535–536
  systemic lupus erythematosus with, 287
Subcutaneous fat necrosis, histopathology of, 131
Subcutaneous granuloma annulare, 361–362
  histopathology of, 100, 100*f,* 118, 130–131, 361–362, 362*f*–363*f*
  necrobiotic xanthogranuloma with paraproteinemia v., 684
  palisaded granulomatous panniculitis v., 524
  rheumatoid nodules v., 368
Subcutaneous JXG, 672
Subcutaneous leiomyosarcoma, 1080, 1082*f*
  histopathology of, 1082
Subcutaneous lymphoma-leukemia, histopathology of, 130
Subcutaneous morphea. *See* Morphea
Subcutaneous nodular fat necrosis, in pancreatic disease, 528–529, 528*f*
  clinical features of, 528, 528*f*
  differential diagnosis of, 529
  histopathology of, 528, 528*f*
  pathogenesis of, 528
  systemic lesions of, 528
Subcutaneous nodules, of sarcoidosis, 370
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL), 948
  clinical features of, 948
  cutaneous γ/δ T-cell lymphoma v., 950–951
  differential diagnosis of, 948
  histogenesis of, 948
  histopathology of, 948, 948*f*
Subcutaneous phaeohyphomycosis, 600*t,* 601–603, 602*f*
  differential diagnosis, 603
  histopathology of, 602–603, 602*f*
  pathogenesis of, 603
Subcutaneous polyarteritis nodosa, 517–518, 518*f*
  clinical presentation of, 517–518
  differential diagnosis of, 518
  erythema induratum v., 521
  histopathology of, 100, 100*f,* 129, 518, 518*f*
Subcutaneous sarcoidosis, histopathology of, 101, 101*f,* 131
Subcutaneous sparganosis, subcutaneous dirofilariasis v., 629
Subcutaneous T-cell lymphoma
  with hemophagocytic syndrome, 532–534, 532*f*–533*f*
  histopathology of, 131
  lupus erythematosus panniculitis v., 522–523
  Weber-Christian disease v., 524
Subcutaneous tuberculosis, erythema nodosum v., 515
Subcutaneous variant of granuloma annulare, 367
Subcutis
  disorders of, 85, 100–102, 100*f*–102*f,* 129–132
    lobular panniculitis without vasculitis, 101, 101*f,* 130–131
    mixed lobular and septal panniculitis, 102, 102*f,* 131
    septal panniculitis without vasculitis, 100, 100*f,* 130
    subcutaneous abscesses, 102, 102*f,* 131–132
    subcutaneous vasculitis and vasculopathy, 100, 100*f,* 129–130
  tumors of, 96–98, 96*f*–98*f,* 121–127
    cysts of dermis and subcutis, 98, 98*f,* 127
    large polygonal and round cell, 97, 97*f,* 122–125
    small cell, 96, 96*f,* 121–122
    spindle cell, pleomorphic, and connective tissue tumors, 98, 98*f,* 125–127
Subepidermal bullous disease, 254–261, 255*t,* 256*f*
  bullous pemphigoid, 256–259, 257–258*f,* 258*t*
  cicatricial pemphigoid, *258*t, 259–260, 260*f*
  herpes gestationis, 260–261, 261*f*
Subepidermal calcified nodule, 437–438, 438*f*
  histopathology of, 121, 438, 438*f*
  pathogenesis of, 438
Subepidermal IgA-mediated vesiculobullous dermatoses, 263–267
Sublaminar densa region
  of basement membrane zone, 256, 256*f*
  linear IgA dermatosis and, 265
Substance P
  mast cells and, 41
  Merkel cells and, 19
  prurigo nodularis and, 174
Subungual exostosis, 1090, 1092*f,* 1093
  histopathology of, 127, 1092*f,* 1093
Subungual hyperkeratosis
  with nail psoriasis, 505
  pachyonychia congenita with, 138
Subungual region, Reiter's disease and, 181
Succinic dehydrogenase
  in nodular hidradenoma, 892
  in syringoma, 885
Sucquet-Hoyer canal, 52–53, 52*f. See also* Arteriovenous anastomoses
Suction blister, 275
  friction blisters v., 357
  histopathology of, 114
Sudan IV stain, for paraffinoma, 374
Sulfasalazine, DRESS with, 311
Sulfonamides
  erythema nodosum with, 515
  leukocytoclastic vasculitis and, 221
  photoallergic drug eruption and, 318
  SJS and TEN with, 313
  toxic epidermal necrolysis and, 269
Sulfur granules, 574
  of eumycetoma, 614, 615*f*

Sulfur, of tonofilaments v. keratohyaline granules, 11
Sulpride, pyoderma gangrenosum with, 411
Sun exposure, 1174*f*
  acantholytic squamous cell carcinoma and, 821
  acquired elastotic hemangioma and, 1025–1026
  actinic comedonal plaques and, 391
  actinic keratosis and, 807
  adult colloid milium and, 429
  basal cell carcinoma and, 823
  cheilitis glandularis and, 381
  chronic actinic dermatitis and, 338
  granuloma annulare and, 362
  Hartnup's disease and, 408–409, 451
  hydroa vacciniforme and, 337
  lentigo maligna melanoma and, 747
  melanocytes and, 15*f,* 17
  melanoma and, 739, 759–760
  Merkel cells and, 19
  polymorphic light eruption and, 333–335
  rosacea and, 464
  solar elastosis and, 389
  squamous cell carcinoma from, 817
  xeroderma pigmentosum and, 141
Sunburn cells, with psoralen and ultraviolet A-induced pigment alterations, 692
Sunburn freckles. *See* Solar lentigo
Sunburn reaction, histopathology of, 112
Sunburn reactivation. *See* Ultraviolet recall
Sunburn recall. *See* Ultraviolet recall
Sunscreens
  for actinic prurigo, 335
  for chronic actinic dermatitis, 338
  for hydroa vacciniforme, 337
  photoallergic drug eruption and, 318
  for polymorphic light eruption and, 334
  for solar urticaria, 340
Superficial acral fibromyxoma, 990
  differential diagnosis of, 990
  histogenesis of, 990
  histopathology of, 990, 991*f*
Superficial angiomyxoma, 997
Superficial atypical melanocytic proliferation of uncertain significance (SAMPUS), 743, 749
  melanocytic tumors of uncertain malignant potential v., 773
  pigmented spindle cell nevus and, 724
Superficial basal cell carcinoma, 824, 824*f,* 826*f,* 831
  growth of, 833–834
Superficial cellular cohesion, of keratinocytes, 12
Superficial cutaneous reactive unit
  inflammation of, 85
  superficial dermatitis of, 89, 89*f,* 106–107
    with epidermal atrophy, 90, 90*f,* 108
    with interface vacuoles, 91, 91*f,* 112
    with irregular epidermal proliferation, 90, 90*f,* 109–110
    with lichenoid infiltrates, 91, 91*f,* 110–111
    with psoriasiform proliferation, 90, 90*f,* 109
    with spongiosis, 89, 89*f,* 108
  superficial vasculitis and vasculopathies, 91, 91*f,* 111–112
Superficial dermatitis with, lichenoid infiltrates, 91, 91*f*
Superficial gyrate erythemas, histopathology of, 107
Superficial leiomyosarcoma, histopathology of, 126
Superficial malignant epithelioid schwannomas, desmoplastic melanoma v., 754
Superficial melanocytic nevi, histopathology of, 122
Superficial migratory thrombophlebitis, 517
  clinical presentation of, 517
  differential diagnosis of, 517
  erythema nodosum v., 515
  histopathology of, 116, 129, 517, 517*f*
Superficial perivascular dermatitis, LCD v., 671
Superficial septic thrombophlebitis, superficial thrombophlebitis and, 209
Superficial shave biopsy, 5–6
Superficial spreading melanoma (SSM), 740*f,* 743–745
  classification of, 738, 739*f*
  differential diagnosis of, 737*t,* 744–745, 745*f*
  extramammary Paget's disease v., 840
  histogenesis of, 744
  histopathology of, 123, 741*f*–742*f,* 744
  Paget's disease v., 839
Superficial thrombophlebitis (STP), 209
  differential diagnosis of, 209
  histopathology of, 209
Superficial vascular plexus, of dermal microvasculature, 50
Superficial vasculitis, 91, 91*f*
Superficial white onychomycosis (SWO), 593
Superficial xanthomatous papules, of progressive nodular histiocytosis, 677
Suppurative folliculitis, papulonecrotic tuberculids v., 554
Suprapapillary epidermis, psoriasis vulgaris and, 176–177
Surgery-associated injury, 357, 358*f*–359*f*
  differential diagnosis of, 357
  histopathology of, 357, 358*f*–359*f*
Sustentacular cell differentiation, deep penetrating nevus and, 730
Sutton's nevus. *See* Halo nevus
Sweat, delivery to skin surface, 32–33, 33*f*
Sweat gland carcinoma, 1156
  acantholytic squamous cell carcinoma v., 821
  extramammary Paget's disease with, 839–840
  tubular apocrine adenoma v., 880
Sweat glands. *See also* Apocrine glands; Eccrine glands
  ectodermal dysplasia and, 142
  hemochromatosis and, 450
  necrosis in coma, 316–317, 316*f*–317*f*
  ochronosis and, 440
  striae distensae and, 398
Sweet's syndrome. *See also* Acute febrile neutrophilic dermatosis; Acute neutrophilic dermatosis
  Behçet's syndrome and, 413, 413*f*
  bowel-associated dermatosis-arthritis syndrome v., 412–413
  drug-induced, 315
  erythema nodosum with, 515
  histopathology of, 115–117
  neutrophils and, 43
  pyoderma gangrenosum v., 224, 411–412
Sweet's-like neutrophilic dermatosis. *See* Acute febrile neutrophilic dermatosis
Swimmer's itch. *See* Dermatitis schistosomica
SWO. *See* Superficial white onychomycosis
Symplastic hemangioma, 1028
  differential diagnosis of, 1028
  histopathology of, 1028, 1028*f*–1029*f*
Synaptophysin
  antibodies against, 76*t,* 77
  Merkel cells and, 19
  peripheral neuroblastoma, 1140
Syncytiotrophoblasts, 1158
Syndecan-1, transient acantholytic dermatosis and, 273
Syndromic acanthosis nigricans, 448
Synovial chondroma, 1094
Synovial chondromatosis, 1094
Synovial lipomatosis. *See* Lipoma arborescens
Synovial sarcoma, 994–995
  histogenesis of, 995
  histopathology of, 125, 995, 995*f*
  malignant peripheral nerve sheath tumor v., 1125
  mesenchymal chondrosarcoma v., 1099
  myopericytoma and, 1049
Synovitis, mixed connective tissue disease with, 292
Syphilides, papulonecrotic tuberculids v., 554
Syphilis
  Behçet's syndrome v., 414
  discoid lupus erythematosus v., 282–283
  endemic, 585
    histopathology of, 585
  histopathology of, 130
  in HIV, 579, 582, 659
  Jessner's lymphocytic infiltration of the skin v., 291
  leprosy v., 566
  macular atrophy and, 400
  plasma cells and, 46
  primary, 579–581, 580*f*–581*f*
    histopathology of, 89, 89*f,* 94, 94*f,* 108, 117
  secondary, 579, 581–583, 581*f*–582*f*
    erythema annulare centrifugum and, 171
    histopathology of, 89, 89*f,* 91, 91*f,* 94, 94*f,* 107–112, 116–119, 129
  tertiary, 579–580, 583
    histopathology of, 94, 94*f,* 117–119
  venereal, 579–583, 580*f*–582*f*
    histopathology of, 580
    yaws v., 584
Syphilis cornee, 579
  of secondary syphilis, 582
Syphilitic alopecia, of secondary syphilis, 582
Syphilitic chancre
  primary, histopathology of, 116
  of venereal syphilis, 579–580, 580*f*
Syphilitic gummas, erythema nodosum v., 515
Syphilitic hepatic cirrhosis, 583
Syringes, injection abscess from use of, 567–568, 568*f*
Syringoacanthoma of Rahbari, 887
Syringocystadenoma papilliferum (SCAP), 878–880
  additional studies of, 879–880
  histopathology of, 123, 127, 879, 879*f*
  with nevus sebaceus, 871
  with tubular apocrine adenoma, 880
Syringoid eccrine carcinoma, 896
  additional studies of, 896
  histopathology of, 123, 896, 896*f*–897*f*
Syringolymphoid hyperplasia
  with alopecia, 490–491
  with follicular mucinosis, 468
  histopathology of, 128, 490–491, 490*f*
Syringoma, 884–885
  additional studies of, 885
  differential diagnosis of, 885
  histopathology of, 123, 884–885, 884*f*–885*f*
  microcystic adnexal carcinoma v., 897
  with nevus sebaceus, 871
Syringometaplasia, with adnexotropic mycosis fungoides, 939–940
Syringosquamous metaplasia, histopathology of, 128, 322
Syringotropic mycosis fungoides, histopathology of, 128
Systemic blastomycosis, 604
Systemic coccidioidomycosis, 608–609
Systemic cryptococcosis, 609
Systemic disease, pigmentary presentations of, 692–693
  histogenesis of, 693
  histopathology of, 692–693
Systemic herpes simplex, 639
Systemic lupus erythematosus (SLE), 285–291, 286*t,* 287*f*–289*f,* 289*t*–291*t*
  Behçet's syndrome v., 414
  bullous systemic lupus erythematosus with, 263
  with chilblains, 353
  classification criteria of, 279
  dermatomyositis v., 293–294
  drugs associated with, 286–287, 286*t*
  erythema elevatum diutinum v., 222

histopathology of, 287, 287*f*–288*f*
mixed connective tissue disease v., 293
pathogenesis and laboratory findings of, 288–291, 289*t*–291*t*
pemphigus vulgaris v., 249
poikiloderma atrophicans vasculare and, 295
with relapsing polychondritis, 493
rheumatoid nodules with, 367
systemic lesions of, 287–288, 289*f*
types of, 286
urticarial vasculitis, 219
Systemic neoplasms, with LCD, 669
Systemic scleroderma, 299–301, 300*t*
collagen matrix aberrations with, 300–301
histopathology of, 299–300
macular atrophy and, 400
microvascular changes of, 300
pathogenesis and laboratory findings of, 300, 300*t*
serologic/immunologic markers of, 301
systemic lesions of, 300
systemic lupus erythematosus with, 286
Systemic sporotrichosis, 613
Systemic vasculitis, Wegener's granulomatosis and, 214

T cells, 44
acute febrile neutrophilic dermatosis and, 223
anaplastic large cell lymphoma, 952
Behçet's syndrome and, 414
eosinophilic pustular folliculitis and, 467
graft-*versus*-host disease and, 270–272
identification of, 45
ILVEN and, 194
infiltration patterns of, 911–913, 913*f,* 913*t*
abnormal, 913–915, 914*f*
lichen planus and, 190
in skin, 911
skin infiltration by, 44–45
T lymphocytes, lepromin reaction of, 566
TA. *See* Takayasu's arteritis
Tache noire eschars, 568
Taenia solium, 632, 632*f*
Taeniasis, 632
Takayasu's arteritis (TA), 208
differential diagnosis of, 208
histopathology of, 208
macular atrophy and, 400
Talc granuloma
foreign-body reactions and, 374
histopathology of, 117, 121, 375
polariscopic examination of, 70, 70*f*
T-ALL. *See* T-lymphoblastic leukemia
Talon noir. *See* Calcaneal petechiae
Talwin. *See* Pentazocine
Tapeworm, subcutaneous cysticercosis, 632, 632*f*
Target stages, of parapoxvirus infections, 648, 648*f*
"Target-like" pattern, in dysplastic nevus, 735
Targetoid hemosiderotic hemangioma. *See also* Hobnail hemangioma
histopathology of, 126
Tattoos
drug-induced pseudolymphoma syndrome with, 320
granuloma annulare and, 361
reactions to, 377–378, 378*f*
histopathology of, 121, 378, 378*f*–379*f*
sarcoidosis and, 370
T-cell leukemia, with adult T-cell leukemia/lymphoma, 954
T-cell lymphoblasts, precursor B-cell lymphoblastic lymphoma v., 925
T-cell lymphoid hyperplasia, primary cutaneous CD4-positive small-/medium-sized pleomorphic T-cell lymphoma v., 950

T-cell lymphoma
actinic prurigo v., 336
angiocentric, histopathology of, 116
chronic actinic dermatitis v., 339–340
Hodgkin's lymphoma v., 935
hydroa vacciniforme v., 338
peripheral T-cell lymphoma v., 952
pigmented purpuric dermatosis v., 228
T-cell prolymphocytic leukemia v., 956
T-cell lymphomatoid hyperplasias, 935–936
clinical features of, 935
differential diagnosis of, 936
histogenesis of, 936
histopathology of, 935–936, 935*f*
T-cell neoplasms, 936–951
cutaneous γ/δ T-cell lymphoma, 950–951
extranodal NK-/T-cell lymphoma, 948–949
mycosis fungoides, 936–944, 936*f*–941*f,* 939*t,* 943*f*
primary cutaneous aggressive CD8-positive T-cell lymphoma, 949–950
primary cutaneous CD4-positive small-/medium-sized pleomorphic T-cell lymphoma, 950
primary cutaneous CD30-positive T-cell, 945–947, 945*f*–947*f*
primary cutaneous peripheral T-cell lymphoma, 949
Sézary syndrome, 944–945, 945*f*
subcutaneous panniculitis-like T-cell lymphoma, 948, 948*f*
T-cell prolymphocytic leukemia (T-PLL), 955–956
clinical features of, 955
differential diagnosis of, 956
histogenesis of, 955–956
histopathology of, 955
TdT. *See* Terminal deoxynucleotidyl transferase
TEE. *See* Perforating disorders
Teeth, ectodermal dysplasia and, 142
Telangiectases
with chemical burns, 346
with nevus flammeus, 1011
of rosacea, 463
Telangiectasia
generalized essential, 1011
hereditary hemorrhagic, 1012
poikiloderma atrophicans vasculare and, 295
radiation dermatitis and, 348
unilateral nevoid, 1012
Telangiectasia macularis eruptiva perstans (TMEP)
histopathology of, 89, 89*f,* 107, 111
urticaria pigmentosa v., 158, 160
Telangiectatic metastatic breast carcinoma, 1152
Telogen effluvium, 478
androgenetic alopecia and, 480
histopathology of, 127, 478–479, 479*f*
pathogenesis of, 479
systemic lupus erythematosus with, 285
trichotillomania v., 477
Telogen hair
in alopecia areata, 474–475
definition of, 472, 472*f*
in eruptive vellus hair cysts, 806
in growth cycle, 26–27, 29*f,* 31
senescent alopecia and, 489
Teloptosis, 479
Temperature regulation, by eccrine gland, 35
TEN. *See* Toxic epidermal necrolysis
Tenascin, in synovial sarcoma, 995
Tendon sheath
fibroma of, 125, 982, 983*f*
giant cell tumor of, 125, 974, 974*f*
lipoma of, 1060
Tendon xanthomas, 680–682, 683
Terazosin, lichenoid drug eruption and, 313

Terbinafine
acute generalized exanthematous pustulosis with, 314
drug-induced lupus erythematosus with, 318
Terminal deoxynucleotidyl transferase (TdT), precursor B-cell lymphoblastic lymphoma, 924–925
Terminal hair, 472, 472*f*
in androgenetic alopecia, 479–481
Tertiary lesion
of pinta, 585
of yaws, 584
Tertiary lesions, of endemic syphilis, 585
Tertiary syphilis, 579–580, 583
Tertiary yaws, 584
Testis, epithelioid hemangioma of, 1023
Testosterone
acne vulgaris and, 460–461
androgenetic alopecia and, 481
Tetracycline
drug-induced pigmentary alterations of, 692
drug-induced pseudoporphyria with, 320
fixed drug eruptions with, 314
photodistributed hyperpigmentation and, 319
phototoxic drug eruption and, 319
pseudoporphyria cutanea tarda with, 435
for rickettsial infections, 568
TGFs. *See* Transforming growth factors
Thalidomide, for leprosy, 565
Therapeutic regional lymph node dissection (TRLND), 770
Thermal burns, 274–275, 343
histopathology of, 108, 112, 114, 274–275
Thiazides
leukocytoclastic vasculitis and, 221
photoallergic drug eruption and, 318
Thibierge-Weissenbach syndrome, 437
Third-degree burns, 275, 343, 345, 345*f*–346*f*
Thrombi
deep, histopathology of, 118–119
histopathology of, 118
Thromboangiitis obliterans. *See* Buerger's disease
Thrombocytopenia
systemic lupus erythematosus and, 288
with T-cell prolymphocytic leukemia, 955
Thrombogenic vasculopathy, Crohn's disease and, 416
Thrombophlebitis
erythema induratum v., 521
histopathology of, 116
polyarteritis v., 518
Thrombotic thrombocytopenic purpura, histopathology of, 111
Thymoma, paraneoplastic autoimmune multiorgan syndrome and, 254
Thymus, Langerhans cells in, 21
Thyroglossal duct cysts, 805
bronchogenic duct cysts v., 805
histopathology of, 127, 805, 805*f*
pathogenesis of, 805
Thyroid adenomas, Cowden's disease with, 869
Thyroid cancer, 1159
Thyroid disease
alopecia areata and, 475
palisaded neutrophilic and granulomatosis with, 369
Thyrotoxicosis, pretibial myxedema and, 441
TIA-1, anaplastic large cell lymphoma, 953
Tick bites
Lyme disease from, 585–586
rickettsial infections from, 568–569, 568*f*–569*f*
TILs. *See* Tumor-infiltrating lymphocytes
Tinea, 591–593, 592*t*
Tinea barbae, 593–594, 593*t*
Tinea capitis, 592–593, 593–594, 593*t,* 594*f*
tufted hair folliculitis with, 487

Tinea corporis, 593, 593*t,* 594, 594*f*
Tinea cruris, 593, 593*t,* 594
Tinea faciei, 593, 593*t,* 594
Tinea of feet and hands, 593, 593*t,* 594
Tinea of glabrous skin, 594
Tinea pedis et manus. *See* Tinea of feet and hands
Tinea unguium, 593, 593*t,* 595, 595*f*
  histopathology of, 100, 100*f,* 129
Tinea versicolor, 60. *See also* Pityriasis (tinea) versicolor
  histopathology of, 103–104
  in HIV, 659
Tinea yaws, 583
Titanium granuloma, 377
  histopathology of, 377
T-LBL. *See* T-lymphoblastic lymphoma
T-lymphoblastic leukemia (T-ALL), 955
  clinical features of, 955
  differential diagnosis of, 955
  histogenesis of, 955
  histopathology of, 955, 956*f*
  T-cell prolymphocytic leukemia v., 956
T-lymphoblastic lymphoma (T-LBL), 955
  clinical features of, 955
  differential diagnosis of, 955
  histogenesis of, 955
  histopathology of, 955, 956*f*
T-lymphocytes, chronic actinic dermatitis and, 339
TMEP. *See* Telangiectasia macularis eruptiva perstans
TNFs. *See* Tumor necrosis factors
TNM staging system. *See* Tumor-node-metastasis staging system
Togaviridae, 637
Tolbutamide, photoallergic drug eruption and, 318
Tongue
  epithelioid hemangioma of, 1023
  lingua geographica of, 795
Tonofilaments
  amyloid filaments and, 429
  cellular cohesion with, 12
  Darier's disease and, 151
  of eccrine hidrocystoma, 884
  in eccrine poroma, 887
  epidermolytic hyperkeratosis and, 135
  friction blisters and, 274
  microanatomy of, 8, 10–11, 10*f*
  nails and, 37–38
  in nodular hidradenoma, 892
  of oral mucosa, 12
  in pilomatricoma, 865
  transient acantholytic dermatosis and, 273
Tophi
  gout and, 438, 438*f*
  staining of, 438
TORCH. *See* Toxoplasm, rubella, cytomegalovirus, or herpesvirus
Touton giant cells
  of juvenile xanthogranuloma, 672, 673*f*
  in necrobiosis lipoidica, 366–367
  of necrobiotic xanthogranuloma with paraproteinemia, 683, 684*f*
  of papular xanthoma, 673, 674*f*
  Spitz nevus and, 723
  of xanthoma disseminatum, 675
  in xanthomas associated with lipid abnormalities, 681
Toxic acral erythema, 315
  histopathology of, 315
Toxic drug eruptions, necrolytic migratory erythema v., 409
Toxic epidermal necrolysis (TEN), 268–270, 269*f*–270*f,* 312–313, 313*f*
  burns and, 343
  differential diagnosis of, 270
  EM and SJS v., 268–269, 269*f*
  fixed drug eruptions v., 314
  histopathology of, 112, 114, 129, 269, 270*f,* 313, 313*f*
  immunofluorescence testing for, 270
  pathogenesis of, 270
  pemphigus vulgaris v., 249
  staphylococcal scalded-skin syndrome v., 541
  ultrastructural study of, 270
Toxic epidermolysis, with nail unit, 506
Toxic shock syndrome (TSS), 541, 546
  histopathology of, 108, 115, 546
  pathogenesis of, 546
Toxic shock syndrome toxin-1 (TSST-1), 546
Toxicity of drugs. *See* Cutaneous toxicities of drugs
Toxins
  exfoliative, 540
  of *Mycobacterium ulcerans,* 558
  staphylococcal enterotoxins, 546
  toxic shock syndrome toxin-1, 546
Toxoplasm, rubella, cytomegalovirus, or herpesvirus (TORCH), 644
Toxoplasmosis, erythema nodosum with, 514
T-PLL. *See* T-cell prolymphocytic leukemia
Traction alopecia, 477
  histopathology of, 477–478–478*f*
Transepidermal elimination (TEE). *See also* Perforating disorders
  of nevus cells, 721
Transepithelial elimination, of schistosomiasis ova, 631
Transformed CD30^{+} lymphoid cells, in arthropod assault reactions, 634
Transformed schwannomas, 1119, 1119*f,* 1121–1122
  histopathology of, 125
Transforming growth factors (TGFs), of keratinocytes, 13
Transglutaminase gene, mutation in, 135
Transient acantholytic dermatosis, 273–274, 273*f*
  differential diagnosis of, 274
  histopathology of, 93, 93*f,* 113–114, 273, 273*f*
  immunofluorescence testing for, 273–274
  pathogenesis of, 274
  ultrastructural study of, 274
Transient neonatal pustular melanosis, 267
  acropustulosis of infancy v., 267
  erythema toxicum neonatorum v., 267
  histopathology of, 112, 267
Transitional cell carcinomas, 1156
Transplacental infection, with herpes simplex, 639
Trauma
  histiocytoses from, 668
  xanthomas with, 686
Traumatic fat necrosis, histopathology of, 130
Traumatic neuromas, histopathology of, 125
Traumatic panniculitis
  histopathology of, 102, 102*f,* 131
  lipomembranous panniculitis with, 531
Trematodes, schistosomiasis, 631–632, 632*f*
Treponema carateum, 584–585
Treponema pallidum subspecies *endemicum,* 585
Treponema pallidum subspecies *pertenue,* 583–584, 584*f*
Treponema pallidum, venereal syphilis from, 579–583, 580*f*–582*f*
Treponemal diseases, 579–589
  nonvenereal treponematoses, 583–589, 584*f,* 586*f*–587*f*
    Lyme disease, 585–589, 586*f*–587*f*
    pinta, 584–585
    yaws, 583–584, 584*f*
  venereal syphilis, 579–583, 580*f*–582*f*
    primary, 579–581, 580*f*–581*f*
    secondary, 579, 581–583, 581*f*–582*f*
    tertiary, 579–580, 583
Trichilemmal carcinoma, 870
  additional studies of, 870
  differential diagnosis of, 803, 870
  histopathology of, 124, 803, 803*f,* 870
  pathogenesis of, 803
Trichilemmal cysts, 802–803, 802*f*–803*f*
  epidermolytic hyperkeratosis in, 793
  foreign-body reactions and, 373
  histopathology of, 127
  pilomatricoma v., 865
Trichilemmal horn, 870
  histopathology of, 870
Trichilemmal keratinization, 27*f,* 30
Trichilemmoma, 867–869
  cutaneous horn and, 811, 811*f*
  histopathology of, 123
  multiple, 869
    differential diagnosis of, 869
    histopathology of, 869
  with nevus sebaceus, 871
  nodular hidradenoma v., 892
  solitary, 867–869
    differential diagnosis of, 869
    histopathology of, 868, 868*f*
  trichoblastoma v., 861
  tumor of the follicular infundibulum v., 870
Trichilemmomal horn, 870
  histopathology of, 870
Trichoadenoma, 862–863
  additional studies of, 863
  histopathology of, 123, 862–863, 862*f*–863*f*
  with nevus sebaceus, 871–872
Trichoblastic carcinoma, 861
Trichoblastic fibroma, histopathology of, 123
Trichoblastoma, 860–862, 861*f*
  histopathology of, 123, 860–862, 861*f*–862*f*
Trichodiscoma, 856–857
  additional studies of, 857
  histopathology of, 123, 856–857, 856*f*–857*f*
Trichoepithelioma, 857–859
  additional studies of, 859
  basal cell carcinoma v., 834–835
  cylindroma and, 881
  differential diagnosis of, 859
  generalized hair follicle hamartoma v., 863
  histopathology of, 97, 97*f,* 123, 858–859, 858*f*
  syringoma v., 885
  trichoblastoma v., 860
Trichofolliculoma, 854–855
  additional studies of, 854–855
  histopathology of, 123, 854, 854*f*
Trichogenic myxoma, neurothekeoma v., 1129
Trichohyaline granules
  in inner root sheath, 29
  of trichofolliculoma, 854
Trichomalacia, with trichotillomania, 477
Trichophyton infections, 592–595
Trichophyton mentagrophytes, 593, 594–595
  nail unit and, 506–507
  onychomycosis with, 507
Trichophyton rubrum, 593, 594–595
  histopathology of, 128
  nail unit and, 506–507
  onychomycosis with, 507
Trichophyton schoenleinii, 592–593, 594, 595
  histopathology of, 128
Trichophyton tonsurans, 592, 593, 594
Trichophyton verrucosum (faviforme), 593, 594–595
Trichophyton violaceum, 594
Trichorrhexis invaginata, histopathology of, 127
Trichorrhexis nodosa, lipedematous alopecia and, 489
Trichostasis spinulosa, 470
  histopathology of, 127, 470, 470*f*
  pathogenesis of, 470

Trichotillomania, 476
  histopathology of, 127, 476–477, 476*f*–477*f*
Trimethoprim-sulfamethoxazole
  adverse reactions to, 660
  fixed drug eruptions with, 314
  SJS and TEN with, 313
  ultraviolet recall and, 346
TRLND. *See* Therapeutic regional lymph node dissection
Trophozoites, 625, 625*f*
Trousseau's syndrome, superficial migratory thrombophlebitis and, 517
True negativity rate, in diagnosis, 1
True positive rate, in diagnosis, 1
Trypanosoma infections, 621–625, 622*t,* 623*f*–624*f*
Trypsin, in pancreatic disease, 528
Tryptase, mast cells and, 41
L-Tryptophan
  drug-induced scleroderma with, 316
  eosinophilic fasciitis and, 303
  scleroderma and, 296
TSS. *See* Toxic shock syndrome
TSST-1. *See* Toxic shock syndrome toxin-1
Tuberculids, 553–555, 554*f*
  lichen scrofulosorum, 553–555, 554*f*
  papulonecrotic tuberculids, 553–554, 554*f*
Tuberculin skin test, granuloma annulare and, 362
Tuberculoid granulomas, of chronic cutaneous leishmaniasis, 624
Tuberculoid leprosy, 559, 559*f,* 563, 566
  histopathology of, 118, 563
  sarcoidosis v., 373
Tuberculosis, 550–555, 551*f*–554*f*
  Behçet's syndrome v., 414
  differential diagnosis of, 553
  erythema induratum and, 521
  erythema nodosum with, 514, 550
  histopathology of, 95, 95*f,* 118–119, 130–131
  leprosy v., 566
  lichen scrofulosorum, 550
  lupus vulgaris, 550, 551–552, 552*f*
  macular atrophy and, 400
  papulonecrotic tuberculid, 550
  primary, 550–551, 551*f*
  sarcoidosis v., 371
  scrofuloderma, 550, 552
  tuberculids, 553–555, 554*f*
    lichen scrofulosorum, 553–555, 554*f*
    papulonecrotic tuberculids, 553–554, 554*f*
  tuberculosis cutis orificialis, 553
  tuberculosis verrucosa cutis, 550, 551, 551*f*
  tuberculous gumma, 552, 553*f*
Tuberculosis cutis orificialis, 553
  histopathology of, 120, 553
Tuberculosis verrucosa cutis, 550, 551, 551*f*
  histopathology of, 118, 551, 551*f*
  miliary tuberculosis, 551
  Mycobacterium marinum infection v., 556
  North American blastomycosis v., 604
Tuberculous chancre, 550–551
Tuberculous gumma, 552, 553*f*
  histopathology of, 119, 552, 553*f*
Tuberoeruptive xanthomas, 680
Tuberous sclerosis, 988–989
  differential diagnosis of, 989
  histopathology of, 989, 989*f*
  systemic lesions of, 989
Tuberous xanthomas, 680–682, 682*f,* 683
Tubular apocrine adenoma, 880
  additional studies of, 880
  differential diagnosis of, 880
  histopathology of, 123, 880, 880*f*
Tubular lumina
  in chondroid syringoma, 894, 894*f*
  cylindroma and, 882
  in nodular hidradenoma, 891, 891*f*
Tubulopapillary hidradenoma, 880
Tufted angioma, 1015–1016
  differential diagnosis of, 1016
  histopathology of, 126, 1015–1016, 1015*f*–1016*f*
  reactive angioendotheliomatosis v., 1009–1010
Tufted hair folliculitis, 487–488, 487*f*
  histopathology of, 128, 488, 488*f*
  pathogenesis of, 488
Tularemia, 568
  erythema nodosum with, 514
  histopathology of, 120, 568
  sporotrichosis v., 614
Tumbu fly, as myiasis vector, 632
Tumid lupus erythematosus, 283, 284*f*
Tumor necrosis factors (TNFs)
  interstitial granulomatous drug reaction and, 381
  of keratinocytes, 13
Tumor of the follicular infundibulum, 869–870
  differential diagnosis of, 870
  histopathology of, 869–870, 869*f*–870*f*
Tumor vascularity, melanoma prognosis and, 768
Tumoral calcinosis
  histopathology of, 121
  idiopathic calcinosis cutis and, 437
Tumoral melanosis, 765*f,* 767
Tumorigenic melanoma, 749–759
  animal-type, 757
  balloon cell, 756–757
  classification of, 738–739, 739*t*
  deep penetrating nevus v., 730
  definition of, 741, 742*f*
  desmoplastic and neurotropic, 753–756, 754*f*–755*f*
  minimal deviation, 757–758
  morphology of, 740–742, 740*f*–742*f*
  myxoid, 757
  nevoid, 758, 759*f*
  nodular melanoma and common, 749–753, 751*f*
  pigmented epithelioid melanocytoma, 757, 758*f*
  polypoid, 756
  signet cell, 757
  verrucous, 756
Tumorigenic primary melanomas, histopathology of, 123
Tumor-infiltrating lymphocytes (TILs)
  melanoma prognosis with, 766*f,* 767
  nodular melanoma and, 750–752, 751*f*
Tumor-node-metastasis (TNM) staging system, for malignant melanoma, 762–764, 763*t*–764*t*
Tumors. *See also* Desmoid tumor; Fibrohistiocytic tumors; Giant cell tumors; Glomus tumors; Granular cell nerve sheath tumor; Granular cell tumor; Malignant extrarenal rhabdoid tumor; Malignant granular cell tumor; Malignant peripheral nerve sheath tumor; Malignant proliferating trichilemmal tumor; Malignant tumors; Melanocytic tumors; Myofibroblastic tumors; Neuroendocrine tumor; Plexiform fibrohistiocytic tumor; Primitive neuroectodermal tumors; Small blue round cell tumors; Small round cell tumors
with apocrine glands differentiation, 876–883
  apocrine adenoma; apocrine fibroadenoma, 880
  apocrine hidrocystoma, 877–878, 877*f*
  apocrine nevus, 876–877
  cylindroma, 881–883, 882*f*
  erosive adenomatosis of the nipple, 881, 881*f*
  hidradenoma papilliferum, 878, 878*f*
  malignant cylindroma, 883
  syringocystadenoma papilliferum, 878–880, 879*f*
  tubular apocrine adenoma, 880, 880*f*
benign appendageal
  classification of, 852–853, 852*t*
  ontogeny of, 853
  terminology for, 853
benign cartilagenous, 1094–1097
  calcifying aponeurotic fibroma, 1096–1097, 1097*f*
  soft tissue chondromas, 1094–1096, 1095*f*–1096*f*
chondro-osseus, 1086–1100
  benign cartilagenous tumors, 1094–1097
  cutaneous ossification, 1086–1094
  extraskeletal myxoid chondrosarcoma, 1097–1098, 1098*f*
  mesenchymal chondrosarcoma, 1098–1099, 1099*f*
  osseous and chondroid lesions, 1099–1100, 1100*f*
chondrosarcoma, 1097–1099
  extraskeletal myxoid chondrosarcoma, 1097–1098, 1098*f*
  mesenchymal chondrosarcoma, 1098–1099, 1099*f*
dermatoradiology of, 1057, 1058*t*
of dermis and subcutis, 96–98, 96*f*–98*f*
  cysts of dermis and subcutis, 98, 98*f,* 127
  large polygonal and round cell, 97, 97*f,* 122–125
  small cell, 96, 96*f,* 121–122
  spindle cell, pleomorphic, and connective tissue tumors, 98, 98*f,* 125–127
desmoplastic melanoma v., 756
diagnosis of, 75–79, 76*t,* 77*f*–79*f,* 79*t*
differentiation in, 1057
with eccrine glands differentiation, 883–895
  chondroid syringoma, 893–894, 893*f*–894*f*
  eccrine hidrocystoma, 884, 884*f*
  eccrine nevus, 883, 883*f*
  eccrine poroma, 885–887, 886*f*
  eccrine spiradenoma, 888–889, 889*f*
  eccrine syringofibroadenoma, 888, 888*f*
  malignant chondroid syringoma, 894–895, 895*f*
  malignant eccrine poroma, 887–888, 887*f*
  malignant eccrine spiradenoma, 890, 890*f*
  malignant nodular hidradenoma, 892, 892*f*–893*f*
  mucinous syringometaplasia, 888
  nodular hidradenoma, 891–892, 891*f*
  papillary eccrine adenoma, 890–891, 890*f*
  syringoma, 884–885, 884*f*–885*f*
of epidermal appendages, 851–900
  classification of, 851–853, 852*t*
  terminology for, 853
of epidermis. *See* Epidermis, tumors and cysts of
with fatty differentiation
  angiolipoma, 1064–1066
  benign lipoblastoma, 1070–1071, 1071*f*
  chondroid lipoma, 1067–1068, 1068*f*
  folded skin with lipomatous nevi, 1058–1060
  hibernoma, 1068–1070, 1069*f*
  lipofibromatosis, 1070
  lipomas, 1060–1064, 1061*f*–1064*f,* 1065*t*
  liposarcoma, 1071–1075, 1073*f*–1074*f*
  nevus lipomatosus superficialis, 1058, 1059*f*
  piezogenic papules, 1060
  pleomorphic lipoma, 1066–1067, 1067*f*
  spindle cell lipoma, 1066, 1066*f*
of fibrous tissue
  classification of, 969, 970*t*
  fibroblastic/myofibroblastic-benign, 979–992
  fibroblastic/myofibroblastic-intermediate biological potential (locally aggressive), 992–993
  fibroblastic/myofibroblastic-intermediate biological potential (rarely metastasizing), 993–994
  fibrohistiocytic tumors-benign, 969–974

Tumors (*continued*)
fibrohistiocytic tumors-intermediate biological potential (locally aggressive), 974–977
fibrohistiocytic tumors-intermediate biological potential (rarely metastasizing), 977–979
fibrohistiocytic tumors-malignant, 979
miscellaneous lesions, 997–998
of uncertain differentiation-benign, 994
of uncertain differentiation-intermediate biological potential (rarely metastasizing), 994
of uncertain differentiation-malignant, 994–997
with hair follicle differentiation, 853–870
desmoplastic trichoepithelioma, 859–860, 860*f*
dilated pore and pilar sheath acanthomas, 855–856, 855*f*–856*f*
fibrofolliculoma and trichodiscoma, 856–857, 856*f*–857*f*
generalized hair follicle hamartoma and basaloid follicular hamartoma, 863, 863*f*–864*f*
hair follicle nevus, 853–854, 853*f*
malignant proliferating trichilemmal tumor, 867
pilomatricoma, 864–865, 864*f*–865*f*
pilomatrix carcinoma, 865–866, 866*f*
proliferating trichilemmal cyst, 866–867, 867*f*
sebaceous trichofolliculoma, 855
trichilemmal carcinoma, 870
trichilemmal horn; trichilemmomal horn, 870
trichilemmoma, 867–869, 868*f*
trichoadenoma, 862–863, 862*f*–863*f*
trichoblastoma, 860–862, 861*f*–862*f*
trichoepithelioma, 857–859, 858*f*
trichofolliculoma, 854–855, 854*f*
tumor of the follicular infundibulum, 869–870, 869*f*–870*f*
modifiers of, 1057
of neural tissue, 1107–1144
cutaneous meningiomas and meningothelial heterotopias, 1141–1143, 1142*f*
degenerative nature, 1143–1144, 1143*f*
heterotopias, 1141, 1141*f*
malignant peripheral nerve sheath tumor, 1122–1126, 1122*f*–1126*f*
nerve sheath-like features, 1126–1132
neurofibromas, 1109–1110, 1109*f*–1110*f*
neurofibromatosis, 1110–1116, 1110*f*–1115*f*
neuromas, 1135–1138
perineural cells, 1132–1135
primitive neuroectodermal tumors, 1140–1141
Schwann cell neoplasms, 1116–1122
small blue round cell tumors, 1138–1140
osseous and chondroid lesions, 1099–1100, 1100*f*
pituitary, pigmentary presentations of, 692
rhabdomyosarcoma, 1084–1085, 1084*f*–1085*f*
with sebaceus gland differentiation, 870–876
Fordyce's spots and Montgomery's tubercles, 872–873, 873*f*
Muir-Torre syndrome, 875
nevus sebaceus, 870–872, 871*f*
sebaceoma, 873–874, 874*f*
sebaceous adenoma, 873, 873*f*
sebaceous carcinoma, 875–876, 875*f*–876*f*
sebaceous hyperplasia, 872, 872*f*
of smooth muscle, 1075–1083
leiomyoma, 1076–1080, 1077*f*–1079*f*
leiomyosarcoma, 1080–1083, 1081*f*–1082*f*
smooth muscle hamartoma, 1075–1076, 1076*f*
vascular, 1007–1051
benign, 1013–1028
CD31 and, 78
classification of, 1007, 1008*t*
of intermediate malignancy, 1029–1039
lymphatic vessels, 1043–1046
malignant, 1039–1043
of perivascular cells, 1047–1051
reactive conditions, 1007–1010
vascular ectasias, 1010–1013
Tumor-stage mycosis fungoides, histopathology of, 121
Tunga penetrans, as tungiasis vector, 633
Tungiasis, 633–634, 633*f*
histopathology of, 633–634, 633*f*
Tunica dartos, 46
Turban tumors. *See* Cylindroma
Twenty-nail dystrophy, 186, 189
Tyndall effect, 701
of apocrine hidrocystoma, 877
Type 1 reactions, 564, 564*f*–565*f,* 566
histopathology of, 564
Type 2 reactions, 564–565, 565*f*
histopathology of, 565
Typhoidal tularemia, 568
Tyrosinase
albinism and, 693
melanogenesis and, 17–18
Tyrosinemia type II. *See* Oculocutaneous tyrosinosis
Tyson's glands, 31

Tzanck preparation
for pemphigus foliaceus, 250
for pemphigus vulgaris, 247
Tzanck smear
of herpes simplex, 641
of herpes zoster and varicella, 643

UEA. *See Ulex europaeus* agglutinin I
Ulcerations. *See also* Buruli ulcer
of aspergillosis, 599, 601*f*
of blastomycosis, 604
of chancroid, 569, 569*f*
with dermatomyositis, 294
of ecthyma, 541
of endemic syphilis, 585
of granuloma inguinale, 570
of herpes simplex, 639
with histiocytic cytophagic panniculitis, 532
for melanoma prognosis, 767–768, 767*f*
microscopic polyarteritis and, 212
with mycosis fungoides palmaris et plantaris, 942
pigmented epithelioid melanocytoma and, 757
porphyria cutanea tarda with, 433
of primary cutaneous aggressive CD8-positive T-cell lymphoma, 950
in *Pseudomonas* septicemia, 547–548, 547*f*
with pyoderma gangrenosum, 535
radiation dermatitis and, 348
in sarcoidosis, 373
of sporotrichosis, 613
stasis dermatitis and, 243
of syphilis, 582
of tuberculosis, 550–551
of tuberculosis cutis orificialis, 553
of tularemia, 568
of yaws, 584
of zygomycosis, 599–601
Ulcerative colitis, 416–417, 416*f*–417*f*
alopecia areata and, 475
erythema nodosum with, 514
histopathology of, 417, 417*f*
Ulcerative lichen planus, 186, 188
Ulceroglandular tularemia, 568
Ulex europaeus agglutinin I (UEA), antibodies against, 76*t,* 78
Ultraviolet A (UVA)
actinic prurigo and, 336
chronic actinic dermatitis and, 338, 340
polymorphic light eruption and, 334
Ultraviolet B (UVB)
actinic keratosis and, 807
actinic prurigo and, 336
chronic actinic dermatitis and, 338, 340
hydroa vacciniforme and, 337
phototherapy
for actinic prurigo, 335
for chronic actinic dermatitis, 338
for hydroa vacciniforme, 337
for PMLE, 333
for solar urticaria, 340
polymorphic light eruption and, 334
Ultraviolet radiation (UVR)
actinic prurigo and, 335–336
burn scars and, 346
free radicals from, 738
hydroa vacciniforme and, 337
Langerhans cells and, 21
melanocytes and, 15, 15*f,* 17–18
pellagra and, 408
photoallergic dermatitis and, 241, 318–319, 319*f*
photoallergic drug eruption and, 318
in photosensitivity disorders, 333
polymorphic light eruption and, 333–334
solar lentigines and, 707
solar urticaria and, 340
trichostasis spinulosa and, 470
Ultraviolet recall, 346–347
Uncein, in lamina lucida, 23
Uncinaria stenocephala, 627
Undifferentiated pleomorphic sarcomas, 979
Ungual fibromas, tuberous sclerosis, 989
Uniform cytological atypia, of superficial spreading melanoma, 744
Unilateral nevoid telangiectasia, 1012
histogenesis of, 1012
histopathology of, 1012
Upgrading reactions, 564, 564*f,* 566
Upper respiratory tract, mucocutaneous leishmaniasis of, 624
Urates
foreign-body reactions and, 373
gout and, 438–439
Urbach-Wiethe disease. *See also* Lipoid proteinosis
histopathology of, 121
Ureaplasma urealyticum, Reiter's disease and, 182
Uremic follicular hyperkeratosis. *See* Acquired perforating dermatosis
Urethritis, Reiter's disease and, 181
Urocanic acid, pellagra and, 408
Urticaria, 169–170, 170*f*
with hepatitis B, 661
histopathology of, 115, 169, 170*f*
middermal elastolysis and, 399
neutrophils and, 43
pathogenesis of, 169–170
polyarteritis nodosa and, 210
Urticaria pigmentosa, 158–160, 158*f*–159*f*
forms of, 158, 159*f*
histopathology of, 94, 94*f,* 107, 117, 159–160, 159*f*
macular atrophy and, 400
systemic lesions of, 160
Urticarial reaction, to arthropod assault, 634
Urticarial vasculitis (UV), 169–170, 219, 219*f*
hepatitis C with, 661
histopathology of, 111, 169, 219
pathogenesis of, 170
systemic lupus erythematosus with, 285
Uterine leiomyoma, 1076
UV. *See* Urticarial vasculitis
UVA. *See* Ultraviolet A
UVB. *See* Ultraviolet B
Uveitis
erythema nodosum with, 514
tattoo reactions and, 378

Uveoparotid fever, erythema nodosum with, 514
UVR. *See* Ultraviolet radiation

Vaccinations
  epithelioid hemangioma v., 1025
  erythema nodosum with, 515
  with vaccinia virus, 647
Vaccines, histopathology of, 121
Vaccinia necrosum, 647
Vaccinia virus, 647
  histopathology of, 647
  Kaposi's varicelliform eruption with, 641–642
Vacuolar degeneration, with lichen planus of the nail, 505
Vacuolization of cells
  of condyloma acuminatum, 655, 655*f*
  of oral focal epithelial hyperplasia, 657, 657*f*
  of verruca plana, 653, 653*f*
Vagina
  Langerhans cells in, 21
  mucosal lentiginous melanoma of, 749
  oral white sponge nevus in, 794
Vaginal candidiasis, 597
Vaginal intraepithelial neoplasia (VIN), giant condyloma acuminata of Buschke and Loewenstein in, 656
Valley fever. *See* Coccidioidomycosis
Variant vertical growth phase melanoma, 742, 742*f*
Varicella, 640*f,* 642–643, 642*f*
  in compromised hosts, 643
  herpes simplex v., 641
  histogenesis and viral identification of, 643–644
  histopathology of, 643
  macular atrophy and, 400
  Tzanck smear of, 643
Varicella of fetus and newborn, 642
Varicella-zoster, histopathology of, 92, 92*f,* 114
Varicose veins
  spindle cell hemangioma with, 1027
  superficial thrombophlebitis and, 209
Variola, 647
  histopathology of, 647
Vascular ectasias
  angiokeratoma, 1011, 1011*f*
  angioma serpiginosum, 1012
  cutaneous collagenous vaculopathy, 1011–1012
  generalized essential telangiectasia, 1011
  hereditary hemorrhagic telangiectasia, 1012
  nevus araneus, 1012
  nevus flammeus, 1010–1011
  unilateral nevoid telangiectasia, 1012
  venous lake, 1012–1013
Vascular hyperplasia, epithelioid hemangioma v., 1025
Vascular injury
  definitions of, 206, 206*t*
  in herpes simplex infection, 641
  of strongyloidiasis, 628
  of zygomycosis, 601
Vascular invasion, melanoma prognosis and, 768, 768*f*
Vascular lipomas, histopathology of, 126
Vascular malformations, histopathology of, 126
Vascular nevi, acantholytic dyskeratosis in, 794
Vascular thrombosis, 206, 228–230, 229*f*
  Behçet's syndrome and, 414
  histopathology of, 228–230
Vascular tumors, 1007–1051
  benign, 1013–1028
    acquired elastotic hemangioma, 1025–1026, 1026*f*
    angiomatosis, 1027
    arteriovenous hemangioma, 1026–1027, 1026*f*–1027*f*
    capillary hemangioma variants, 1014–1016
    cavernous hemangioma, 1019–1020
    congenital hemangiomas, 1013–1014
    cutaneous epithelioid angiomatous nodule, 1025, 1025*f*–1026*f*
    epithelioid hemangioma, 1022–1025, 1023*f*–1024*f*
    hobnail hemangioma, 1021–1022, 1022*f*
    microvenular hemangioma, 1020–1021, 1021*f*
    pyogenic granuloma, 1016–1019, 1016*f*–1018*f*
    spindle cell hemangioma, 1027–1028, 1027*f*–1028*f*
    symplastic hemangioma, 1028, 1028*f*–1029*f*
    verrucous hemangioma, 1020, 1020*f*
  CD31 and, 78
  classification of, 1007, 1008*t*
  of intermediate malignancy, 1029–1039
    composite hemangioendothelioma, 1037, 1037*f*
    giant cell angioblastoma, 1038–1039
    Kaposi-like infantile hemangioendothelioma, 1038, 1038*f*
    Kaposi's sarcoma, 1029–1035, 1030*f*–1034*f*
    papillary intralymphatic angioendothelioma, 1036–1037, 1037*f*
    retiform hemangioendothelioma, 1035–1036, 1036*f*
  of lymphatic vessels, 1043–1046
    atypical vascular proliferation after radiotherapy, 1046, 1046*f*–1047*f*
    cavernous lymphangioma and cystic hygroma, 1044, 1044*f*
    lymphangioma circumscriptum, 1044–1045, 1045*f*
    lymphangiomatosis, 1045–1046
    progressive lymphangioma, 1045, 1046*f*
  malignant, 1039–1043
    angiosarcoma, 1040–1043, 1041*f*–1042*f*
    epithelioid hemangioendothelioma, 1039–1040, 1039*f*–1040*f*
  of perivascular cells, 1047–1051
    glomus tumor, 1047–1049, 1047*f*–1048*f*
    myopericytoma, 1049–1051, 1049*f*–1050*f*
  reactive conditions, 1007–1010
    angioendotheliomatosis, 1007
    glomeruloid hemangioma, 1010, 1010*f*
    intravascular papillary endothelial hyperplasia, 1007, 1009*f*
    reactive angioendotheliomatosis, 1008–1010, 1009*f*
  vascular ectasias, 1010–1013
    angiokeratoma, 1011, 1011*f*
    angioma serpiginosum, 1012
    cutaneous collagenous vaculopathy, 1011–1012
    generalized essential telangiectasia, 1011
    hereditary hemorrhagic telangiectasia, 1012
    nevus araneus, 1012
    nevus flammeus, 1010–1011
    unilateral nevoid telangiectasia, 1012
    venous lake, 1012–1013
Vasculitis, 205–233
  of acanthamoebiasis, 625
  acute febrile neutrophilic dermatosis, 223–224, 223*f*
  acute generalized exanthematous pustulosis with, 315
  bowel-associated dermatosis-arthrosis syndrome, 224
  bullous systemic lupus erythematosus and, 261
  with chronic meningococcemia, 548, 548*f*
  Churg-Strauss syndrome, 213–214, 214*f*
  criteria for, 205–206, 206*f,* 206*t*
  deep, histopathology of, 118–119
  eosinophilic panniculitis and, 515
  evaluation of, 206–207, 207*t*
  giant cell arteritis, 207–208, 208*f*
  granulomatous vasculitis and granulomatous vascular reactions, 212–213, 212*f,* 213*t*
  with herpes zoster, 643
  histopathology of, 94, 94*f,* 118
  Kawasaki's disease, 208–209
  leukocytoclastic vasculitis, 215–222, 215*f,* 216*t*
    ANCA-associated vasculitis, 221
    autoimmune diseases, 221
    Behçet's syndrome, 221
    connective tissue disease, 220–221
    cryoglobulinemias, 219–220, 220*f*
    drug-induced vasculitis, 221
    erythema elevatum diutinum, 221–222
    granuloma faciale, 222
    Henoch-Schöenlein purpura, 218–219, 218*f*
    infectious, 217–218, 218*f*
    paraneoplastic vasculitis, 221
    polyarteritis nodosa, 209–211, 211*f*
    serum sickness, 220
    urticarial vasculitis, 219, 219*f*
    Wegener's granulomatosis, 214–215
    lymphocytic small-vessel vasculitis, 224–225, 226*f,* 226*t*
    medium-sized and small vessels, 208
    microscopic polyarteritis, 211–212
    Mondor's disease, 209
    neutrophilic dermatoses, 223
    palisaded neutrophilic and granulomatosis with, 369
    of papulonecrotic tuberculids, 554, 554*f*
    pigmented purpuric dermatosis, 225–228, 227*f*–228*f*
    pyoderma gangrenosum, 224, 225*f*
    with reticular dermis, 94, 94*f,* 116
    with rheumatoid nodules, 367–368
    from scabies, 627
    subcutaneous, 100, 100*f*
    superficial, 91, 91*f*
    superficial thrombophlebitis, 209
    Takayasu's arteritis, 208
Vasculopathic reactions, 228–233, 229*t*
  atrophie blanche, 231–232, 231*f*
  calciphylaxis, 230, 230*f*
  coagulopathies and vascular thrombosis, 228–230, 229*f*
  connective tissue deficiencies, 231
  cutaneous cholesterol embolism, 230–231
  Dego's syndrome, 232–233
  livedo reticularis, 231
  metabolic vasculopathies, 230
Vasculopathy, 91, 91*f,* 206
  with reticular dermis, 94, 94*f,* 116
  subcutaneous, 100, 100*f*
  superficial, 91, 91*f*
Vasoactive intestinal polypeptide, Merkel cells and, 19
Vater-Pacini end organs
  of dermal microvascular unit, 53
  in dermis, 54*f,* 55
Vegetating plaques, of blastomycosis-like pyoderma, 546
Veins, of dermal microvasculature, 50, 51*f*
Vellus hairs
  aging of, 56
  in androgenetic alopecia, 479–481
  definition of, 472, 472*f*
  in eruptive vellus hair cysts, 806
  of face, 56–57, 57*f*
  regional variation of, 30
Venereal syphilis, 579–583, 580*f*–582*f*
  histopathology of, 580
  primary, 579–581, 580*f*–581*f*
  secondary, 579, 581–583, 581*f*–582*f*
  tertiary, 579–580, 583
  yaws v., 584

Venipuncture, silicone granuloma and, 374
Venous lake, 1012–1013
  histopathology of, 126, 1012–1013
Venous malformations, glomus tumor v., 1047
Verhoeff-van Gieson stain
  for annular elastolytic giant cell granuloma, 364
  for elastic tissues, 69, 69*t,* 70*f*
Verocay bodies, 1116–1117, 1117*f*
  palisaded angiolipoleiomyoma, 1079
  in sebaceoma, 874, 874*f*
Verruca, 685
  with follicular mucinosis, 468
Verruca plana, 653, 653*f*
  histogenesis of, 653
  histopathology of, 653
Verruca vulgaris, 650–652, 651*f*
  epidermolytic hyperkeratosis v., 793
  histogenesis and viral identification of, 651–652
  histopathology of, 88, 88*f,* 105, 650–651, 651*f*
  linear epidermal nevus v., 792
Verruciform xanthoma (VX), 685–686, 685*f*
  histopathology of, 106, 118, 124, 685–686, 685*f*
  pathogenesis of, 686
Verrucose sarcoidosis, histopathology of, 118
Verrucous carcinoma, 818, 822
  histopathology of, 106, 813, 822
  of the oral mucosa, 812–813
  pathogenesis of, 822
  pseudocarcinomatous hyperplasia v., 823
Verrucous cutaneous leishmaniasis, histopathology of, 118
Verrucous endocarditis, systemic lupus erythematosus with, 288
Verrucous hemangioma, 1020, 1020*f*
  histopathology of, 126, 1020, 1020*f*
Verrucous hyperkeratotic mycosis fungoides, histopathology of, 109
Verrucous hyperplasia
  histopathology of, 813
  of the oral mucosa, 812–813
Verrucous lesions, of blastomycosis, 604
Verrucous lupus erythematosus, 282*f,* 283
  histopathology of, 118
Verrucous melanoma, 749, 756
  histopathology of, 104, 106
  nodular melanoma and, 750
Verrucous nodules, of coccidioidomycosis, 609
Verrucous trichoadenoma, 863
Verrucous/hyperkeratotic mycosis fungoides, 942
Vertical growth phase melanoma. *See also* Tumorigenic melanoma
  definition of, 741, 742*f*
  staging for, 764
Vesicles
  definition of, 235
  of hand-foot-and-mouth disease, 658, 658*f*
  of herpes simplex, 638–639
  of herpes zoster, 643, 643*f*
  of Kaposi's varicelliform eruption, 642
  with mycosis fungoides palmaris et plantaris, 942
  of scabies, 626
  of varicella, 642, 642*f*
Vesicopustule, of impetigo contagiosa, 539, 540*f*
Vesicular disorders, 85
  intraspinous keratinocyte separation
    acantholytic, 92, 92*f*
    spongiotic, 92, 92*f*
  subcorneal or intracorneal separation, 92, 92*f*
  subepidermal vesicular dermatitis, 93, 93*f*
  suprabasal keratinocyte separation, 93, 93*f*
Vesicular lichen planus, 185, 187
Vesicular pemphigoid, 259
  differential diagnosis of, 259
Vesiculation
  burns and, 343
  of measles, 662
Vesiculobullous dermatoses
  with autoimmunity to type VII collagen, 261–263
  subepidermal IgA-mediated, 263–267
Vesiculopustular dermatoses, 267–274
  acropustulosis of infancy, 267
  coma blisters, 273
  diabetic bullae, 273
  edema blisters, 273
  erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis, 268–270, 269*f*–270*f*
  erythema toxicum neonatorum, 267
  graft-*versus*-host disease, 270–273, 271*f*–272*f*
  subcorneal pustular dermatosis, 267–268, 268*f*
  transient acantholytic dermatosis, 273–274, 273*f*
  transient neonatal pustular melanosis, 267
Vesiculopustular eruption of hepatobiliary disease,
  histopathology of, 115
VGP regression, 766, 766*f*
Vibrio vulnificus septicemia, 548
  histopathology of, 114, 548
  pathogenesis of, 548
Vimentin
  antibodies against, 75, 76*t*
  atypical fibroxanthoma and, 979
  chondroid syringoma and, 894
  in epithelioid sarcoma, 996
  granular cell nerve sheath tumor and, 1131
  in nodular hidradenoma, 892
VIN. *See* Vaginal intraepithelial neoplasia; Vulvar intraepithelial neoplasia
VIN III. *See* Vulvar intraepithelial neoplasia
Vinyl chloride disease. *See* Acro-osteolysis
Viral folliculitis, histopathology of, 128
Viral infections, 637–662
  Bowenoid papulosis of genitalia, 656–657, 657*f*
  cytomegalovirus, 644–646, 645*f*–646*f*
    Epstein-Barr virus, 644–645, 646*f*
    human herpesvirus-6, -7, -8, 645–646
  erythema nodosum with, 514
  hepatitis B, 660–661, 661*f*
  hepatitis C, 661
  Herpesviridae, 637–646, 638*f*–640*f,* 642*f*–643*f,* 645*f*–646*f*
    herpes simplex, 638–639, 638*f*
    herpes zoster infection, 640*f,* 642–644, 643*f*
    Kaposi's varicelliform eruption, 638, 638*f,* 641–642
    varicella, 640*f,* 642–643, 642*f*
measles, 662
oral focal epithelial hyperplasia, 657, 657*f*
Papillomaviridae, 649–656, 651*f*–655*f*
  condyloma acuminatum, 654–656, 655*f*
  deep palmoplantar warts, 652–653, 652*f*
  epidermodysplasia verruciformis, 653–654, 654*f*
  giant condyloma acuminata of Buschke and Loewenstein, 655*f,* 656
  verruca plana, 653, 653*f*
  verruca vulgaris, 650–652, 651*f*
parvovirus B19, 661–662, 662*f*
Picornaviridae, 637, 658–659, 658*f*
  hand-foot-and-mouth disease, 658, 658*f*
  hepatitis A virus, 659
Poxviridae, 637, 646–649, 648*f*–649*f*
  human cowpox infection, 647
  molluscum contagiosum, 649, 649*f*
  parapoxvirus infections, 647–648, 648*f*
  vaccinia virus, 647
  variola, 647
  Retroviridae, 659–660
    acquired immunodeficiency syndrome, 659–660
  rubella, 662
  verrucous carcinoma and, 822
Virchow cells, 561
Virologic approach, to virus detection, 637–638
Virulence, in histopathological diagnosis, 3
Visceral carcinoma, with arsenic, 816–817
Visceral leishmaniasis, 621, 622*t,* 624–625
  histopathology of, 625
Viscerotropic leishmaniasis, 621, 622*t,* 625
Visible light
  chronic actinic dermatitis and, 340
  photoallergic dermatitis and, 241
  solar urticaria and, 340
Visible tract
  of hookworm-related cutaneous larva migrans, 627*f,* 628
  of strongyloidiasis, 628
Vitamin A deficiency, 407–408, 450–451
  differential diagnosis of, 408, 451
  histopathology of, 103, 127, 407–408, 450–451
  scurvy v., 407
Vitamin C deficiency. *See* Scurvy
Vitiligo, 694, 695*f*
  alopecia areata and, 475
  histogenesis of, 694, 695*f*
  histopathology of, 87, 87*f,* 104, 694
  primary biliary cirrhosis with, 417
Vogt-Koyanagi-Harada syndrome, 694
Vomiting, Behçet's syndrome and, 413
von Kossa method
  for calcium deposits, 436
  for pseudoxanthoma elasticum, 154
von Willebrand factor
  angiosarcoma, 1042
  composite hemangioendothelioma and, 1037
  epithelioid angiosarcoma, 1043
  epithelioid hemangioendothelioma, 1040
  microvenular hemangioma, 1021
Voriconazole, drug-induced pseudoporphyria with, 320
Vulva
  angiomyofibroblastoma of, 990–991
  cicatricial pemphigoid and, 259
  extramammary Paget's disease of, 839
  lichen sclerosus et atrophicus and, 303–304
  mucosal lentigines of, 705
  sebaceous hyperplasia in, 872
Vulvar intraepithelial neoplasia (VIN), 816
  Bowenoid papulosis of genitalia v., 656–657
  histopathology of, 816
Vulvar leiomyosarcoma, 1080
Vulvar lentigo, 705
Vulvar nevi, 717
Vulvar seborrheic keratoses, 656
Vulvitis circumscripta plasma-cellularis, 815–816
VX. *See* Verruciform xanthoma
VZV infection, 642–644, 642*f*–643*f*

Waardenburg syndrome IIa, 14, 693–694
Wade-Fire stain, of *Mycobacterium leprae,* 561, 561*f*–562*f*
Waldenström's macroglobulinemia, paraneoplastic autoimmune multiorgan syndrome and, 254
Waldeyer ring, nodal follicular lymphoma of, 927
Warble, 633
Warthin-Starry stain, of syphilis, 580–582
Warts, 649–656, 651*f*–655*f*
  Bowenoid papulosis of genitalia, 656–657, 657*f*
  condyloma acuminatum, 654–656, 655*f*
  deep palmoplantar warts, 652–653, 652*f*
  epidermodysplasia verruciformis, 653–654, 654*f*

giant condyloma acuminata of Buschke and Loewenstein, 655*f,* 656
granuloma annulare and, 362
verruca plana, 653, 653*f*
verruca vulgaris, 650–652, 651*f*
verrucous melanoma v., 756
Warty dyskeratoma, 806–807
histopathology of, 113, 806–807, 806*f*–807*f*
pathogenesis of, 807
Wasps, reactions to stings of, 634–635, 634*f*
Waterhouse-Friderichsen syndrome, 547
Weakness
polyarteritis nodosa and, 209
with self-healing juvenile cutaneous mucinoses, 445
Weber-Christian disease, 523–524
clinical presentation of, 523, 523*f*
differential diagnosis of, 524
histopathology of, 101, 101*f,* 130–131, 523–524, 523*f*
lupus erythematosus panniculitis v., 522
pancreatic disease v., 529
pathogenesis of, 524
Wegener's granulomatosis (WG), 214–215
Behçet's syndrome v., 414
c-ANCA for, 207, 207*t*
Churg-Strauss syndrome v., 214
Crohn's disease v., 416
differential diagnosis of, 215
granulomatous vasculitis and, 213
histopathology of, 111, 116, 130, 215
microscopic polyarteritis v., 212
palisaded neutrophilic and granulomatosis v., 370
parvovirus B19 in, 662
ulcerative colitis with, 416
Wegener's syndrome, 214
Wegener's vasculitis, 214
Weibel-Palade body, of dermal microvasculature, 50–51
Weigert's resorcin-fuchsin, for elastic tissues, 69, 69*t*
Weight loss
with angioimmunoblastic T-cell lymphoma, 952
polyarteritis nodosa and, 209
Well-differentiated liposarcoma, 1072
histopathology of, 1072, 1073*f*
Well's syndrome. *See also* Eosinophilic cellulitis
eosinophilic panniculitis and, 515
eosinophilic pustular folliculitis v., 467
histopathology of, 107, 117
Werner's syndrome, 145
scleroderma and, 295–296
WG. *See* Wegener's granulomatosis
White fibrous papulosis of the neck, papillary dermal elastolysis v., 399
White macules, with idiopathic guttate hypomelanosis, 691
White plaques, of acute mucocutaneous candidiasis, 597
White sponge nevus, oral focal epithelial hyperplasia v., 657
Wickham's striae, lichen planus and, 185, 185*f*
Winchester syndrome, 155
Wind exposure, cheilitis glandularis and, 381
Wiskott-Aldrich syndrome, 245
Wood, foreign-body reactions and, 374, 374*f*
Woringer-Kolopp disease. *See* Solitary pagetoid reticulosis
World Health Organization Melanoma Program, 763
Worms. *See also* Nematodes
of onchocerciasis, 630–631, 630*f*
subcutaneous cysticercosis, 632, 632*f*
subcutaneous dirofilariasis, 621, 628–629, 629*f*
Wound myiasis, 632–633
Wuchereria bancrofti, 630

Xanthelasma, 672, 675, 680–682, 683*f*
histopathology of, 117, 124
Xanthoerythrodermia perstans of Crocker. *See* Small-plaque parapsoriasis
Xanthogranuloma family, 671–678, 672*f*–677*f,* 672*t*
benign cephalic histiocytosis, 677–678, 677*f*
factor XIIIa and, 78
generalized eruptive histiocytosis, 678
juvenile xanthogranuloma, 672–673, 673*f*
papular xanthoma, 673–674, 674*f*
progressive nodular histiocytosis, 676*f,* 677
reticulohistiocytosis, 675–676, 676*f*
scalloped cell xanthogranuloma, 674, 674*f*
spindle cell xanthogranuloma, 676, 676*f*
xanthoma disseminatum, 674*f*–675*f,* 675
Xanthoma
balloon cell melanoma v., 756
granuloma annulare v., 363
histopathology of, 97, 97*f,* 117, 124
with LCD, 669
leprosy v., 567
in lipid abnormalities, 680–683, 680*t,* 681*f*–683*f*
histopathology of, 681–682, 681*f*–683*f*
pathogenesis of, 682–683
miscellaneous, 686
normolipemic, 683–686, 684*f*–685*f*
polariscopic examination for, 70
Xanthoma disseminatum, 674*f*–675*f,* 675
histopathology of, 124, 675, 675*f*
Xanthomatous reactions, in LCD, 669–671
Xeroderma pigmentosum, 141
Xerophthalmia, vitamin A deficiency and, 407
Xerosis
in HIV, 660
radiation dermatitis and, 348
X-linked ichthyosis
histogenesis of, 133
histopathology of, 103, 133

Yangtze fever, 631
Yaws, 583–584, 584*f*
differential diagnosis of, 584
histopathology of, 584, 584*f*
primary, 583
histopathology of, 110, 117
secondary, 583
histopathology of, 110, 117
tertiary, 584
histopathology of, 119
Yeasts, 591, 592*t*
candidiasis, 597–599, 597*f,* 598*t*
cryptococcosis, 600*t,* 609–611, 610*f*
histoplasmosis, 600*t,* 611–612, 612*f*
Malassezia furfur, 596–597, 596*f,* 598*t*
Yellow cadmium sulfide, tattoo reactions and, 377
Yellow-mutant OCA, 693
Yersinia enterocolitica, erythema nodosum with, 514
Yersinia, Reiter's disease and, 182

Zebra-like hyperpigmentation, 690
Ziehl-Neelsen stain, of *Mycobacterium leprae,* 559
Zinc deficiency. *See* Acrodermatitis enteropathica
Zinc granuloma, 377
histopathology of, 377
Zinc-beryllium silicate, berylliosis and, 377
Zirconium granuloma, 374, 376
Crohn's disease v., 416
histopathology of, 376
pathogenesis of, 376
Zirconium lactate, zirconium granuloma and, 376
Zirconium oxide, zirconium granuloma and, 376
Zoon's plasma cell balanitis circumscripta, histopathology of, 107, 111
Zoster sine herpes, 643
Zoster-related granulomas, 381
histopathology of, 381
Zygomycosis, 599–601, 600*t,* 602*f*
histopathology of, 119, 601, 602*f*